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Rice functional genomics: decades' efforts and roads ahead

Rongzhi Chen[5†], Yiwen Deng[6†], Yanglin Ding[7†], Jingxin Guo[2†], Jie Qiu[4†], Bing Wang[1†], Changsheng Wang[3†], Yongyao Xie[2†], Zhihua Zhang[9†], Jiaxin Chen[4], Letian Chen[2], Chengcai Chu[1], Guangcun He[5], Zuhua He[6], Xuehui Huang[4], Yongzhong Xing[8], Shuhua Yang[7], Daoxin Xie[10*], Yaoguang Liu[2*] & Jiayang Li[1*]

[1]*State Key Laboratory of Plant Genomics, Institute of Genetics and Developmental Biology, Innovation Academy for Seed Design, Chinese Academy of Sciences, Beijing 100101, China;*
[2]*State Key Laboratory for Conservation and Utilization of Subtropical Agro-Bioresources, South China Agricultural University, Guangzhou 510642, China;*
[3]*National Center for Gene Research, Center of Excellence in Molecular Plant Sciences, Shanghai Institute of Plant Physiology and Ecology, Chinese Academy of Sciences, Shanghai 200233, China;*
[4]*Shanghai Key Laboratory of Plant Molecular Sciences, College of Life Sciences, Shanghai Normal University, Shanghai 200234, China;*
[5]*State Key Laboratory of Hybrid Rice, College of Life Sciences, Wuhan University, Wuhan 430072, China;*
[6]*National Key Laboratory of Plant Molecular Genetics, CAS Center for Excellence in Molecular Plant Sciences, Shanghai Institute of Plant Physiology & Ecology, Chinese Academy of Sciences, Shanghai 200032, China;*
[7]*State Key Laboratory of Plant Physiology and Biochemistry, College of Biological Sciences, China Agricultural University, Beijing 100193, China;*
[8]*National Key Laboratory of Crop Genetic Improvement and National Centre of Plant Gene Research, Huazhong Agricultural University, Wuhan 430070, China;*
[9]*College of Plant Science, Jilin University, Changchun 130062, China;*
[10]*MOE Laboratory of Bioinformatics, School of Life Sciences, Tsinghua University, Beijing 100084, China*

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Rice (*Oryza sativa* L.) is one of the most important crops in the world. Since the completion of rice reference genome sequences, tremendous progress has been achieved in understanding the molecular mechanisms on various rice traits and dissecting the underlying regulatory networks. In this review, we summarize the research progress of rice biology over past decades, including omics, genome-wide association study, phytohormone action, nutrient use, biotic and abiotic responses, photoperiodic flowering, and reproductive development (fertility and sterility). For the roads ahead, cutting-edge technologies such as new genomics methods, high-throughput phenotyping platforms, precise genome-editing tools, environmental microbiome optimization, and synthetic methods will further extend our understanding of unsolved molecular biology questions in rice, and facilitate integrations of the knowledge for agricultural applications.

rice, omics, GWAS, phytohormone action, nutrient use, biotic and abiotic responses, photoperiodic flowering, reproductive development

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†Contributed equally to this work
*Corresponding authors (Jiayang Li, email: jyli@genetics.ac.cn; Yaoguang Liu, email: ygliu@scau.edu.cn; Daoxin Xie, email: daoxinlab@tsinghua.edu.cn)

Introduction

As one of the three major food crops, rice (*Oryza sativa* L.) is the staple food source for around 4 billion of the population throughout the world (Sasaki and Burr, 2000). Its importance is even more evident in China due to its long history of cultivation, given that it is the most dominant staple food for over 60% of the Chinese population. As a Chinese saying goes, "food is the first necessity of humans, and rice is always people's first choice." The significant role of rice in facilitating economic development, promoting social stability, and maintaining national security is fully demonstrated from a variety of aspects.

The two prominent breakthroughs in genetic breeding, dwarf breeding and rice hybridization technology, not only substantially increased the rice yield but also set the trend of rice breeding in the world (Bai et al., 2018; Sasaki et al., 2002a). However, despite the remarkable rise in the yield of rice, plant biologists are still facing the huge challenge of ensuring food security to cope with rapid population growth and climate change. Crops, especially rice, are necessarily further modified to raise their yield, improve their quality, and enhance their stress resistance.

The study in rice biology has pioneered crop research, and established a basis for crop improvement. Given the importance of rice as a major staple food and model crop, the research in rice biology has now stepped into the era of multi-omics. In agronomy, extensive allelic variation of important genes is the basis of rice breeding (Wei et al., 2021b). Therefore, using multi-omics to efficiently determine the genetic diversity of beneficial germplasm resources and accurately identify the regulatory genes responsible for complex traits will provide an essential theoretical foundation for rice breeding. Complemented by genome-wide association study—the cornerstone of the efficient identification of genes related to complex rice traits—scientists are able to use metabolomics to systematically reveal the genetic and biochemical basis of natural variations of rice metabolome, which is of great significance for the genetic improvement of crops (Chen et al., 2016; Huang et al., 2010). At the same time, the massive use of genomics in rice biology has provided innovative insights into a great number of biological topics such as rice heterosis and domestication (Huang et al., 2012; Huang et al., 2016b; Zhao et al., 2018b). Especially, multi-omics methods such as genetics and genomics have been successfully applied to the genetic improvement of rice, achieving more efficient and accurate breeding by molecular design (Wu et al., 2021; Zeng et al., 2017).

Rice yield is a polygenic complex quantitative trait composed of three main elements: effective tiller number, grain number per panicle and grain weight. In recent years, scientists have not only obtained a series of significant original research findings in the gene analysis of important agronomic rice traits, but also pioneered a new field to study the gene regulatory network of complex traits using rice as a model crop. For instance, the elucidation of the molecular regulatory network of Strigolactones involved in rice tillering offers important theoretical support for rice molecular breeding of ideal plant architecture with high yield (Jiang et al., 2013a; Song et al., 2017a; Zhou et al., 2013). Moreover, besides the three elements that define yield, a series of regulatory genes controlling rice growth and development have been cloned successively, which provides crucial genetic resources for molecular breeding. For example, the heading date affects the yield and growth period of rice and determines the adaptability of rice varieties to different regions and seasons as well (Wei et al., 2010; Xue et al., 2008). With the continuous in-depth research on the heading date of rice throughout the world, scientists have managed to clone a vast number of heading date genes, which preliminarily revealed the regulation pathway of rice flowering. Therefore, speeding up the research on rice heading date genes would be particularly conducive to the stable cultivation of early-maturing rice with high yield, and the determination of the molecular mechanism of plant flowering.

Considering the threats posed by biotic stresses such as rice blast, bacterial blight and planthoppers that seriously affect rice production, researchers have put intensive efforts in cloning and studying the molecular mechanisms of rice resistance genes over the past two decades, leading to some remarkable breakthroughs (Deng et al., 2020; Guo et al., 2018a; Liu et al., 2015c; Sun et al., 2004). Cloning of broad-spectrum and high resistance genes and elucidating the molecular mechanisms involved in rice resistance not only expand the knowledge of plant immunity and crop disease resistance, but also provide breeding strategies of successful rice breeding with high yield and resistance (Deng et al., 2017; Wang et al., 2018c). Notably, recent illustrating of plant immune receptor structure and biochemical features will provide new insights into the mechanism of immune regulation in plants (Bi et al., 2021).

In addition, abiotic stresses such as heavy metal pollution, soil salinization, drought, heat and coldness are also the major problems that impact the production of crops, further imposing a severe challenge to the sustainable development of agriculture. However, the discovery of a series of genes responsible for high tolerance to salinity, drought and extreme temperatures largely enriched the genetic resources of rice and laid a good foundation for sustainable agricultural development (Ma et al., 2015; Ren et al., 2005). Despite the fact that nitrogen, phosphorous, and potassium—the essential elements that provide the necessary nutrients for plants—perform vital physiological functions in the growth and development of rice, long-term overuse of chemical fertilizers

will cause severe damages to the environment as well as a serious waste of resources. To date, represented by *NRT1.1B* that confers divergence in nitrate-use efficiency between *indica* and *japonica*, a great deal of nitrogen, phosphorus, and potassium utilization genes have been cloned, which further revealed the molecular mechanism of the efficient utilization of nutrients in rice (Hu et al., 2015a; Ma et al., 2021). This is especially important to the protection of the environment and the reduction of agricultural costs. Furthermore, from the aspect of breeding, hybrid sterility is the biggest obstacle in the interbreeding of *indica* and *japonica* and impedes the successful development of hybrid vigor. Yet fortunately, the cloning and effective utilization of fertility regulation genes will greatly promote this breeding process (Chen et al., 2008; Luo et al., 2013). The latest research achievements on fertility and breeding relationship will also be presented in this review.

In summary, ensuring food security is an eternal task. In this review, we aim to systematically and comprehensively review the major research achievements in rice molecular biology over the last few decades from seven aspects, which would provide strong theoretical support for breeding super rice with high yield, high quality, high stress resistance, and high nutritional efficiency.

Omics and genome-wide association studies

Research achievements on rice genomics

A high-quality rice reference genome is the basis for various genetic studies and functional characterizations of genes. More than 20 years ago, the International Rice Genome Sequencing Project (IRGSP) was established to complete sequencing of the rice genome by a map-based clone-by-clone shotgun strategy (Sasaki and Burr, 2000). As an international project, researchers from different countries shared their rice genomic libraries (bacterial artificial chromosome and P1-derived artificial chromosome libraries) and cooperated in sequencing the 12 chromosomes. In 2005, IRGSP completed a highly accurate *japonica* rice reference genome IRGSP 2005 (cultivar Nipponbare), representing 95% coverage of the genome. Meanwhile, an *indica* draft genome was also achieved (Yu et al., 2002).

In parallel to the genome sequencing work, full-length complementary DNAs from over 28,000 clones were sequenced and were publicly available for the rice community, providing a powerful resource for improving gene annotations (The Rice Full-Length cDNA Consortium 2003). To facilitate rice research, the Rice Annotation Project Database (RAP-DB, http://rapdb.dna.affrc.go.jp/) conducted rice genome annotations in 2005. The genome annotations have been updated for several times, with literature-based manually curated data (Sakai et al., 2013). The MSU Rice Genome Annotation Project Database (http://rice.plantbiology.msu.edu/) serves as another platform that provides an integrated display of rice annotation data with unique features (Ouyang et al., 2007). These efforts greatly accelerated subsequent functional genomics studies in rice.

For in-depth gene annotations, RNA sequencing (RNA-seq) is a powerful approach that can feasibly quantify the expression levels of transcripts across the genome in various tissues during different development stages or conditions. This approach has been widely applied in rice transcriptome studies. For example, Lu et al. (2010) examined the transcriptome profilings of multiple Nipponbare tissues, and found that alternative splicing patterns could be observed in ~48% of rice genes. In addition, 15,708 novel transcriptional active regions were identified (Lu et al., 2010). Furthermore, diverse rice omics data including chromatin accessibility, DNA methylation and transcriptome, and comprehensive epigenomic landscapes have been generated in recent years (Joly-Lopez et al., 2020; Liang et al., 2018; Zhao et al., 2020c). Similar to Encyclopedia of DNA Elements project for the human genome, the increasingly comprehensive rice multi-omics information (e.g., genomics, transcriptomics, and epigenomics) will facilitate better understanding of rice gene functions.

There are numerous rice varieties with a high level of genetic and phenotypic diversity across the world. With the advent of high-throughput sequencing technologies, the diverse rice varieties could be genome resequenced to help comprehensively uncover the genomic variation. Using this approach, 40 cultivated rice accessions and 10 wild rice accessions were firstly sequenced, and 6.5 million single nucleotide polymorphisms (SNPs) were identified (Xu et al., 2011). The resequencing work enabled the investigation of genome-wide variation patterns and domestication sweeps in the rice genome. Furthermore, a large collection including 446 geographically diverse accessions of wild rice species (*O. rufipogon*) and 1,083 *indica* and *japonica* accessions were sequenced for unveiling the domestication history of Asian cultivated rice (Huang et al., 2012). Population genetics analyses suggested that early *japonica* rice was firstly domesticated from *O. rufipogon* (Or-III type) in southern China, while *indica* rice was subsequently developed from crosses between the early *japonica* rice and local divergent *O. rufipogon* (Or-I, Or-II types) in South East and South Asia (Figure 1A) (Huang et al., 2012; Xie et al., 2021). For African cultivated rice (*Oryza glaberrima*), a genetic analysis based on genome sequences of 20 *O. glaberrima* and 94 *Oryza barthii* accessions demonstrated that *O. glaberrima* was domesticated in a single region along the Niger river. Comparative analysis suggested that a set of genes (e.g., *qSh1*, *Sd1*, and *Dep1*) were under convergent yet independent selection during domestication of Asian and African cultivated rice subspecies (Wang et al., 2014).

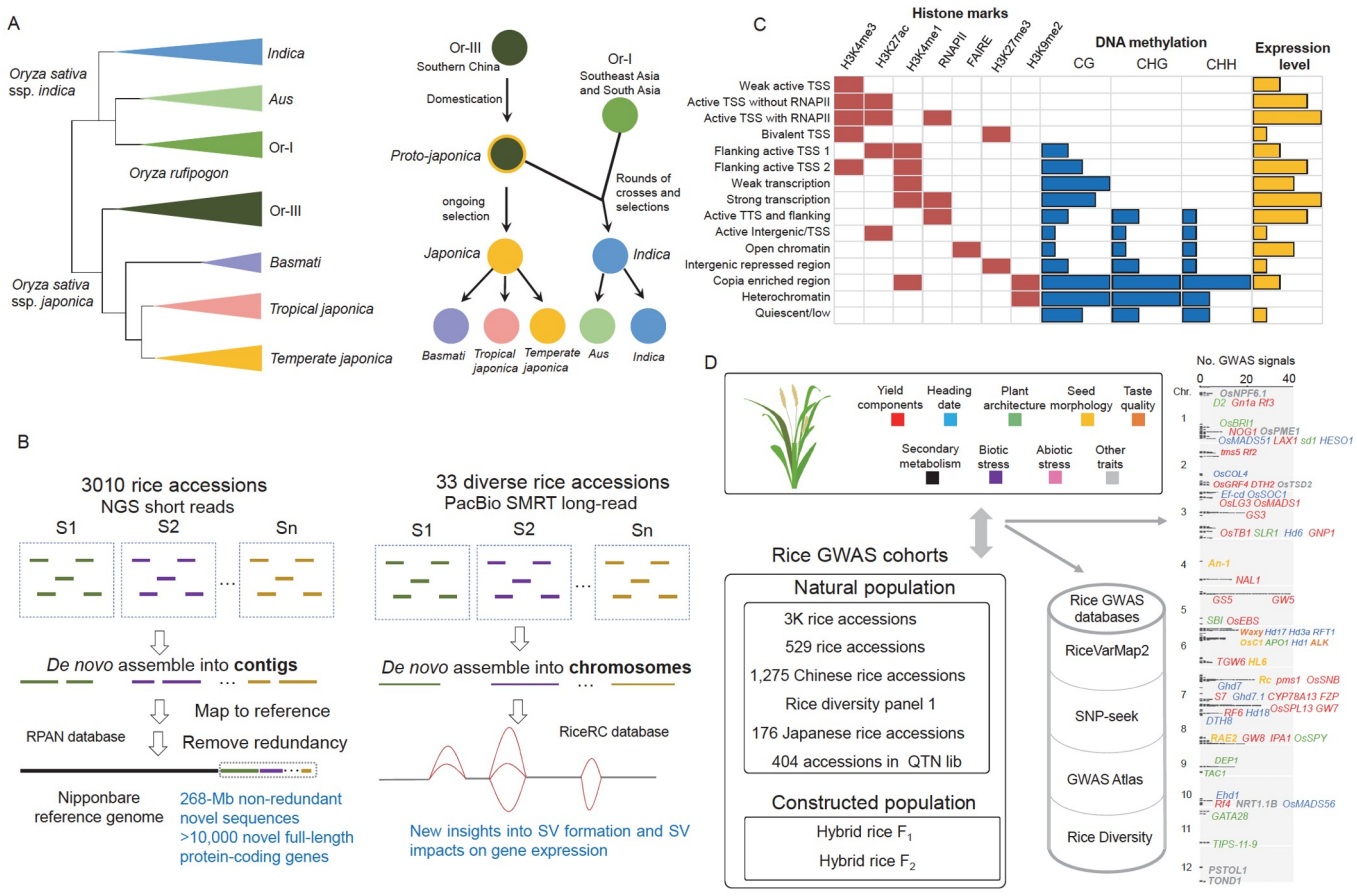

Figure 1 Examples of the achievements in rice genomics and epigenomics. A, Domestication origin model of Asian cultivated rice. Left, phylogeny topology of Asian wild and cultivated rice; Right, single-origin model of rice domestication. B, Construction of rice pan-genomes based on NGS short reads 3K rice and long reads of 33 rice accessions. C, Summary of rice genome chromatin states based on combinations of histone marks and DNA. D, Summary of rice GWAS studies and databases.

In addition to genomic loci targeted by artificial selection during domestication (e.g., selection on grain shattering gene *sh4*), intensive breeding selections over the past decades also left genomic signatures in rice genome. For example, by analyzing genome sequences of 1,479 accessions, genomic changes associated with modern breeding efforts were identified, which include strong selection signals around *sd1* (the famous green revolution gene), *Rf1* (for nuclear fertility restorer), *Xa4* and *Xa26* (two genes for disease resistance) (Xie et al., 2015).

De-domestication, or feralization, is a unique evolutionary process in rice, which means that rice cultivars are converted into "wild-like" forms. To investigate the genomics underlying the de-domestication process, genomes of 524 global weedy rice were analyzed (Qiu et al., 2020). The results showed that weedy rice materials have evolved multiple times from cultivated rice. Comparisons of selective signatures between domestication and feralization suggested that the latter occurs largely through changes at loci unrelated to domestication. Moreover, key de-domestication related genes were found under convergent evolution. Besides, quantitative trait loci (QTLs) underlying weedy-specific traits are identified using a recombinant inbred line (RIL) population, which contains 168 individuals from a cross between weedy rice and cultivated rice (Sun et al., 2019b).

In rice genomics studies, characterizations of genetic variants through reads mapping approaches relied on relatively high levels of sequence similarity with the Nipponbare reference genome. However, the genetic variation in highly divergent regions and the information of the presence and absence of genes relative to Nipponbare would be inevitably underestimated. To construct a pan-genome dataset of rice, the genomes of 66 phylogenetically representative accessions (including *O. sativa* and *O. rufipogon*) were deep sequenced (115-fold coverage). The draft genomes of 66 rice accessions were constructed and annotated (Zhao et al., 2018b). With comparative genomic analyses, this study found that each rice gene contained 10 missense SNP sites and 6 polymorphic sites of relatively large effect on average (Zhao et al., 2018b). Wang et al. (2018e) employed a "map-to-pan" strategy to build a rice species pan-genome based on resequencing data of over 3,000 rice accessions, which yielded 268-Mb non-redundant novel sequences absent in

the Nipponbare reference genome. In a recent study, high-quality genome assemblies of 33 rice accessions were generated using PacBio long read sequencing, and 171,072 structural variations (SVs) and 25,549 gene copy number variations (gCNVs) were detected (Qin et al., 2021a). These pan-genome datasets provide plentiful population-scale resources for functional genomics and evolutionary biology research (Figure 1B).

Genomic tools are also powerful in genotype calling and linkage mapping for various genetic studies in rice. A high-throughput approach for genotyping recombinant populations (e.g., F_2 or RIL populations) was developed by utilizing whole-genome low-coverage resequencing data (Huang et al., 2009b). High-density genomic bins can be genotyped for each individual line in the population with the software package SEG-Map (Zhao et al., 2010), which can be directly used in linkage mapping. Moreover, for mutant mapping, MutMap was developed based on deep sequencing of DNA pools from a segregating F_2 population under the crossing of a mutant to the wild-type parental line that has been used in the mutagenesis (Abe et al., 2012). Furthermore, the approach of bulked-segregant analysis is applied for QTL mapping and the package GradedPool-Seq was developed for mapping complex quantitative traits by sequencing multiple graded-pool samples from recombinant populations (Wang et al., 2019b). These genomics-based methods are now widely applied in rice genetic studies.

Rice epigenomics

Epigenomics focuses on study of all the epigenetic changes in a cell or organism. During recent years, some epigenomic information, including DNA methylation, histone modification, chromatin accessibility, and three-dimensional genomics, has been characterized for rice.

DNA methylation is a conserved epigenetic modification involved in multiple pivotal processes, like gene expression state, genome stability, and gene imprinting. Plant DNA cytosine methylation occurs in CG, CHG, and CHH contexts (H=A, T, C, or G). The global methylation profiles were investigated in the rice genome, which indicated that CG methylation occurs at high levels in protein-coding gene bodies, while both CG and non-CG methylation are abundant in TEs. Compared with *Arabidopsis*, the methylation level of all cytosine for the rice genome is about four times higher than that of *Arabidopsis* (Li et al., 2012). In contrast to significantly enriched methylation around centromere regions in *Arabidopsis*, the enrichment feature was not obvious for rice, which is probably due to differences of the amount and distribution of TEs between the two plant genomes (Li et al., 2012; Tan et al., 2016). Examination of the relationship for genetic and methylation divergence between cultivated and wild rice suggested that regions with high CG methylation divergence are often associated with high genomic divergence, while the trend is not obvious for non-CG methylation (Li et al., 2012).

The effects of rice DNA methylation on gene expression were assessed, which indicated that for promoter regions, the methylation level is negatively correlated with the gene expression level. In gene-body regions, there exist low levels of CHG and CHH methylation, and the CG methylation level is generally associated with active transcription (Tan et al., 2016). Notably, methylation level in transcriptional termination regions showed a negative correlation with the expression, and the correlation coefficient is even higher than that of promoter regions (Li et al., 2012).

Profiling of rice DNA methylation has also brought some new implications for its environmental adaptations and heterosis. Genes involved in environmental responses have been reported to be regulated by DNA methylation. For example, drought-responsive genes show a significant enrichment of DNA methylation (Zheng et al., 2017). In addition, heritable CHG hypomethlation was observed for rice under heavy metal stresses (Cong et al., 2019). Integrative analysis of bisulfite-sequencing, RNA-sequencing, and siRNA-sequencing data in two rice inbred lines (Nipponbare and 93-11) and two hybrid offsprings suggested that 0.79% of cytosines were epimutated between the parent and corresponding hybrid. The epimutations are clustered in the genome and are overlapped with differential siRNA regions in parents (Chodavarapu et al., 2012). In addition, most gene expression changes are not related to the *cis*-acting DNA methylation changes, possibly indicating a role of *trans* effects playing in the transcriptional differences in hybrids (Chodavarapu et al., 2012).

Histone modifications play a crucial role in modulating genome activities in rice. Zhao et al. (2020c) developed an enhanced chromatin immunoprecipitation (eChIP) approach, and generated genome-wide profilings for five histone modifications (H3K4me3, H3K27ac, H3K4me1, H3K27me3, and H3K9me2) and RNA polymerase II (Figure 1C). Integrated with chromatin accessibility, DNA methylation and transcriptome profiles, the researchers constructed comprehensive epigenomic maps across multiple tissues for 20 rice varieties. The researchers found that 81.8% of rice genomes could be annotated with different epigenomic properties. Active histone marks, like H3K4me3 and H3K27ac, were found associated with active genes, and are frequently located close to the 5′ regions of the genes, and also downstream of transcriptional start site. The transcribed regions of active genes are often marked with H3K4me1. RNA polymerase II (RNAPII) was more abundant in transcription terminal sites (TTSs) than in transcription start sites (TSSs), indicating a transcriptional regulation role of TTS. For repressive marks, H3K27me3 showed over-presented in genomic regions with LINE (long interspersed nuclear ele-

ment) and SINE (short interspersed nuclear element) retrotransposons and DNA transposons. H3K9me2 was associated with *Copia* and *Gypsy* retrotransposons, and covered mainly in the intergenic regions. The expression patterns of genes with different combinations of histone marks were also examined, and the researchers further proposed that H3K4me3 modification might be responsible for the initiation of gene regulation, and the additional H3K27ac and RNAPII modification could lead to increased regulation of transcript abundance. In addition, in contrast to inactive chromatin states showing relatively stable state across different tissues, active and repressive histone modifications greatly vary among different tissues. With the comprehensive epigenomic dataset, the researchers further constructed a rice Encyclopedia of DNA Elements database (RiceENCODE) (Xie et al., 2021).

Open chromatin regions show lower nucleosomal density, and these regions are highly sensitive to DNase I. DNase-seq (DNase I hypersensitive sites sequencing) has been applied to identify open chromatin regions in rice genome (Zhang et al., 2012), which revealed that highly expressed genes are more often associated with DNase I hypersensitive (DH) sites within the gene bodies or 200 bp upstream regions from the TSS. In addition, the gene expression level is also found to be associated with the intensity of DNase-seq signal of DH sites within 200 bp upstream or downstream from the gene. Genes differentially expressed in different tissues are associated with DH sites. In addition, the DNA methylation levels of DH sites are dramatically lower compared with other regions.

In addition to DNase-seq, assay for transposase-accessible chromatin sequencing (ATAC-seq) and formaldehyde-assisted isolation of regulatory elements followed by sequencing (FAIRE-seq) has also been commonly applied to identify open chromatin regions in plants. For example, Wilkins et al. (2016) used ATAC-seq and identified 8 Mb (~2%) nucleosome-free or open chromatin regions of the rice genome. The distribution profiling showed a sharp peak around 50 bp before the TSS. Consistently, they also observed the association between gene expression and promoter openness. Based on FAIRE-seq analysis by Zhao et al. (2020c), FAIRE regions could be classified into proximal regulatory element (PRE) and distal regulatory element (DRE). PRE regions showed high levels of active marks and low repressed marks. For genes flanked DREs, the expression levels in specific tissues were significantly higher than that in other tissues. The self-transcribing active regulatory region sequencing (STARR-seq) has been applied for enhancer identification in rice (Sun et al., 2019a), which revealed that most identified enhancers are located within the 5′UTR and coding regions with H3K4me3 and H3K27ac marked (Sun et al., 2019a).

The rice genome forms a hierarchical 3D organization including chromosome territories, compartments, and chromatin loops. The high-throughput chromosome conformation capture (Hi-C) technology has been a useful tool in analyzing the rice overall chromatin architecture, which suggested that each rice chromosome could be divided into A or B compartment, where A compartment is mostly comprised of euchromatin and active marks, while B compartment includes heterochromatin and high methylation (Liu et al., 2017; Dong et al., 2018). However, the limited resolution of Hi-C hinders the exploration of the detailed 3D genome architecture, including interactions between active and inactive elements and their effects on transcriptional regulation. Zhao et al. (2019) generated chromatin interaction analysis paired-end tag sequencing (ChIA-PET) data for young leaves of two rice cultivars, Minghui 63 and Zhenshan97. Based on the ChIA-PET map, the general high-order genome architecture organization was assessed, which revealed that ~65% of the rice genome belongs to A compartment with abundant active histone marks and higher transcriptional levels, while the B compartment harbors more heterochromatic marks. Taking advantage of the high-resolution ChIA-PET strategy, the chromatin architecture was separated into diverse spatially active and inactive interactive modules. By examining the features of promoter-promoter interactions, the researchers found that promoter-promoter interacting genes in the active modules are likely to transcribe cooperatively, while inactive heterochromatin loops may act as stable scaffolds of the 3D architecture.

Genome-wide association studies

Genome-wide association studies (GWAS) involve examining millions of genetic variants across the genomes of many individuals to identify genotype-phenotype associations. For plant research, compared with QTL mappings using conventional biparental populations, the abundant genetic diversity and the numerous historical genomic recombination events in plant populations are helpful for identification of associated loci with higher resolution in GWAS (Takeda and Matsuoka, 2008). GWAS has been successfully applied in rice research for more than 10 years, which has unveiled hundreds of associated loci related to numerous agronomically important characteristics and metabolites in rice (Wang et al., 2020d).

Before whole-genome resequencing became practical in plants, Tian et al. (2009) performed a pioneer research using candidate gene-based association study to map the genes controlling eating and cooking quality in rice. Genomic fragments of 18 starch synthesis-related genes for 33 *indica* and 37 *japonica* were sequenced to perform association mapping. The research successfully mapped major-effect genes for eating and cooking quality traits. Moreover, a second-step model using the major-effect genes as the con-

trol was performed to map minor-effect genes contributing to these traits. The work demonstrated that the genes involving starch synthesis form a regulatory network and cooperatively control eating and cooking quality.

In 2010, the first rice GWAS study was performed by Huang et al. (2010), in which the first high-density rice haplotype map was constructed based on skim-sequencing of 517 rice landraces with genotypes imputated by a *k*-nearest neighbor (KNN) algorithm method. GWAS for 14 agronomic traits of 373 *indica* lines identified 80 associations, with peak SNPs explaining ~36% of the phenotypic variance on average. In 2012, the researchers further performed GWAS for a more diverse rice panel, which included 950 worldwide rice varieties, and revealed new genomic loci associated with rice flowering time and grain yield traits. Moreover, causal genes and variants could be successfully identified by developing an analytical framework that integrated variant information, expression, and functional genome annotation. Zhao et al. (2011) collected 413 diverse cultivated accessions from 82 countries and systematically phenotyped 34 traits. With the genotyping based on 44K SNP array, GWAS analyses revealed high heterogeneity in the genetic architecture with different subpopulations and response to environments. Based on a mini-core rice germplasm collection of 533 rice accessions, Xie et al. (2015) carried out GWAS for grain yield and bacterial blight disease resistance. Integration of the GWAS results with genomic signatures of recent breeding suggested a positive correlation between the number of breeding signatures and the variety yield. Yano et al. (2016) focused on a *japonica* rice panel of 176 accessions with limited population structure. They successfully identified four new genes associated with agronomic traits with the utilization of both single polymorphisms and gene-based association analyses. Li et al. (2020b) resequenced 1,275 rice accessions consisting of widely planted modern cultivars and parental hybrid rice lines from China. Twenty-nine agronomic traits in total were investigated under 10 geographical environments for different subpopulations, which uncovered 143 significant associations. Detailed investigations for the alleles of agronomically important genes suggested that many favorable alleles are still underused in elite accessions. The study provided valuable genomic resource for genetic studies of Chinese modern rice varieties. Recently, Wei et al. (2021b) performed GWAS analysis based on eight rice cohorts, which identified 470 associated loci corresponding to 69 quantitative trait genes (QTGs) (Figure 1D). These QTGs underlie 50 agronomic traits that are associated mostly with yield components, heading date, plant architecture, and taste quality.

GWAS has not only been useful to uncover loci responsible for important agronomic traits, but also facilitated the dissection of heterotic loci in rice. To explore the genetic basis of rice heterosis, Huang et al. (2015c) investigated the genomic landscape for 1,495 elite hybrid rice varieties. A total of 130 associations were identified on GWAS of 38 agronomic traits. Dissecting the GWAS signatures suggested that most loci showed incomplete dominate effect, with only 13 loci having strong overdominance effects. In addition, for most grain number associated loci, the average effects of heterozygous genotypes exceeded that of homozygous genotypes, while the case for heading date was opposite. The research also proposed that accumulation of rare superior alleles with positive dominance could contribute to the rice heterosis.

Building collaborative recombinant-mapping plant populations could not only help alleviate the influences imposed by population structure, but also identify alleles with small effects or low frequency in the populations, which are long-standing challenges in GWAS. To have a deeper dissection of heterosis, Huang et al. (2016a) used 17 representative hybrid combinations and selfed their F_1 hybrids to generate 17 sets of large F_2 recombination populations containing 10,074 lines. These populations included nine *indica-indica* crosses of a three-line system (type A), six *indica-indica* crosses of a two-line system (type B), and *indica-japonica* crosses (type C). Sixteen key gene loci were detected with main effect associated with heterosis, but they were not universally shared on different population systems. In addition, positive partial dominance effects serve as the major causes of heterosis in rice yield-related traits. Some loci with overdominant effects , e.g., *Ideal Plant Architecture 1* (*IPA1*) and *Heading date 3a* (*Hd3a*), are probably due to dosage effects. Lv et al. (2020) resequenced 1,143 *indica* accessions selected from the parents of superior hybrid rice cultivars. Investigating the crossing patterns of the parents suggested that parents of three-line hybrids are more genetically distant than those of the two-line hybrids. With evaluation of the differences for the frequencies of parental variation, 98 and 36 loci were potentially involved in heterosis for the superior hybrid varieties, respectively. The genomic data and variation resources will be valuable for geneticists and rice breeders.

The comprehensive identification of heterotic loci is fundamental for a better understanding of the molecular mechanism of heterosis. Liu et al. (2020c) have proposed several perspectives for utilization of heterosis in rice breeding. It could be more efficient to create superior hybrids by selecting or designing individuals of complementary genotypes for these loci. The heterosis could be maintained or fixed by strategies including traditional male-sterile and recently developed asexual propagation through seeds (Khanday et al., 2018; Wang et al., 2019a). Furthermore, after the in-depth understanding of heterosis, one promising goal is to create elite inbred lines that have similar superior performance as elite hybrids.

The developments of sequencing technologies have facilitated high throughput genotyping with accurate results. However, the plant phenotyping technologies still lag behind, which is a bottleneck in functional genomics and plant breeding. During recent years, massive progress has been made in developing high-throughput phenotyping (HTP) techniques, such as remote sensing and robotic vehicles. In addition, HTP has also been successfully integrated with GWAS for dissecting genetic architecture of complex agronomic traits in rice (Xiao et al., 2021).

For example, in 2014, Yang et al. (2014) developed a high throughput rice phenotyping facility (HRPF), which could efficiently measure 15 agronomic traits (such as morphology, biomass, and yield) during rice growth stages. HRPF consists of two platforms, the rice automatic phenotyping platform (RAP) and yield traits scorer (YTS). Comparisons of GWAS results with HRPF and traditional phenotyping data suggested that HRPF showed a more complete representation in dissecting genetic architecture. In addition, HRPF could measure novel traits (e.g., plant compactness and grain-projected area) that are infeasibly measured manually. Guo et al. (2018b) extended the RAP platform to phenotype 51 image-based traits to monitor drought response in rice with enclosing the genetic code. Campbell et al. (2015) used high-throughput visible and fluorescence imaging to quantify the dynamic growth and chlorophyll responses to salinity of rice accessions during the stress treatment. Four genomic loci were identified to be linked with salinity-induced fluorescence responses. With the rapid development of phenotyping machines and image recognition algorithms, HTP will be a more routine and cost-efficient tool for crop phenotyping in the future, as sequencing technologies did for genotyping. Given the fast, nondestructive, and high-throughput detection of high-throughput phenotyping techniques, the combination of HTP and GWAS could greatly accelerate genetic mapping and discovery of genes.

In addition to traditional traits, the contents of metabolites and mineral elements are also important targets in metabolic GWAS (mGWAS) of rice. For example, through comprehensive profiling 840 metabolites, substantial sub-species differences in leaf metabolome were observed (Chen et al., 2014b). Metabolites like C-glycosylated and malonylated flavonoids are preferentially accumulated in *indica*, while *japonica* rice harbors significantly higher levels of phenolamides and arabidophl alcohol derivatives (Chen et al., 2014b). Based on 840 metabolic traits from a global collection of 529 rice accessions, mGWAS was performed, which revealed 634 genomic loci significantly associated with 598 metabolites. Detailed interpretation of GWAS results identified a number of candidate genes encoding critical enzymes for metabolites that contribute to plant physiology and nutrition contents. The mGWAS approach facilitates better understanding of genetic and biochemical insights into rice metabolome variation. By taking advantage of high-throughput inductively coupled plasma mass spectrometry, Yang et al. (2018) quantitatively measured the contents of 17 mineral elements in vegetative tissues of 529 rice accessions at the heading and maturity stages. GWAS for the rice ionomic profiles identified 72 association signatures with high consistency among different growth stages, tissues, and field conditions. The comparison of rice and *Arabidopsis* GWAS data suggested that the contents of some mineral elements (e.g., sodium (Na) and Molybdenum (Mo)) are governed by the same genes, indicating that there are conserved features of genetic architecture underlying ionomic variations across monocots and dicots. The identified causative genes and variants could be used for marker assisted selection and engineering of crops with more beneficial nutrients and better stress resistance (Yang et al., 2018).

Since GWAS associations have been performed between genetic variants and diverse traits in rice, it is of great significance to construct integrated databases that could comprehensively restore diverse genotype-phenotype associations with biological information. During recent years, several online databases have been developed, such as "Rice Diversity" (Wang et al., 2018b), "RiceVarMap2" (Zhao et al., 2015a), "SNP-seek" (Mansueto et al., 2016). Recently, "GWAS Atlas," a curated resource incorporating high-quality GWAS associations was developed with friendly web interfaces for plant and animal research (Tian et al., 2020). In addition, Wei et al. (2021b) generated a rice gene encyclopedia "RiceNavi" containing hundreds of known trait-related causative variants. Recently, Zhao et al. (2021) quantitatively inferred the millions of variants in both coding and regulatory regions across the rice genome. The constructed rice functional impact map was integrated into "RiceVarMap2," which greatly assisted in pinpointing the causal variants and genes within GWAS signatures. All these integrated GWAS resources will help improve our understanding of genetic architecture of rice complex quantitative traits.

Phytohormone and growth

Phytohormones are chemicals present at very low concentration but have indispensable roles in the regulation of plant growth and development. Plant hormones include auxin, cytokinins (CKs), abscisic acid (ABA), ethylene (ETH), gibberellins (GAs), brassinosteroids (BRs), salicylic acid (SA), jasmonates (JAs), strigolactones (SLs), and peptides. Phytohormones play central roles in almost every aspect of plant growth and development, and integrate responses to various environmental signals. Phytohormones act individually or synergistically, and roles of different hormones can be complementary or antagonistic.

The development of semi-dwarf cereals has underpinned the huge increase in global cereal grain production in the last 70 years. Genetic and functional analyses of *SLENDER RICE1* (*SLR1*)/*REDUCED HEIGHT* (*RHT*) and *SEMIDWARF1* (*SD1*) genes in rice and wheat have greatly improved the understanding of the biosynthesis and signaling pathways of GAs, and provide a powerful strategy to reduce plant height and increase grain yield in crops (Sasaki et al., 2002a; Spielmeyer et al., 2002; Yamaguchi, 2008). Synthetic phytohormones have also been exogenously applied to improve grain yield and stress tolerance. In this section, we briefly introduce advances in functions, biosynthesis and metabolism, distribution and transport, and signaling of phytohormones in rice. We also listed genes involved in biosynthesis, metabolism, transport, and signaling of phytohormones in rice (Table S1 in Supporting Information).

Biological functions of phytohormones in rice

Phytohormones play indispensable roles in regulating important agronomic traits of rice (Figure 2). Plant height is important for adaption of rice plants to different environments and is controlled by several hormones including GAs, BRs, SLs, and auxin, which mainly promote stem elongation through induction of cell expansion and elongation. Cell expansion and elongation also involves cell wall that forms a physical barrier surrounding plant cells. GAs and BRs regulate cellulose biosynthesis and cell wall remodeling by promoting the expression of genes encoding cellulose synthase and cell wall-loosening enzymes, respectively (Wang et al., 2018a).

Tiller number and the proportion of tillers bearing panicles are critical for grain yield. Tiller bud initiation and outgrowth are regulated by phytohormones including auxin, SLs, BRs, ABA, GAs, and CKs (Figure 2). In rice, SLs, auxin, GAs, and ABA can repress bud outgrowth, whereas BRs and CK promote bud outgrowth (Liu et al., 2020d; Wang et al., 2018a). The SL deficient or signaling mutants show typical dwarf and high tillering phenotypes in different subspecies of rice, indicating that SLs play essential roles in tillering regulation (Al-Babili and Bouwmeester, 2015; Waters et al., 2017). SLs repress tiller bud outgrowth mainly through regulating transcriptional activities of several important transcription factors such as IPA1 and OsBZR1 in rice (Fang et al., 2020; Jiao et al., 2010; Song et al., 2017a). Auxin can indirectly repress bud outgrowth mainly through repressing CK biosynthesis and activating SL biosynthesis in *Arabidopsis*, but its effect on tiller development is relatively weak in rice and the mechanism remains elusive. GA signaling triggers proteasomal degradation of SLR1, leading to degradation of MONOCULM1 (MOC1) and hence repression of bud formation and outgrowth in rice (Li et al., 2003; Liao et al., 2019). ABA preferentially exists in dormant buds and represses bud outgrowth in coordination with SLs in rice (Liu et al., 2020d). In addition, BRs promote bud outgrowth through regulating the expression of *O. sativa TEOSINTE BRANCHED1* (*OsTB1*)/*FINECULM1* (*FC1*), which encodes an essential inhibitor of tillering and functions as an integrator of endogenous hormone signals and exogenous environmental signals in rice (Fang et al., 2020).

Tiller and leaf angle are vital for light interception and plant density, thus making important contribution to crop productivity. Tiller angle is closely associated with gravitropism and is controlled by sedimentation of starch granules in gravity-sensing cells called statocytes. Studies of the tiller angle mutant *lazy1* (*la1*) and its suppressors indicate that auxin transport and redistribution in response to gravity stimulation are essential for tiller and leaf angle in rice, and SLs promote tiller angle probably by suppressing auxin biosynthesis (Li et al., 2007; Sang et al., 2014). BRs play important roles in the regulation of leaf and tiller angle, and the rice mutants with altered BR content or signaling showed improved grain yield under dense planting, indicating great potential to improve crops through modulating the leaf and tiller angle (Sakamoto and Matsuo, 2006). Tiller angle is also regulated by a series of domestication-related QTLs and genes, such as *PROSTRATE GROWTH1* (*PROG1*), *TILLER ANGLE CONTROL1* (*TAC1*), and *TAC3* (Jin et al., 2008; Tan et al., 2008; Wang et al., 2018a; Yu et al., 2007). And leaf angle is also affected by ABA, JAs, GAs, and IAA, which show complex crosstalk with BRs in rice (Figure 2).

The size of panicles and seeds directly affects grain yield of crops and undergoes strict selection in evolution and breeding. In rice, BRs positively regulate grain size through promoting cell expansion in the spikelet hulls (Li et al., 2019d; Tong and Chu, 2018). *Grain Size 5* (*GS5*) controls grain size in rice likely through regulating endocytosis of OsBAK1-7 and thus modulating BR signaling. Moreover, auxin influences seed size probably through maternal tissues. SHAGGY-like kinase 41 (OsSK41)/OsGSK5 interacts with *O. sativa* AUXIN TRANSCRIPTION FACTOR4 (OsARF4) to regulate grain size and weight, possibly through modulating auxin signaling. Loss of function of *OsSK41* or *OsARF4* results in large and heavy grains and their beneficial alleles can be applied for rice improvement (Hu et al., 2018b). Genetic evidence from a dominant mutant showed that *BIG GRAIN1* (*BG1*) regulates polar auxin transport and grain size, giving a clue that auxin distribution may play important roles in grain size control (Liu et al., 2015b). Phytohormones also control panicle size and grain number (Figure 2). Generally speaking, homeostasis of CK levels in the inflorescence meristem, which was determined by its biosynthesis, activation, and degradation, plays essential roles in the regulation of panicle branching and grain yield (Ashikari et al., 2005). GAs and the small peptide GRAIN

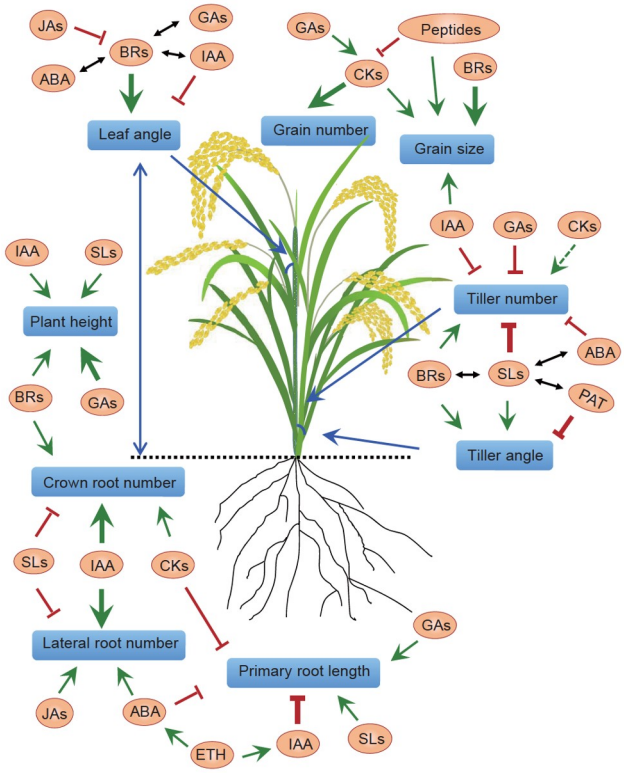

Figure 2 Roles of phytohormones in the regulation of rice architecture. In rice, plant architecture is mainly determined by factors regulating plant height, tiller number, tiller and leaf angles, grain number and size, primary root length, as well as crown and lateral root number. Phytohormones function as key integrators of environmental and developmental signals, thus playing essential roles in the control of plant architecture. Each trait is regulated by multiple hormones that show complex synergistic or antagonistic relationships. Generally speaking, plant height is mainly promoted by GAs, SLs, BRs, and IAA. Tiller number is repressed by SLs, IAA, GAs, and ABA, but promoted by BRs and probably CKs. SLs can regulate tiller number coordinately with BRs and ABA. For tiller angle regulation, the PAT shows negative effects through regulating spatial auxin distribution, whereas BRs and SLs show positive regulations. For leaf angle regulation, BRs have a strong promotion effect, but IAA shows negative effects. ABA, JAs, GAs, and IAA show complex crosstalk with BRs in the regulation of leaf angle. Grain number and grain size are important agronomic traits determining grain yield. CKs and BRs are phytohormones showing main effects on grain number and size, respectively. GAs can increase grain number and yield by promoting CK activity in panicle. Whereas the small peptide GRAIN NUMBER, GRAIN LENGTH AND AWN DEVELOPMENT1 (GAD1) represses grain number through regulating CK levels, while promotes grain size via unknown mechanism. IAA is generally considered to promote grain size, and several OsARF proteins involved in auxin signaling pathway can regulate grain size and yield. For root development, IAA plays dominant roles in promoting initiation and elongation of crown and lateral root, and also in inhibiting growth of primary root. But SLs have opposite roles in development of crown, lateral, and primary roots. GAs can positively regulate primary root growth, but CKs can inhibit primary root and promote crown root growth. ABA can repress primary root growth, but promote lateral root number. In addition, ETH can inhibit primary root elongation through activation of IAA and ABA pathways. Green arrows indicate positive regulation, red lines ending with a perpendicular bars indicate negative regulation, and black bidirectional arrows denote coordination of different hormones. Dotted lines denote mechanisms of regulation that are not fully understood. Thickness of the line and arrow represents the regulation strength, with bold lines and arrows indicating relatively more important regulations. Abbreviations: ABA, abscisic acid; BRs, brassinosteroids; CKs, cytokinins; ETH, ethylene; GAs, gibberellins; IAA, indole-3-acetic acid; JAs, jasmonates; PAT, polar auxin transport; SLs, strigolactones.

NUMBER, GRAIN LENGTH AND AWN DEVELOPMENT1 (GAD1) can regulate grain number by promoting or repressing CK activities in the panicle, respectively (Hedden, 2020; Jin et al., 2016).

Root architecture is important for rice development and nutrient absorption. Among 10 kinds of phytohormones, IAA plays the most significant roles in promoting initiation and elongation of crown and lateral root, and also in inhibiting growth of primary root (Guo et al., 2021). SLs play the opposite role to auxin in the development of crown, lateral and primary roots, and the mechanism underlying crosstalk between SLs and auxin needs further investigation (Waters et al., 2017). In dark grown rice seedlings, ETH can inhibit primary root elongation mainly through activation of IAA and ABA pathways (Zhao et al., 2020a, 2020b). JAs can promote lateral root growth, while GAs positively regulate development of primary root. In addition, CKs and ABA can both inhibit primary root development, but promote formation of crown root and lateral root, respectively (Figure 2).

Biosynthesis and metabolism of phytohormones

Phytohormones are synthesized from common metabolic precursors by specific pathways. For instance, BRs, GAs, ABA, and SLs are all derived from terpenoids. Specifically, BRs are derived from sterol campesterol, GAs from C-20 geranylgeranyl pyrophosphate, while SLs and ABA from carotenoids. In addition, IAA, SA, ETH, and CKs are derived mainly from tryptophan, phenylalanine, methionine, and adenine, respectively. The biosyntheses of phytohormones are strictly regulated, both spatially and temporally. For instance, local auxin biosynthesis plays an essential role in shaping local auxin gradient, thus modulating embryogenesis, root hair development, and formation of floral organs and leaf vascular tissues (Zhao, 2010). Metabolism and degradation are also important for controlling endogenous hormone levels. For instance, ABA is inactivated by oxidation through phaseic acid and dihydrophaseic acid, while CKs and GAs are inactivated by CK oxidase/dehydrogenase (CKX) and GA 2-oxidase (GA2ox) enzymes, respectively (Steven et al., 2017).

A series of genes involved in phytohormone biosynthesis and metabolism play critical roles in controlling agricultural traits in rice (Table S1 in Supporting Information). The *SD1* gene responsible for the "Green Revolution" in rice encodes a GA20ox isoenzyme (GA20ox-2) that catalyzes the conversion of GA_{53} to GA_{20} (Sasaki et al., 2002a; Spielmeyer et al., 2002). And a beneficial allele of the SL biosynthesis gene *HIGH TILLERING AND DWARF 1* (*HTD1*), also known as *DWARF17* (*D17*), contributes to increased tiller number and improved grain yield in rice, and has been widely utilized and co-selected with *SD1* since the "Green Revolution" (Wang et

al., 2020f). In addition, OsCKX2 negatively regulates CK levels in the shoot apical meristem that control numbers of inflorescence meristems and reproductive organs, and mutation in *OsCKX2*/*Gn1a* leads to enhanced grain yield (Ashikari et al., 2005). Thus, fine regulation of biosynthesis, modification, and breakdown of plant hormones determines the amount and location of active hormones, which play important roles in growth and development of rice.

Distribution and transport of phytohormones

Phytohormones can be transported from sites of biosynthesis to distant sites of action. These processes occur by the passive diffusion through plasma membrane and active transport between cells and organs. The polar auxin transport plays key roles in establishing auxin gradients and thus regulates pattern formation. For instance, auxin is mainly synthesized in apical meristems and leaf primordia, and is transported in a basal direction. This long-range auxin transport sets the basis of apical dominance and is important for branching patterns. Besides, the short-ranged polar auxin transport is an essential determinant of pattern formation, especially in shoot apical meristems and root tips. Polar auxin transport is mediated by different types of auxin transporters including the efflux carriers PIN-formed (PIN) and PIN-LIKES (PILS) proteins, ATP-Binding Cassette subfamily B (ABCB) transport proteins, and a family of influx carriers Auxin transporter (AUX1) and Like-AUX1 (LAX) proteins. The asymmetric distribution of auxin transporters in the apical, basal, or lateral plasma membrane can establish polar or lateral auxin transport pathways (Adamowski and Friml, 2015; Semeradova et al., 2020). In addition, transporters of SLs, CKs, GAs, and ABA have also been identified in plants. The SL transporter PLEIOTROPIC DRUG RESISTANCE 1 (PDR1) is responsible for the SL transport from root to shoot and the SL exudation into soil, thus playing key roles in regulation of axillary branches and the development of arbuscular mycorrhizal fungi (Wang et al., 2017a). The CK transporters, such as purine permeases (PUPs), nucleoside transporters (equilibrative nucleoside transporters, ENTs), and ATP-binding cassette (ABC) transporters, mediate CK uptake into cells and long-distance CK transport from root to shoot (Feng et al., 2017). The nitrate or peptide transporter family (NPF) proteins have been found to transport different kinds of substrates, including nitrate, peptides, GAs, and ABA. NPF3.1 and GTR1 have been proven to be GA transporters and the nitrate transporter NRT1.2 in *Arabidopsis* has been identified as an influx transporter of ABA (Gao et al., 2017).

Perception and signal transduction of phytohormones

Phytohormones are perceived by receptors and co-receptors, which are localized in the plasma membrane, endomembrane system, cytosol or nucleus. Receptors for BRs and peptide hormones are mainly leucine-rich-repeat receptor kinases (LRR-RLKs) localized in the plasma membrane. BRs are perceived by a receptor and co-receptor complex, including BRI1 and BRI1-ASSOCIATED RECEPTOR KINASE 1 (BAK1). When BRs bind to its receptor BRI1, the cytoplasmic kinase domain of BRI1 phosphorylates the negative regulator BRI1 KINASE INHIBITOR 1 (BKI1), then BRI1 dissociates from BKI1 and phosphorylates BAK1 to trigger signaling (Wang et al., 2017c). Peptide hormones such as CLAVATA 3 (CLV3) and other CLV3/Endosperm surrounding region (CLE) peptides can bind to the extracellular domain of LRR-RLK receptors CLV1 and CLV2, and activate their cytoplasmic kinase domain to phosphorylate target proteins (Hirakawa and Sawa, 2019; Song et al., 2017b).

Receptors for ETH and CKs are two-component system regulators that are composed of conserved histidine kinases (HK) and response regulator (RR) proteins. The CK receptor CK1 is located to the plasma membrane, but other CK receptors like AHKs are present in the endomembrane system. CK1 and AHKs are His sensor kinases that perceive the CK signal by auto-phosphorylation at a highly conserved His residue. The phosphoryl group is subsequently transferred to phosphotransfer proteins that further phosphorylate transcriptional regulators and trigger signal transduction (Feng et al., 2017; Hwang et al., 2012). ETH is perceived by a family of endoplasmic reticulum (ER)-localized ethylene receptors (ETRs). Upon ETH binding, ETRs are inactivated and fail to activate the kinase activity of CONSTITUTIVE TRIPLE RESPONSE 1 (CTR1), leading to dephosphorylation of ETHYLENE INSENSITIVE 2 (EIN2). The C-terminal of EIN2 is further cleaved off from the ER membrane and translocated into the nucleus (Hao et al., 2017; Yang et al., 2015a). ABA is perceived mainly by cytosolic receptors PYRABACTIN RESISTANCE 1 (PYR1) and PYR1-Like (PYL) proteins, which can interact with cytosolic PROTEIN PHOSPHATASE TYPE 2C (PP2C) and regulate phosphorylation of other proteins such as the protein kinase SUCROSE NON-FERMENTING KINASE 2 (SnRK2) (Li et al., 2017c).

Receptors for GAs, SA, and SLs have dual localizations, and may migrate between cytosol and nucleus. Binding of SA induces migration of the SA receptor NPR1 (NON-EXPRESSER OF PATHOGENESIS-RELATED PROTEIN 1) to the nucleus, where NPR1 acts as a co-activator of transcription factors to stimulate expression of defense genes (Jin et al., 2017; Ding and Ding, 2020). The amount of NPR1 is regulated by other SA receptors through direct protein-protein interaction, and the activity of NPR1 is regulated by posttranslational modifications, such as phosphorylation, ubiquitination, and sumoylation. Both the GA receptor GID1 (GA-INSENSITIVE DWARF 1) and the SL receptor D14

belong to a large family of α/β-fold hydrolases, but GID1 does not have hydrolase activity. The binding of GAs and SLs with their respective receptors triggers conformational changes, which lead to formation of protein complexes of GID1-GID2-DELLA and D14-MAX2 (MORE AXILLARY GROWTH2)-D53, respectively (Gao et al., 2017; Wang et al., 2017a).

Receptors for auxin and JAs are F-box proteins localized in the nucleus. The binding of auxin to TRANSPORT INHIBITOR RESPONSE 1 (TIR1) provides a binding surface for the co-receptor AUXIN/IAA-INDUCIBLE PROTEIN (AUX/IAA), indicating that auxin functions as a "molecular glue." Similarly, the binding of JAs to CORONATINE INSENSITIVE 1 (COI1) also induces the formation of a co-receptor complex consisting of COI1, JASMONATE-ZIM DOMAIN (JAZ), and an inositol pentakisphosphate. Structural and pharmacological studies have revealed that COI1 contains an open pocket that recognizes the bioactive hormone JA-Ile (Zhai et al., 2017).

After perception of phytohormones, the downstream signaling pathways are mainly involved in the ubiquitination, proteolysis, and phosphorylation of transcriptional regulators. The protein degradation and phosphorylation mechanisms operate in almost all hormone systems but each hormone tends to use one as the primary mechanism (Steven et al., 2017). Proteasomal degradation of transcriptional regulators is essential for signaling of auxin, JAs, GAs, and SLs. Specifically, the binding of hormones to their receptors triggers formation of protein complexes consisting of receptors, F-box proteins, and transcriptional regulators, which are ubiquitinated and degraded through the 26S proteasome. The auxin receptor TIR1 and the JA receptor COI1 are themselves F-box proteins, which target repressor proteins of AUX/IAA and JAZ for degradation. This leads to the release of transcription factors such as ARFs, MYC2, bHLH3/13, 14, 17, and MYB21/24, resulting in consequent changes in the expression of target genes (Luo et al., 2018b; Zhai et al., 2017). The transcription factors and transcriptional repressors work coordinately and convert phytohormone signals into specific context-dependent responses. In GA signaling, the receptor GID1 recruits the F-box protein GID2 and the transcriptional repressor proteins DELLA, which are targeted for degradation and trigger regulation of downstream gene expression. Similarly, upon SL binding, the receptor D14 undergoes conformational changes and forms a complex with F-box proteins D3/MAX2 and repressor proteins D53/SMXL6, 7, 8. The repressor proteins then undergo a quick ubiquitination and degradation, triggering subsequent regulation on downstream gene expression (Jiang et al., 2013a; Yao et al., 2016; Zhou et al., 2013). It is generally considered that repressor proteins in phytohormone signaling lack the ability to bind DNA, and thus modulate gene expression through interaction with transcription factors and inhibiting their DNA-binding or transcriptional activities. However, recent study has shown that SMXL6, 7, 8 can directly bind DNA and repress their own transcription, functioning as autoregulated transcription factors to maintain the homeostasis of SL signaling (Wang et al., 2020c). In addition, D53 and SMXL6, 7, 8 can also interact with different transcription factors, such as IPA1, OsBZR1, SPL9, SPL15, and BES1, to regulate gene expression in rice and *Arabidopsis*. Thus, re-evaluation of potential direct targets of transcriptional repressors in hormone signaling is promising to find unknown mechanisms regulating plant development and environmental adaption.

Another general mechanism in hormone signaling is protein phosphorylation. In the signaling pathways of BRs, ABA, peptides, CKs, and ETH, perception of hormones mainly triggers signal transduction through changing the status of protein phosphorylation, which is modulated by a series of protein kinase, such as SnRK2s, SnRK3s, CBL-interacting protein kinases (CIPKs), calcium-dependent protein kinases (CDPKs), and the mitogen-activated protein kinase (MAPK/MPK) module. Specifically, SnRK2s are involved in ABA and BR signaling, and may function as nodes of crosstalk between ABA and BRs. Similarly, the MAPK module that typically contains MAPK, MAPK kinase (MAPKK/MPKK), and MAPKK kinase (MAPKKK/MPKKK) are potentially involved in crosstalk between ABA and CLV-type peptides. In CK signaling, phosphoryl groups are transferred from CK receptors to Arabidopsis Histidine Phosphotransfer (AHP) proteins, which can further phosphorylate transcriptional regulators including Arabidopsis Response Regulators (ARRs) (Feng et al., 2017). Whereas in ETH signaling, ETH perception leads to dephosphorylation and cleavage of the ER-localized protein EIN2, triggering the C-terminnus of EIN2 (CEND) fragment to participate in translational repression in cytoplasmic processing body (P-body), or migrate from ER membrane into the nucleus to activate master of the transcriptional regulators EIN3 and EIN3-LIKE 1 (EIL1) (Hao et al., 2017).

Together, the rapid increase in our understanding of plant hormones offers new opportunities to improve the plant architecture and nutrient use efficiency, to break the trade-off between growth and biotic/abiotic stress resistances, and to meet the demand for food production under inevitable climatic changes and diminishing availability of arable lands.

Deciphering nutrient use efficiency

The application of chemical fertilizers, which are mainly composed of the macronutrients nitrogen (N) and phosphorus (P), has made great contribution to the global food security. However, due to the low nutrient use efficiency (NUE) of cereal crops, including rice, large amounts of

fertilizers either retain in soil or enter into water and air, causing severe environmental problems. Therefore, deciphering the molecular mechanisms underlying NUE and exploring elite alleles would pave the way for breeding high NUE varieties, which will guarantee the rice production with less fertilizer input. The signaling components and transporters for N and P have been systematically summarized in several recent reviews (Ham et al., 2018; Wang et al., 2021d; Xuan et al., 2017; Zhang et al., 2020c; Zhang et al., 2020d). Here, we focused on the new breakthroughs and promising directions emerging recently in the area of improving N and P use efficiency of rice.

Further steps after transporting

The uptake and transport of nutrients is the first step in the nutrient utilization. Therefore, transporters of various protein families have received much more attention in the molecular biology study of plant nutrients (Sasaki et al., 2016; Wang et al., 2018g). With increasing number of transporters identified in the model plant *Arabidopsis*, more and more their homologs in rice have been characterized by reverse genetics (Li et al., 2017a), while a few of them show potentials in yield and NUE enhancement and their functions are not limited to transport alone (Wang et al., 2020e).

OsNRT1.1B, the homolog of nitrate transport gene *AtNRT1.1*, was identified through QTL mapping based on the difference in chlorate sensitivity between *indica* and *japonica* rice varieties, which represents the nitrate use divergence between those two subspecies. Introducing the elite allele of $OsNRT1.1B^{indica}$ into *japonica* varieties can significantly improve not only nitrate uptake and transport, but also nitrate assimilation, therefore achieving higher grain yield and N-use efficiency (Hu et al., 2015a). More importantly, under a high nitrate supply, OsNRT1.1B can recruit an E3-ligase NBIP1 and promote the degradation of OsSPX4, a sensor for intracellular P levels and repressor for central regulators in both nitrate and phosphate signaling, i.e., OsNLP3 and OsPHR2, respectively (Hu et al., 2019; Lv et al., 2014). A nuclear-localized transcription factor HINGE1/RLI1 was also identified downstream of the nitrate-NRT1.1B-SPX4 cascade, further fine-tuning the nitrate-induced Pi response in rice (Zhang et al., 2021d). Besides, OsNRT1.1B contributes to the recruitment of *indica*-enriched root bacteria, which contain more genera with nitrogen metabolism functions (Zhang et al., 2019d). Interestingly, *OsNR2*, a nitrate reductase gene which was also identified through QTL mapping of the *indica-japonica* divergence in chlorate-sensitivity shows a feedforward interaction with *OsNRT1.1B* (Gao et al., 2019). Concurrently introducing the elite alleles of $OsNRT1.1B^{indica}$ and $OsNR2^{indica}$ can synergistically enhance grain yield and N use efficiency (Gao et al., 2019; Zhang and Chu, 2020). Therefore, OsNRT1.1B acts as a hub for nitrogen utilization, transducing the nitrate signaling from plasma membrane to nucleus, promoting a balanced utilization of nitrate and phosphate, and recruiting more functional root microbiota. In addition, OsNRT2.3b harbors a cytosolic pH regulatory motif and overexpression of *OsNRT2.3b* can enhance the pH-buffering capacity, leading to improved grain yield and N use efficiency (Fan et al., 2016a).

The distribution of nutrients among different tissues, especially in the developing grains, are critical for the final yield (Yamaji and Ma, 2017). In cereal crops, more than 60% of total P are allocated into grains, where the majority of them are in the form of phytate (Raboy, 2009). Although phytate is a major P source supporting seedling growth during germination, it is a key anti-nutrient for both human and monogastric animals and also a major source of water pollution (Raboy, 2001). Yamaji et al. (2017) reported a node-localized SULTR-like phosphorus distribution transporter (SPDT), acting as a switch that controls the P allocation to the grains. Interestingly, knockout of *SPDT* can reduce the total P and phytate in brown rice without any penalty on yield, seed germination, and seedling vigor. Modification of SPDT provides a potential strategy to reduce the P removal from soil due to grain harvest, alleviate environmental pollution, and improve the nutritional value of rice (Hu and Chu, 2017). Besides, OsSULTR3;3, belonging to the same protein family of SPDT, shows similar functions in regulating phytate concentration in rice grains (Zhao et al., 2016a). Very recently, a PHO1 family Pi transporter OsPHO1;2, which mediates Pi efflux in the developing seeds, was identified to be necessary for the grain starch biosynthesis (Ma et al., 2021). Mutation of *OsPHO1;2* caused over-accumulation of Pi in seeds and inhibited the ADP-glucose pyrophosphorylase activity, leading to grain filling defect, while overexpressing *OsPHO1;2* can significantly improve grain yield and P use efficiency (Ma et al., 2021).

Interplay between N and plant hormones

Plant hormones are master regulators of various biological processes, which ultimately influence NUE and crop yield. With increasing knowledge of plant hormone signaling pathways and nitrate signaling pathway, more and more components have been shown to participate in the direct interplay between N and plant hormones (Kiba et al., 2011; Krouk, 2016). Recently, the role of GAs, BRs, and auxin in regulating NUE of rice have been revealed (Li et al., 2018; Liu et al., 2021c; Zhang et al., 2021c).

GAs belong to a class of tetracylic diterpenoids, regulating various processes associated with plant growth and development (Xu et al., 2014a). The mutations in the GAs biosynthesis or signaling pathways causing the semi-dwarfism

in many crop species, especially rice and wheat, have led to the Green Revolution in modern agriculture, with the help of increasing tolerance to chemical fertilizers (Gao and Chu, 2021). However, the adverse effect is the reduced N use efficiency and increased N fertilizer demand, making the Green Revolution not "green." Reports have shown that applying GA can improve the growth and yield of rice under different N levels (Wang et al., 2016b). To improve the NUE of green revolution varieties (GRVs) in rice, an in-depth evaluation of the NH_4^+ uptake rates was performed among GRVs and *OsGRF4*^{ngr2} was identified as a causal gene for the increased NH_4^+ uptake (Li et al., 2018). Functional analysis of OsGRF4 revealed that it promotes N uptake and assimilation, while SLR1 (DELLA protein in rice) inhibits these processes by repressing the accumulation of OsGRF4 and interfering the interaction of GRF4-GIF1. Moreover, OsGRF4 can activate the genes involved in photosynthesis, carbon assimilation, and cell division, while SLR1 can antagonize those processes, enabling the OsGRF4-SLR1 module to integrate nitrogen and carbon metabolism. Applying the elite allele *OsGRF4*^{ngr2} in modern GRVs, which tips the GRF4-DELLA balance towards increased GRF4 abundance, further promotes the grain yield and also NUE (Li et al., 2018). In addition, a downstream component of OsGRF4 in regulating C-N balance is further elucidated. *OsMYB61* was identified for the divergence in the nitrogen-mediated leaf area changes between *indica* and *japonica* subspecies by QTL mapping, which encodes a transcription factor that activates cellulose synthase genes (Gao et al., 2020; Huang et al., 2015a). Interestingly, *OsMYB61* functions downstream of OsGRF4, thereby providing another component for improving NUE by coordinating C-N balance. Wu et al. (2020) further discovered a nitrogen-induced whole-genome histone H3 lysine 27 trimethylation (H3K27me3) mediated by the interaction between an AP2 domain transcription factor NGR5 (Nitrogen-mediated Tiller Growth Response 5) and PRC2 (polycomb repressive complex 2), which is essential for the nitrogen-induced tillering in rice. More importantly, NGR5 can be regulated at protein level through a GID1-promoted proteasomal degradation, which is competitively inhibited by the DELLA-NGR5 interaction, thereby enhancing the tiller number and yield in GRVs.

BRs are a class of polyhydroxylated steroids, positively regulating various biological processes, especially many important agronomic traits including grain size, lamina inclination, and plant height (Tong and Chu, 2018; Wang et al., 2012). However, their roles in regulating NUE have just been unveiled. OsTCP19 was identified as a key modulator of rice tillering response to nitrogen through genome-wide association study and its natural variation contributes to the adaption to soil nitrogen content (Liu et al., 2021c). Interestingly, OsTCP19 directly represses the expression of *DLT*, which encodes a key tiller-promoting transcription factor involved in BR signaling, thereby connecting the nitrogen signaling and BR signaling (Liu et al., 2021c; Tong et al., 2009, 2012a). Actually, the above-mentioned OsGRF4 was first identified to regulate grain length (Che et al., 2015; Duan et al., 2015; Hu et al., 2015b). Furthermore, OsGRF4 activates BR response to promote grain development, while OsGSK2, the central negative regulator in BR signaling, can repress the transactivation activity of OsGRF4 through direct protein-protein interaction (Che et al., 2015). In addition, NGR5 was also previously named as SMOS1 (Small Organ Size1) for regulating cell expansion in an auxin-dependent manner (Aya et al., 2014). Two research groups reported the involvement of SMOS1 in BR signaling, one reporting the interaction of SMOS1-OsBZR1 and SMOS1-OsGSK2 (Qiao et al., 2017), and the other demonstrating the interaction of SMOS1-DLT (Hirano et al., 2017), both suggesting a role of SMOS1 in BR signaling. Together with the close interaction between BR and GA (Tong et al., 2014), it is reasonable that BR is also involved in regulating NUE through OsGRF4 and NGR5.

The crosstalk between auxin and nitrate signaling in regulating nitrate-dependent root architecture changes has been well studied in *Arabidopsis* and rice (Krouk et al., 2010; Ma et al., 2014; Meier et al., 2020; Song et al., 2013; Vidal et al., 2010; Zhang et al., 2019f); however, few reports showed the potentials in improving NUE by regulating auxin signaling or biosynthesis. Recently, *DNR1* (*Dull Nitrogen Response1*), encoding an aminotransferase, was identified to regulate nitrate uptake and assimilation through modulating auxin homeostasis in rice (Zhang et al., 2021c). The elite *DNR1*^{indica} allele harbors a 520-bp deletion in its promoter, conferring lower transcript level, higher auxin content, and higher expression of *OsARFs*, which activates the genes involved in nitrate uptake and assimilation. More importantly, knocking out *DNR1* in *japonica* variety ZH11 can enhance both NUE and grain yield, thereby providing another target for improving NUE in the future molecular breeding (Zhang et al., 2021c).

Balance between heading date and NUE

Heading date represents the time of transition from vegetative to reproductive growth in rice, i.e., the floral transition, which is one of the key determining factors for the geographic distribution and the final grain yield and quality formation of rice (Sun et al., 2014). The appropriate heading date of rice can maximize the utilization of resources including light, heat, water, and nutrients with the rational design of planting scheme. Studies from the model plant *Arabidopsis* and other species have revealed a complex regulation network of flowering, which is affected by many exogenous factors, especially photoperiod and temperature

(Cao et al., 2021; Cho et al., 2017). The nutrient availability, especially nitrogen level, also plays a pivotal role in the floral transition of plants and many regulatory components have been identified in *Arabidopsis* (Lin and Tsay, 2017; Vidal et al., 2014). In agricultural practices, it is well recognized that nitrogen fertilizer postponed heading date and maturation time, posing a threat to the final yield and quality and the heading date is delayed by either extreme deficiency or excess of nitrogen (Ye et al., 2019; Zhang et al., 2021b). However, the molecular mechanism of N-regulated floral transition in rice remains largely elusive.

Recently, N-mediated heading date 1 (Nhd1), also named as OsCCA1/OsLHY, was identified to mediate the N regulated flowering in rice (Murakami et al., 2007; Sun et al., 2021; Wang et al., 2020a). The transcription level of *Nhd1* is upregulated by both N supply (glutamine level specifically) and floral transition, while Nhd1 can directly activate the expression of *Hd3a*, the rice florigen gene (Komiya et al., 2008), thereby connecting the exogenous N supply and endogenous floral transition of rice. Interestingly, Nhd1 can suppress the expression of *OsFd-GOGAT* and *OsLHT1*, which encode a key enzyme in N-assimilation and an amino acid transporter, respectively, forming a negative feedback regulatory pathway of N assimilation. Knockout of *Nhd1* can increase both N uptake efficiency (NUpE) and N utilization efficiency (NUtE). More importantly, there exist natural variations of *Nhd1*, which correlate with the N-mediated flowering time in different varieties, enabling the future breeding of high NUE varieties with appropriate flowering response to N (Zhang et al., 2021b). Besides, overexpression of a nitrate transporter gene *OsNRT1.1A*/*OsNPF6.3* can significantly promote the grain yield, NUE, and maturation time, providing another component in the N-regulated floral transition signaling (Wang et al., 2018e).

Genes regulating rice heading date have also been revealed to participate in N signaling and metabolism (Fang et al., 2019; Wang et al., 2021c). *Grain number*, *plant height and heading date7* (*Ghd7*) encoding a CCT-domain transcription factor has been reported to negatively regulate heading date and drought resistance, while positively regulate plant height and panicle size (Weng et al., 2014; Xue et al., 2008). It was recently reported that Ghd7 can directly repress the expression of *ARE1*, which encodes a negative regulator of NUE and heading date (Wang et al., 2018d), thereby promoting nitrogen utilization (Wang et al., 2021c). Although the Ghd7-ARE1 module in enhancing NUE is concomitant with delayed heading date, they provide a possible solution for improving NUE with different geographical fitness. Interestingly, a quantitative trait locus *Early flowering-completely dominant* (*Ef-cd*) was shown to capacitate shortened maturation without yield penalty in rice. More importantly, both nitrogen utilization and photosynthetic rates are enhanced by *Ef-cd* (Fang et al., 2019). Therefore, it is promising to pyramid the elite haplotypes of the above-mentioned genes to achieve the balance of NUE and heading date.

Perspectives in rice NUE

Transporters are thought to be the key components in improving NUE of crops. Different transporters have distinct functions, which are involved in nutrient signaling, uptake, transport, partitioning, and remobilization, etc. (Figure 3). In rice, there are more than 80 NRT1/PTR and 4 NRT2 members, but only a few were well characterized so far; therefore, a comprehensive understanding of each transporter will be helpful in NUE improvement of crops.

Current studies of NUE in crops including rice are actually yield-oriented. However, with the improvement of living standard, the demand for higher eating-quality and nutritional value products is increasing. Therefore, the molecular mechanisms underlying the relationship between NUE and eating-quality need to be dissected.

NRT1.1B and SPX4 are recognized as sensors for extracellular nitrate and intracellular P levels, respectively. However, the sensors for intracellular nitrate or nitrogen and extracellular phosphate remain unknown. In addition, most of the current understanding of nutrient signaling is focused on the local signaling transduction, while the progress in systemic nutrient response is very limited. Therefore, efforts are still needed to fill the gaps in nutrient signaling pathways especially systemic response in rice.

Although many important components have been identified in the crosstalk between NUE and phytohormone signaling, our understanding on the integration of environmental nutrient levels and internal hormone status is still fragmented. A more detailed and comprehensive map needs to be drawn, particularly, from the signal initiation at nutrient sensors and hormone receptors to their downstream regulators.

Perception and responses to abiotic stress

Abiotic stresses are major adverse environmental factors (such as drought, floods, extreme temperatures, and salinity) that influence the morphology and physiology of crops at the vegetative and reproductive stages, leading to decreases in yield. These stress events have been occurring more frequently over the past several decades due to the increasingly variable weather patterns associated with global climate change (Gourdji et al., 2013; Pryor et al., 2013). Drought, salt, and cold stress have detrimental effects on the growth and development of crops such as rice, including decreases in seed germination, growth rate, leaf size, and tiller number (Mahmood-ur-Rahman et al., 2019). Abiotic stresses also

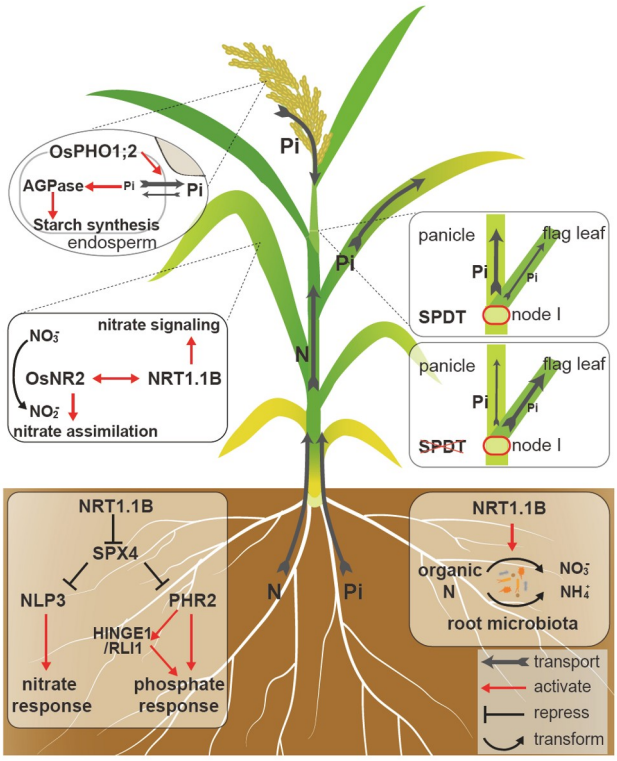

Figure 3 Transporter-associated modules in improving N and P use efficiencies of rice. The uptake of N and P is promoted both directly (activating NLP3 and PHR2) and indirectly (recruiting root microbiota) through NRT1.1B (the nitrate transceptor) in roots. In the aboveground tissues where nitrate is assimilated by OsNR2, the feedforward interaction between OsNR2 and NRT1.1B promotes N use efficiency by simultaneously activating nitrate assimilation and nitrate signaling. In node I where Pi is distributed between panicle and flag leaf, SPDT acts like the switch controlling Pi allocation to grains. Knockout of *SPDT* can enhance the allocation of Pi to the flag leaf, thereby reducing the removal of P from soils and promoting P use efficiency. OsPHO1;2 mediates the Pi homeostasis in the developing grains by promoting Pi efflux in the endosperm. Enhanced OsPHO1;2 activity can reduce Pi accumulation and activate starch biosynthesis in grains, promoting P use efficiency. Abbreviations: Pi, phosphate; AGPase, ADP-glucose pyrophosphorylase; OsPHO1;2, *Oryza sativa* PHO1-type Pi transporter 2; OsNR2, *Oryza sativa* nitrate reductase 2; SPDT, SULTR-like phosphorus distribution transporter; SPX4, a rice SPX domain protein 4; HINGE1/RLI1, highly induced by nitrate gene 1/ regulator of leaf inclination 1.

hamper water/nutrient absorption and use efficiency. In addition, heavy metal pollution, which is broadly present worldwide, has significant impacts on rice grain productivity and quality. Heavy metals in crops are also dangerous to human health (Rai et al., 2019). Rice is particularly susceptible to extreme temperatures during the reproductive stage. Both heat stress and cold stress lead to spikelet sterility and reduced grain filling, resulting in substantial yield losses (Sánchez et al., 2014; Zhang et al., 2019c; Zhang et al., 2017d; Zinn et al., 2010).

Since plants are not able to physically move away from abiotic stresses, they have evolved complex strategies to cope with these challenges, including stress tolerance, stress avoidance, and recovery from stress (Mickelbart et al., 2015). After perceiving stress signals, plants transduce them to a variety of cellular machinery and respond appropriately, thus re-establishing homeostasis at the cellular and organismal levels or mitigating the effects of episodic stress events.

Abiotic stress-sensing mechanisms

To adjust to abiotic stress, plants undergo specific changes in gene expression, metabolism, and physiology in response to the precise perception of different environmental signals (Zhu, 2016). Abiotic stresses such as temperature stress are mostly physical signals that may be sensed anywhere in the plant cell, including membrane-bound organelles/structures such as the cell membrane, endoplasmic reticulum (ER), chloroplasts, mitochondria, and peroxisomes (Gong et al., 2020; Zhu, 2016) and membrane-less organelles such as stress granules and speckles (Gong et al., 2020). After these physical signals are sensed by various organelles, they must be decoded by downstream macromolecules to regulate gene expression and other cellular activities.

Different abiotic stresses can have common effects on plants. For example, abiotic stresses such as drought, heat, cold, and high salinity cause osmotic stress in plant cells. They also trigger a rapid and transient increase in cytosolic $[Ca^{2+}]$ ($[Ca^{2+}]_{cyt}$), which acts as a universal second messenger to initiate abiotic stress responses by activating certain Ca^{2+}-permeable channels and/or Ca^{2+} transporters (Gong et al., 2020; Zhu, 2016). An analysis of populations of cold sensitive *indica* (cultivar 93-11) and cold-tolerant *japonica* (Nipponbare) rice using genetic, biochemical, and physiological approaches identified *Chilling tolerance divergence 1* (*COLD1*), which confers chilling tolerance to Nipponbare rice; *COLD1* encodes a potential cold sensor (Ma et al., 2015). COLD1 is a transmembrane protein located in the plasma membrane and ER that forms a complex with Rice G-protein α subunit 1 (RGA1), leading to a transient increase in $[Ca^{2+}]_{cyt}$ upon cold stress. The loss-of-function *cold1* mutant is deficient in the cold-induced increase in $[Ca^{2+}]_{cyt}$ and is therefore sensitive to chilling stress. However, the exact role of COLD1-RGA1 in regulating Ca^{2+} influx remains unclear. It would be interesting to determine whether COLD1 functions as a calcium-permeable channel or as a regulator of such a channel.

Plants contain large families of Ca^{2+} channels and transporters, such as cyclic nucleotide-gated channels (CNGCs), glutamate receptor-like (GLR) channels, and the Ca^{2+}-permeable transporters annexins, which orchestrate specific cytosolic Ca^{2+} signals in plants under stress (Chen et al., 2021a). OsCNGC9 (Wang et al., 2021a) and the calcium transporter ANNEXIN 1 (AtANN1) (Liu et al., 2021b) were recently shown to mediate cold-induced Ca^{2+} influx in rice and *Arabidopsis thaliana*, respectively. In addition, RE-

DUCED HYPEROSMOLALITY-INDUCED CALCIUM INCREASE 1 (OSCA1) is a mechanosensitive Ca^{2+}-permeable ion channel that senses osmotic stress in *Arabidopsis* (Yuan et al., 2014). Moreover, in *Arabidopsis*, salt stress-triggered Ca^{2+} influx depends on the salt sensors glycosyl inositol phosphorylceramide (GIPC) sphingolipids, which are synthesized by MONOCATION-INDUCED $[Ca^{2+}]_{cyt}$ INCREASE 1 (MOCA1) (Jiang et al., 2019b). However, it is unclear whether these calcium channels or lipids perceive abiotic stress signals in rice.

Because receptor-like protein kinases (RLKs) perceive external signals in plants (Liang and Zhou, 2018), it is possible that RLKs are involved in sensing abiotic stress signals in rice. There are over 1,000 *RLK* genes in the rice genome (Osakabe et al., 2013), some of which are known to regulate abiotic stress responses. For instance, several RLKs, including ERECTA (Shen et al., 2015a), 25L1 and 25L2 (Chen et al., 2014a), THERMO-SENSITIVE GENIC MALE STERILE 10 (TMS10), and TMS10-like protein (TMS10L), play critical roles in the responses of rice to temperature stress (Yu et al., 2017a). The RLK *Oryza sativa* STRESS-INDUCED PROTEIN KINASE 1 (OsSIK1) is involved in improving drought and salt tolerance (Ouyang et al., 2010). Whether these proteins are responsible for sensing abiotic stress signals requires further investigation.

Abiotic stress response mechanisms

Drought stress

Due to climate change, drought has become the abiotic stress with the greatest negative effects on agriculture worldwide, particularly the productivity of field crops such as rice (Hu and Xiong, 2014). It is estimated that 50% of global rice production is affected by drought stress (Bouman et al., 2005). Therefore, it is crucial to understand the drought tolerance mechanisms in rice, which will help improve drought resistance and crop production in drought-prone areas.

The root system plays an important role in drought avoidance in crops, as it is responsible for the absorption and translocation of water and nutrients (Figure 4A). A vigorous root system, including fine root diameter, deep roots, and high root density, enables crops to obtain more water. Therefore, improving root structure will help crops avoid drought stress (Uga et al., 2013a). In recent decades, many studies have been devoted to isolating major quantitative trait loci (QTLs) involved in root traits in rice via linkage mapping and genome sequencing, and performing GWAS, with the aim of uncovering the genetic basis of root traits and thereby improving drought resilience. A good example of such a study is the cloning and characterization of the QTL *Deeper rooting 1* (*DRO1*) from a breeding population derived from a cross between the shallow-rooting rice cultivar IR64 and deep-rooting landrace Kinandang Patong, which show these traits under normal conditions (Uga et al., 2013a). DRO1 participates in the elongation of root tip cells, leading to asymmetric growth and downward bending of the root tip in response to gravity (Figure 4A). A single nucleotide deletion in the coding region of the IR64 allele of *DRO1* (*DRO1-ir*) causes a reduction in the curvature of the root in response to gravity. The introduction of *DRO1* into shallow-rooted rice varieties helped them avoid drought by increasing the production of deep roots. Several other major drought-related QTLs in rice have been discovered, including *DRO2* and *DRO3* (Uga et al., 2013b; 2015), which control deep rooting under normal conditions, and *qRL6.1* (Obara et al., 2010) and *qRL7* (Wang et al., 2013a) are associated with root length under hydroponic conditions. GWAS as a powerful tool is widely used to discover the QTLs associated with underlying genetic traits in a population. Li and colleagues performed GWAS using a panel of 529 representative rice accessions and identified more than 100 association loci regulating various root traits, providing a genetic basis for improving drought avoidance in rice (Li et al., 2017e).

Emerging evidence indicates that precisely controlling stomatal aperture is also an effective strategy employed by plants to resist drought stress (Figure 4A). Under water-abundant conditions, stomatal opening in response to light allows CO_2 to enter into leaves for photosynthesis and water to evaporate via transpiration to regulate leaf temperature (Caine et al., 2019; Qi et al., 2018). However, under water-limited drought conditions, stomata close to slow water loss to enhance survival and increase water use efficiency. The phytohormone ABA plays a pivotal role in regulating stomatal movement to reduce transpiration during drought stress across plant species (Chen et al., 2021a; Ma et al., 2009b; Park et al., 2009). PYR1 and PYL proteins function as ABA receptors in *Arabidopsis* and rice. The combinatorial mutations of group I ABA receptors (OsPYL1–OsPYL6 and OsPYL12) in rice promote growth and grain productivity; however, these mutants may not be tolerant to drought stress, as they show severe defects in stomatal movement and water loss control (Miao et al., 2018). Conversely, overexpressing *OsPYL3*, *OsPYL5*, *OsPYL9*, or *OsPYL11* improves drought stress tolerance in rice but may negatively affect yield under non-stress conditions (Kim et al., 2012; Kim et al., 2014; Tian et al., 2015). Therefore, it is important to precisely modify the activities of individual or multiple ABA receptors to enhance drought tolerance without growth and yield penalties.

In recent years, chemical manipulation of ABA receptors has been employed to dynamically manipulate plant water use in agriculture (Cao et al., 2013; 2017; Dejonghe et al., 2018; Okamoto et al., 2013; Vaidya et al., 2019). The value of these chemical approaches is that they can be used on demand and therefore do not have adverse effects on crop

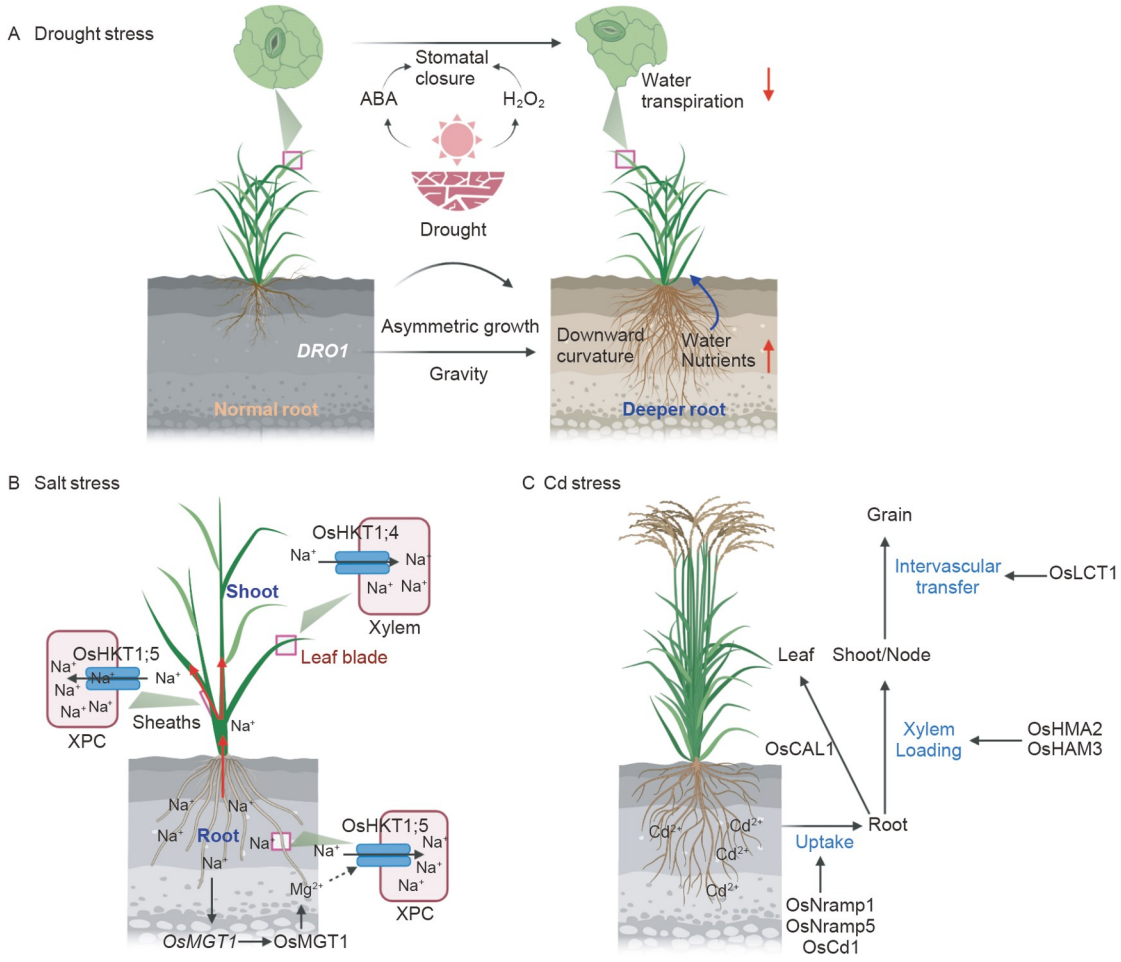

Figure 4 Model for drought and ionic stress responses in rice. A, Schematic diagram of drought tolerance in rice. A vigorous root system is important for plant tolerance to drought stress, as fine root diameter, deep roots, and high root density allow the plant to obtain more water. DEEPER ROOTING 1 (DRO1) promotes asymmetric growth and downward bending of the root tip in response to gravity, leading to deeper roots and enhanced drought tolerance. The phytohormone abscisic acid (ABA) and reactive oxygen species (ROS) promote stomatal closure, thereby reducing transpiration. B, HKT1 proteins are required for salt tolerance in rice. Salt stress leads to ionic injury. Plants minimize cytosolic and organellar ion toxicity using transporters. High-affinity K^+ transporters (HKTs) are crucial determinants of cellular Na^+ homeostasis. OsHKT1;5 plays an important role in maintaining Na^+ homeostasis by promoting Na^+ exclusion from xylem parenchyma cells (XPC) in roots and sheaths. In roots, Na^+ induces the expression of *OsMGT1*, a Mg^{2+} transporter gene, to promote the uptake of Mg^{2+}, thereby enhancing OsHKT1;5 activity. In addition, OsHKT1;4 removes Na^+ from the xylem, thus preventing Na^+ toxicity in leaf blades. C, The absorption and translocation of Cd in rice. Cd is absorbed from the soil into the plant root system via transporters. The Cd is transported long distance to shoots and accumulates in grains. OsNramp1, OsNramp5, and OsCd1 participate in the uptake of Cd at the roots. OsHMA2 and OsHMA3 function in the unloading of Cd in the xylem forlong-distance transport to shoots. OsLCT1 in shoot nodes is responsible for the transport of Cd to the grains via a xylem-to-phloem transfer process. Moreover, OsCAL1, a defensin-like protein, positively regulates Cd content in leaves.

growth and productivity during the growing season. In addition to ABA, emerging evidence indicates that H_2O_2 plays a critical role in stomatal closure in rice under drought stress conditions in both ABA-dependent and ABA-independent manners. For instance, *ABSCISIC ACID*, *STRESS AND RIPENING 5* (*OsASR5*) from upland rice promotes drought tolerance via a stomatal closure pathway associated with ABA and H_2O_2 signaling (Li et al., 2017b), whereas *DROUGHT AND SALT TOLERANCE* (*DST*) and *OsSRO1* regulate stomatal closure by modulating H_2O_2 accumulation independently of ABA in rice (Huang et al., 2009a; You et al., 2013).

In addition to stomatal movement, aspects of stomatal development, such as stomatal density, stomatal index, and stomatal size, are also important for drought tolerance in rice. Overexpression of *EPIDERMAL PATTERNING FACTOR 1* (*OsEPF1*), a negative regulator of stomatal development, in the high-yielding rice IR64 reduced stomatal density, stomatal index, and in some cases stomatal size. As a result, these transgenic plants displayed decreased water loss and (consequently) increased drought tolerance without obvious effects on growth and productivity (Caine et al., 2019), making this locus a good candidate for crop improvement via breeding. Multiple transcription factors such as OsSPCHs, OsMUTE, OsFAMA, and OsICEs also control stomatal development in rice (Wu et al., 2019). How-

ever, it is unclear whether these transcription factors function in drought stress responses. In the future, attention should be paid to controlling stomatal development, which may be beneficial to the development of drought-resistant rice varieties.

Ionic stress

(1) Salt stress. Increased salt concentrations in the soil not only decrease water absorption but also cause plants to take up large amounts of Na^+ and Cl^-, leading to both osmotic and ionic stress (Deinlein et al., 2014). Plants reduce water loss while maximizing water uptake to alleviate osmotic stress. The accumulation of osmoprotectants to decrease cytoplasmic water potential is a basic strategy that protects plants from salinity (Reddy et al., 2017). Under high-salt conditions, genes encoding enzymes for the production of osmoprotectants are rapidly induced, resulting in the accumulation of osmoprotectants and decreased water potential in cells, thereby enhancing plant tolerance to salt stress (Li et al., 2011a). In addition, plants control net Na^+ uptake across the plasma membranes and tonoplasts of both root and shoot cells to minimize cytosolic and organellar ion toxicity, a process mediated by transporters (Gong et al., 2020; Zhu, 2016). Moreover, plants maintain K^+/Na^+ homeostasis to cope with salt stress. Maintaining ion homeostasis at the cellular level is essential for plant survival under salt stress (Figure 4B).

In *Arabidopsis*, transporters such as high-affinity K^+ transporters (HKT), the Na^+/H^+ antiporter SALT OVERLY SENSITIVE 1 (SOS1), and Na^+/H^+ antiporter/exchanger (NHX) are crucial determinants of cellular Na^+ homeostasis (Yang and Guo, 2018). HKT isoforms are plasma membrane-localized Na^+ transporters that partition Na^+ from xylem vessels to adjacent parenchyma cells in roots and mediate Na^+ translocation through the phloem to roots or senescent tissues (Hamamoto et al., 2015; Rubio et al., 1995). Rice contains seven functional HKT transporters that are divided into two classes, Class I and II. Transporters in Class I selectively transport Na^+, whereas Class II HKTs are usually Na^+/K^+ symporters (Ali et al., 2019; Hamamoto et al., 2015). Class I transporters are evolutionarily important determinants of salt tolerance; major salt tolerance QTLs involving these transporters have been identified (Kobayashi et al., 2017; Ren et al., 2005). OsHKT1;5 is thought to maintain Na^+ homeostasis by promoting Na^+ exclusion from xylem parenchyma cells (XPC) in root and sheaths to reduce Na^+ accumulation in these tissues. OsHKT1;5 alleles containing specific amino acid variations effectively maintain shoot Na^+/K^+ homeostasis. Furthermore, the activity of OsHKT1;5 is enhanced by Mg^{2+}, which is modulated by the Mg^{2+} transporter OsMGT1 (Chen et al., 2017b). OsHKT1;1 might be involved in controlling Na^+ exclusion from roots or shoots (Campbell et al., 2017). Moreover, OsHKT1;4 removes Na^+ from the xylem, thus preventing sodium toxicity in leaf blades (Suzuki et al., 2016).

SOS1 is plasma membrane-localized Na^+/H^+ antiporter that uses a H^+ gradient to drive Na^+ efflux and decreases cytosolic Na^+ concentrations (Shi et al., 2002; Zhu, 2016). The SOS pathway has been well established in the model plant *Arabidopsis* (Yang and Guo, 2018). The SOS pathway is conserved in rice. OsSOS1 reduces Na^+ contents and positively regulates salt tolerance in rice (Kumar et al., 2013). Unlike SOS1, vacuole-localized NHX transporters are involved in Na^+ sequestration into the vacuole, which ultimately confers salt tolerance by reducing Na^+ levels in the cytosol, and OsNHX5 is as an endosomal Na^+/H^+ antiporter, while OsNHX1, OsNHX2, OsNHX3, and OsNHX4 are vacuolar Na^+/H^+ antiporters (Bassil et al., 2012). Overexpression of *OsNHX1* enhances drought tolerance in rice by enhancing the compartmentalization of Na^+ into the vacuole (Chen et al., 2007). These findings highlight the important roles of sodium transporters in regulating ion homeostasis and the salt stress response. Additional studies should focus on understanding the regulation of these transporters in rice under normal and stress conditions (Diédhiou and Golldack, 2006; Kurusu et al., 2012; Shen et al., 2015b).

(2) Heavy metal stress. Elements in the soil such as zinc (Zn) and iron (Fe) are essential nutrients at low concentrations but may be toxic when present in excess. Some other elements such as cadmium (Cd) and arsenic acid (As) are not essential for plant growth; instead, they are harmful to plants, even at very low concentrations (Mickelbart et al., 2015). Therefore, plants must restrict the uptake of these soil elements to limit cellular accumulation. As Cd is one of the most dangerous heavy metals to human health (Rai et al., 2019), we will focus on how rice responds to Cd stress (Figure 4C).

Cd is absorbed from the soil by the root system, a process mediated by transporters. The Cd is then transported long distance to shoots and ultimately accumulates in grains (Uraguchi and Fujiwara, 2013). OsNramp1 and OsNramp5 are plasma-membrane localized proteins in the rice exodermis and endodermis that transport Mn, Fe, and Zn, which have similar chemical characteristics to Cd, and are also involved in the uptake of Cd (Sasaki et al., 2012; Takahashi et al., 2011). A knockout mutant of *OsNramp5* largely lost its ability to take up Cd (Sasaki et al., 2012). However, given that OsNramp5 is also a transporter of Mn, which is essential for plant growth and yield, editing Cd transporters such as OsNramp5 may not be a good approach for crop improvement. OsCd1, a member of the facilitator superfamily of membrane transporters, participates in the uptake of Cd (Yan et al., 2019). Natural variation in OsCd1 (V449D) is responsible for the divergent Cd accumulation patterns in grains between *indica* and *japonica* rice subspecies. The *indica* allele $OsCd1^{V449}$ reduces Cd content in grains,

pointing to its potential application for the selection of low-Cd rice, especially *indica* cultivars. Hence, precisely controlling Cd uptake is an effective strategy for protecting plants from Cd toxicity.

After Cd is absorbed by roots, it is unloaded to the xylem for long-distance transport to shoots. This process is governed by heavy metal ATPases (HMAs) (Gong et al., 2020). OsHMA2, an efflux-type Zn transporter, is involved in Cd loading into the xylem, mediating the translocation of Cd from root to shoot, and distributing Cd to panicles via nodes (Satoh-Nagasawa et al., 2012; Takahashi et al., 2012). OsHMA3, a tonoplast-localized ATPase, is preferentially expressed in roots and functions in the sequestration of Cd into the vacuoles of roots. Misregulation of *OSHMA3* expression results in altered Cd accumulation in shoots and grains (Miyadate et al., 2011; Sasaki et al., 2014; Ueno et al., 2011; Ueno et al., 2010; Yan et al., 2016). Polymorphisms in the *OSHMA3* promoter drive the natural variation in Cd accumulation in *indica* and *japonica* rice (Liu et al., 2020a). The plasma membrane-localized low-affinity cation transporter OsLCT1 in shoot nodes is responsible for Cd transport to grains via a xylem-to-phloem transfer process (Uraguchi et al., 2011). In addition to transporters, CD ACCUMULATION IN LEAF 1 (OsCAL1), a defensin-like protein that is preferentially expressed in root exodermis and xylem parenchyma cells, chelates Cd in the cytosol and facilitates its secretion into the extracellular space, thereby reducing cytosolic Cd concentrations (Luo et al., 2018a). Therefore, metal chelators also play important roles in the compartmentalization of Cd in vacuoles or cell walls and in reducing the toxicity of Cd. In summary, compartmentalization is another strategy for limiting Cd toxicity.

Cold stress

Rice, including *indica* and *japonica* varieties that originated from tropical or subtropical areas, is highly sensitive to cold stress. Understanding the mechanisms underlying plant tolerance to cold stress would lay the foundation for improving temperature resilience in this important crop.

Over the past decades, many major chilling-related QTLs have been identified in rice using forward genetic approaches; however, few of the genes conferring cold tolerance at the vegetative (germination and seedling) or reproductive (booting and flowering) stage have been cloned and characterized (Zhang et al., 2017d). The G-protein regulator COLD1 is a cold sensor that positively regulates chilling tolerance in rice at the vegetative stage (for details, see *Abiotic stress-sensing mechanisms*) (Ma et al., 2015). *Quantitative trait locus for low-temperature germinability on chromosome 3* (*qLTG3-1*) is specifically expressed in the embryo during seed germination and controls cold tolerance at the germination stage (Fujino et al., 2008). *LOW TEMPERATURE GROWTH 1* (*LTG1*) encodes a casein kinase that modulates plant growth at low temperature via an auxin-dependent pathway (Lu et al., 2014a). The recently cloned *HAN1* ("HAN" is the Chinese word for "chilling") gene encodes an oxidase that is critical for rice (*japonica*) chilling tolerance at the seedling stage by mediating the conversion of JA from the active form (JA-Ile) into the inactive form (12OH-JA-Ile) (Mao et al., 2019; Miao et al., 2018). OsbZIP73 was identified by associated and population genetic studies, which positively regulate chilling tolerance at the seedling stage (Liu et al., 2018a). OsbZIP71 interacts with and helps OsbZIP73 modulate reactive oxygen species (ROS) and ABA levels in response to chilling stress (Liu et al., 2018a) (Figure 5A).

Early chloroplast development is protected in plants under chilling stress, which is important for plant tolerance to low temperatures at the vegetative stage. *NUS1* is specifically expressed in pre-emergent immature leaves, and its expression is upregulated by low temperature (Kusumi et al., 2011). In the *nus1* mutant, the accumulation of chloroplast rRNA is impaired during early leaf development, and chloroplast translation/transcription capacity is severely repressed in response to cold treatment (Kusumi et al., 2011). *TEMPERATURE-SENSITIVE VIRESCENT* (*TSV*) encodes a putative plastidic oxidoreductase that protects rice chloroplasts from chilling stress by interacting with and enhancing the stability of the plastid-encoded RNA polymerase subunit thioredoxin Z (Sun et al., 2017). WHITE STRIPE LEAF 5 (WSL5), a chloroplast-targeted pentatricopeptide repeat protein, is essential for chloroplast biogenesis in rice under chilling stress by regulating the expression of photosynthetic and chloroplast-encoded genes (Liu et al., 2018c).

Several genes positively regulate cold tolerance in rice at the booting stage, including *COLD TOLERANCE AT THE BOOTING STAGE* (*CTB1*) (Saito et al., 2010), *CTB4a* (Zhang et al., 2017d), and *CTB2* (Li et al., 2021), which encode an F-box protein (Saito et al., 2010), a leucine-rich repeat receptor-like kinase, and a UDP-glucose sterol glucosyltransferase, respectively. *CTB4a* and *CTB2* are located within a 56.8 kb region on chromosome 4. Phylogenetic analysis suggested that *CTB4a* and *CTB2* underwent stepwise selection to facilitate plant adaptation to cold, which helped expand rice cultivation from low-altitude to high-altitude regions and finally to high-latitude regions.

Apart from genes isolated by forward genetics, a number of genes encoding protein kinases that regulate cold stress responses in rice have been identified and characterized by reverse genetics. *Orysa sativa* mitogen-activated protein kinase 3 (OsMAPK3) positively regulates chilling tolerance by phosphorylating and enhancing the stability and transcriptional activity of OsbHLH002/OsICE1, a positive regulator of chilling tolerance, which in turn activates *OsTPP1* expression, leading to the accumulation of the osmoprotectant trehalose (Zhang et al., 2017c). Calcium-dependent

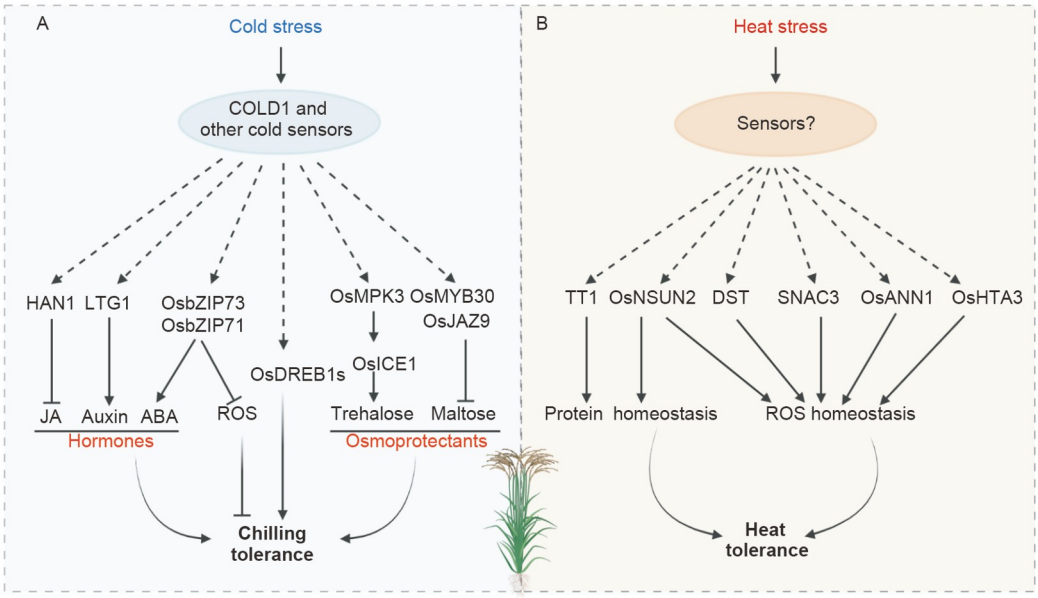

Figure 5 Cold and heat stress responses in rice. A, Cold stress response. After the cold signal is perceived by CHILLING TOLERANCE DIVERGENCE 1 (COLD1) and unknown cold sensors, chilling tolerance is enhanced in the plant via hormones or the production of osmoprotectants such as trehalose and maltose. LOW TEMPERATURE GROWTH 1 (LTG1) modulates plant growth at low temperatures via an auxin-dependent pathway. HAN1 promotes the conversion of the active form of JA (JA-Ile) into the inactive form (12OH-JA-Ile), thereby negatively regulating chilling tolerance. OsbZIP71 forms a complex with OsbZIP73 to regulate ROS and ABA levels under chilling stress. OsMPK3 enhances chilling tolerance by increasing the accumulation of trehalose, whereas OsMYB30 interacts with OsJAZ9 to repress the production of maltose in response to chilling stress. The transcription factors OsDREB1s play important roles in promoting chilling tolerance. B, Heat stress response. Heat stress leads to the accumulation of misfolded proteins and excessive ROS, which cause severe damage to rice cells. The precise regulation of protein and ROS homeostasis is crucial for plant survival under heat stress. *THERMOTOLERANCE 1* (*TT1*) encodes a 26S proteasome α2 subunit that efficiently eliminates cytotoxic proteins. ROS levels are regulated by several important factors, including DST, SNAC3, OsANN1, and OsHTA3. OsNSUN2 is an RNA 5-methycytosine (m^5C) methyltransferase that promotes heat tolerance by modulating protein and ROS homeostasis.

protein kinase 24 (OsCDPK24), CBL-interacting protein kinase 3 (CIPK3), CIPK7, CIPK12, and CIPK15 play positive roles in chilling tolerance in rice (Liu et al., 2018f; Xiang et al., 2007; Zhang et al., 2019b). In addition to protein kinases, transcription factors, such as OsDREB1s, OsbHLHs (described above), and MYBs also regulate the tolerance of rice to cold stress. The role of OsDREB1s, homologs of *Arabidopsis* DREB1s/CBFs, in positively regulating cold tolerance is conserved in rice (Ito et al, 2006). OsMYB3R-2 confers chilling tolerance in rice by regulating the expression of the cyclin genes (Ma et al., 2009a). Plants overexpressing the R2R3-type MYB gene *OsMYB2* showed enhanced chilling tolerance (Yang et al., 2012a). Conversely, OsMYB30 interacts with OsJAZ9 to repress the expression of *β-AMYLASE*, leading to reduced levels of the osmoprotectant maltose and thereby negatively regulating cold tolerance (Lv et al., 2017). The transcription factor OsMADS57 interacts with OsTB1 to regulate the trade-off between plant growth and chilling tolerance in rice (Chen et al., 2018c). Moreover, the cyclophilin OsCYP20-2 also participates in the balance between chilling tolerance and cell elongation by interacting with SLR1 and OsFSD2 (Ge et al., 2020). Although much progress has been made over the past decades, our knowledge of the mechanisms underlying chilling tolerance in rice is still incomplete.

Heat stress

Heat stress causes great yield losses in rice, as reproductive processes including the fertility of male gametes, pollen–pistil interactions, and female fertility are particularly vulnerable to heat stress (Endo et al., 2009; Zinn et al., 2010). Heat stress also negatively affects seed maturation, thereby decreasing grain quality (Hakata et al., 2012). At the molecular level, heat stress leads to the accumulation of misfolded proteins and excessive ROS, thereby causing cell death (Ding et al., 2020). Therefore, protein and ROS homeostasis must be properly maintained during heat stress (Figure 5B).

During heat stress, genes encoding heat shock proteins (HSPs) are rapidly induced by heat shock transcription factors (HSFs), and HSPs act as chaperones and assist in protein folding and limit protein aggregation in multiple cellular compartments (Ding et al., 2020). OsHSP101 confers thermotolerance and thermomemory in rice (Lin et al., 2014). Overexpression of the small HSP gene *sHSP17.7* in rice improved plant tolerance to heat stress (Murakami et al., 2004). In addition to HSPs, proteasome-mediated degradation also plays important roles in removing toxic proteins following heat stress. The major QTL *THERMOTOLERANCE 1* (*TT1*) from African rice (*Oryza glaberrima*) encodes a 26S proteasome α2 subunit that efficiently eliminates cytotoxic denatured proteins and protects plant cells

from heat stress (Li et al., 2015b). Different *TT1* alleles were selected during evolution and domestication to improve the adaptation of rice to local climate conditions (Li et al., 2015b).

Heat stress-induced misfolded proteins trigger the unfolded protein response (UPR) in the ER. In *Arabidopsis*, the UPR causes the ER membrane-localized bZIP transcription factors ZIP28 and bZIP60 to relocate from the ER to the nucleus, leading to the activation of heat-responsive gene expression (Deng et al., 2011; Mao et al., 2019). Similarly, heat stress and ER stress cause the plasma membrane-localized protein OsNTL3, a NAC (NAM, ATAF1/2, and CUC2) transcription factor, to relocate to the nucleus, thereby activating the expression of genes involved in the heat stress response and ER protein folding (Liu et al., 2020e).

ROS significantly accumulate in chloroplasts and mitochondria under heat stress, leading to oxidative damage and eventually to cell death (Zhao et al., 2018c). Plants have evolved a variety of mechanisms to minimize the overproduction of ROS. One such mechanism is the activation of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) to detoxify ROS (Gill and Tuteja, 2010). Heat-tolerant rice cultivars exhibit higher antioxidant enzyme activities than heat-susceptible cultivars under heat stress (Krishnan et al., 2011), which may be associated with decreased lipid peroxidation and increased membrane stability. Heat stress induces a ROS burst in developing rice anthers, which is correlated with decreased CAT and SOD activities, causing severe defects in fertility (Zhao et al., 2018c). Several proteins modulate the antioxidant enzyme system. The transcription factors SNAC3 and DST activate the expression of genes encoding H_2O_2-scavenging enzymes, thus enhancing plant tolerance to heat stress (Fang et al., 2015; Huang et al., 2009a). The RING finger ubiquitin E3 ligase OsHTAS positively regulates heat tolerance in rice by controlling H_2O_2 homeostasis via ABA- and DST-dependent pathways (Liu et al., 2016b). The annexin protein OsANN1 promotes the activities of SOD and CAT, thus conferring heat tolerance in rice (Qiao et al., 2015). Finally, a recent study showed that the RNA 5-methycytosine methyltransferase OsNSUN2 is required for heat tolerance by enhancing the translation of mRNAs involved in photosynthesis and detoxification systems (Tang et al., 2020). These findings highlight the importance of maintaining protein and ROS homeostasis in rice in response to heat stress (Figure 5B).

Perspectives in the study of abiotic stress in rice

Although much progress in dissecting the responses of rice to various abiotic stresses has been made during the past decade, several key questions remain unanswered. How rice senses abiotic stress signals is the most urgent question to be addressed, but this is quite challenging due to the complexity of abiotic stresses and the limited research approaches currently available. Multidisciplinary technologies will be helpful for identifying stress sensors. Rice is often subjected to multiple stresses at the same time, such as drought stress accompanied by heat stress. Therefore, it is crucial to dissect the underlying mechanisms by which rice resists multiple stresses. Moreover, accurately evaluating the abiotic stress tolerance traits of different rice germplasms will be beneficial for crop improvement via breeding. Finally, to facilitate the selection or development of stress-tolerant rice varieties, it is imperative to understand how rice tolerates abiotic stress under natural conditions.

Defense activation and signaling in rice biotic interactions

Rice production is continuously threatened by pathogens and herbivore insects during the entire growth season, which causes an estimated 10%–30% of annual rice yield loss (Douglas, 2018; Savary et al., 2019). To protect rice production, large amounts of chemical pesticides are used in agriculture, which not only cause severe environment pollution and food safety concerns, but also increase the pressure of pesticide-resistance in insects and pathogens. Therefore, breeding and deploying of resistant cultivars have been the most effective and environmental-friendly strategy for preventing crop diseases and insects in agriculture (Cheng et al., 2013; Deng et al., 2020; Li et al., 2020a). Hence, identification of resistance (*R*) genes and dissection of resistance mechanism are critical for the success in crop breeding for disease and insect resistance (Cheng et al., 2013; Deng et al., 2020; Li et al., 2020a).

The three most destructive rice diseases are rice blast, bacterial leaf blight, and sheath blight, which are caused by the hemibiotrophic fungus *Magnaporthe oryzae* (*M. oryzae*), the hemibiotrophic bacterium *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), and the necrotrophic fungus *Rhizoctonia solani* (*R. solani*) (Lee and Rush, 1983; Mizukami and Wakimoto, 1969; Ou, 1980), respectively. Recently, several new or re-emerging rice diseases have been prevalent, such as rice false smut caused by the obligate fungus *Ustilaginoidea virens* (Cooke) Takah (Tanaka et al., 2008), bacterial panicle blight caused by the bacterium *Burkholderia glumae* (Ham et al., 2011), and rice stripe disease induced by *rice stripe virus* (*RSV*) (Washio et al., 1968).

Rice insect pests can be generally categorized into chewing and piercing-sucking insects according to their feeding modes. Chewing insects, including leaf folders and stem borers, can cause direct damage to plant by breaking off and ingesting stems, leaves, and other important tissues. Insects with phloem-feeding habits, such as brown planthoppers

(BPH, *Nilaparvata lugens* Stål), the most destructive pest of rice (Cheng et al., 2013), access nutrients from the phloem through the specialized stylet and cause whole plant wilting. Rice piercing-sucking insects are also important vectors of many plant viruses (Fujita et al., 2013).

During co-evolution with pathogens, plants have obtained a highly effective and sophisticated innate immune system to deal with attacks by diverse pathogens, which comprises two-layer immune response based on the subcellular localization of immune receptor proteins (Jones and Dangl, 2006; Yu et al., 2017b). The first layer of plant immunity is activated by plasma membrane-localized pattern recognition receptors (PRRs) through perceiving conserved pathogen-associated molecular patterns (PAMPs), called as PAMPs/pattern-triggered immunity (PTI). The second layer of plant immunity is effector-triggered immunity (ETI), which is activated by intracellular nucleotide-binding site and leucine-rich repeat receptors (NLRs) upon recognizing specific pathogen-secreted virulence effectors. NLR immune receptors directly or indirectly detect pathogenic effectors in the "gene-for-gene" manner to trigger race-specific disease resistance, which often involves localized programmed cell death called hypersensitive response (HR) (Dodds and Rathjen, 2010; Jones and Dangl, 2006; Yu et al. 2017b). Recent studies suggested that ETI is dependent on PTI, and the two layers of immunity mutually potentiate in immune activation (Ngou et al., 2021; Yuan et al., 2021). So far, a considerable number of *R* genes have been isolated in crops including rice, most of which encode NLR receptor proteins (Dangl et al., 2013; Deng et al., 2020; Deng et al., 2017; Li et al., 2020a; Nelson et al., 2017). Interestingly, the majority of R proteins against rice brown planthoppers are also NLRs (Cheng et al., 2013; Zhao et al., 2016b). Therefore, NLRs are major targets of crop breeding for disease and insect resistance.

NLR proteins are subdivided into three major subclasses according to their N-terminal domains, TIR-NLR (TNL) with a Toll Interleukin-1 (TIR) domain, CC-NLR (CNL) containing a coiled-coil (CC) domain, and RPW8-NLR (RNL) carrying a RPW8 domain (Adachi et al., 2019). The rice genome encodes more than 400 NLR-like genes, the majority of which are CNLs, and no typical TNLs are found in the rice genome (Baggs et al., 2017; Luo et al., 2012; Wang et al., 2019c). Over the past two decades, the rice-*M. oryzae* and rice-*Xoo* pathosystems have been gradually established as research platforms for studying rice-pathogen interactions. Besides, the rice BPH interaction is also recognized as a model system along with the identification of several BPH *R* genes. This section will focus on progress on rice-pathogen and -insect interactions, key signaling events in immune responses, *R* gene digging, and molecular strategies for breeding of disease-resistant and insect-proof varieties in rice.

PTI signaling in rice

Our understanding of the plant PTI machinery is largely based on the PRRs identified in the model plant *Arabidopsis*. In particular, the extensively studied RLK PRRs, such as FLS2, EFR, and CERK1, constitute core knots of PTI mechanisms underlying the activation of early immune signaling events (Boutrot and Zipfel, 2017; Gómez-Gómez and Boller, 2000; Miya et al., 2007; Zipfel et al., 2006). In rice, several important PRR proteins, including XA21, XA3/XA26, XA4, OsCEBiP, OsCERK1, LYP4, and LYP6, are also well investigated (Figure 6) (Akamatsu et al., 2013; Deng et al., 2020; Hu et al., 2017a; Kaku et al., 2006; Liu et al., 2012; Pruitt et al., 2015; Shimizu et al., 2010; Sun et al., 2004).

OsCEBiP, a lysin motif-containing receptor-like protein lacking intracellular kinase domain as does its *Arabidopsis* ortholog, recognizes the fungal pattern molecule chitin to form homodimers, and interacts with the co-receptor OsCERK1 to form a receptor complex that transduces chitin signaling (Figure 6) (Hayafune et al., 2014; Kaku et al., 2006). The OsRacGEF1-OsRac1 module and OsRLCK185-MAPK signaling cascade act downstream of OsCERK1-mediated chitin-triggered immunity (Akamatsu et al., 2013; Wang et al., 2017b). Moreover, the two rice lysin motif (LysM)-containing proteins, OsLYP4 and OsLYP6, act as dual functional PRR. OsLYP4 and OsLYP6 interact with OsCERK1 to participate in the chitin elicitor signaling pathway, and also directly sense bacterial peptidoglycan (PGN) and fungal chitin, forming homo- and hetero-dimers to activate rice basal defense against *M. oryzae* and *Xoo* (Ao et al., 2014; Liu et al., 2012). However, OsCERK1 also interacts with the symbiotic receptor OsMYR1 to form additional receptor complex, which interferes with the formation of the OsCERK1-OsCEBiP complex to suppress the chitin-triggered immunity, suggesting that OsCERK1 is a convergent node for both immunity and symbiosis (Carotenuto et al., 2017; Miyata et al., 2014; Zhang et al., 2021a). This is probably unique in rice and other cereals, given that Cruciferous plants such as *Arabidopsis* do not have *Mycorrhizae* symbiosis. Therefore, chitin perception and signaling are likely more sophisticated in rice immunity. Nevertheless, it will be worth further elucidating how these two signaling pathways coordinate chitin-mediated immunity in rice.

The RLK XA21 is the first *R* gene cloned in rice which confers race-specific resistance to *Xoo* (Song et al., 1995). The XA21-mediated signaling network has been studied extensively (Figure 6). XA21 binds to the tyrosine-sulfated peptide RaxX encoded by the *Xoo raxX-raxSTAB* gene cluster to activate immunity (Liu et al., 2019; Luu et al., 2019; Pruitt et al., 2015). Interestingly, the XA21/RaxX interaction fits into the "gene-for-gene" theory, providing a paradigm that a PRR can also confer race-specific resistance.

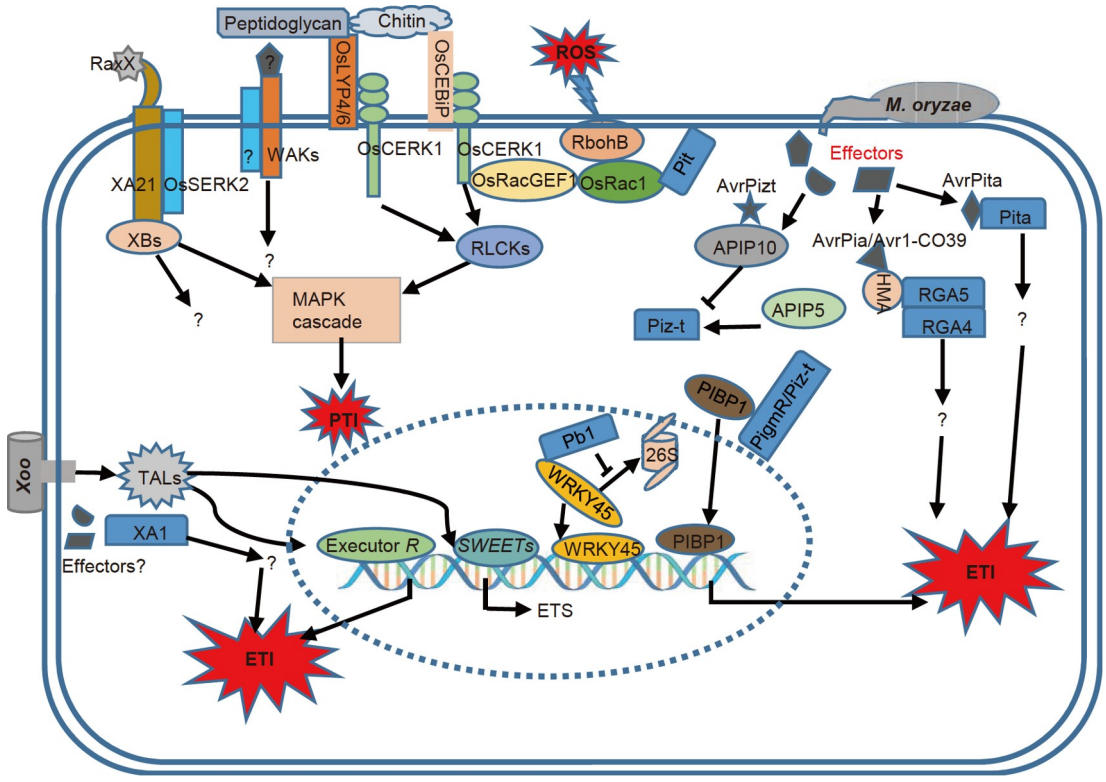

Figure 6 PTI and ETI signaling pathways identified in rice. Several PRRs and NLRs have been isolated and functionally identified in immune signaling activation and regulation of disease resistance in rice. The RLK receptor XA21 recognizes the sulfated RaxX (PAMP), and interacts with OsSERK2 to activate downstream immune signaling. The RLP receptor proteins OsLYP4 and OsLYP6 recognize bacterial peptidoglycan and fungal chitin and interact with OsCERK1 to trigger basal resistance to *M. oryzae* and *Xoo*. The receptor-like protein OsCEBiP directly binds to chitin and cooperates with OsCERK1 to induce the innate immune response through the MAPK cascade pathway. OsRac1 interacts with RbohB to regulate ROS production, which is essential for PTI and ETI immune activation. So far, only three types of R and AVR interaction models have been identified in rice: (1) the direct interaction model: the direct interaction between AvrPita and Pi-ta triggers ETI against *M. oryzae*; (2) the Integrated Decoy model: the HMA domain of NLR protein RGA5 bind to effector proteins AvrPia and Avr1-CO39, which lead to the release of NLR RGA4 to activate ETI immune response; (3) the Guard model: NLR Piz-t recognizes effector Avr-Piz-t indirectly by guarding the target proteins APIP10, APIP5 to trigger ETI signaling. Interestingly, the bacterial pathogen *Xoo* also secretes TAL effectors into rice cells to bind specific promoter sequences to activate executor R or susceptibility genes including SWEET genes to elicit ETI or ETS in rice.

XA21 interacts with another RLK OsSERK2 to form a heteromeric complex and phosphorylates mutually to trigger immune responses (Chen et al., 2014c). Several XA21-binding proteins (XB) were identified, including an ATPase (XB24) (Chen et al., 2010), an E3 ubiquitin ligase (XB3) (Wang et al., 2006a), a PP2C phosphatase (XB15) (Park et al., 2008), a WRKY62 transcription factor (TF) (XB10) (Peng et al., 2008), and an ankyrin-repeat protein (XB25) (Jiang et al., 2013b), which play important roles in regulating the XA21-mediated resistance to *Xoo*. Importantly, Chaperone proteins are also likely to be involved in the XA21-mediated immunity through nuclear translocation. RAR1 and SGT1 interact with the XA21 kinase domain in yeast and plant cells (Seo et al., 2011b). Interestingly, XA21 is cleaved to release the intracellular kinase domain, which carries a functional nuclear localization sequence and interacts with the transcriptional regulator OsWRKY62 in the nucleus of rice protoplasts (Park and Ronald, 2012). The cleavage of XA21 and translocalization of the kinase domain to the nucleus is required for the XA21-mediated immune responses, suggesting a new model for PRR function: upon recognition of conserved microbial signatures by PRR, the functional kinase domain is released and translocated to the nucleus where it directly interacts with transcriptional regulators to initiate immune responses (Park and Ronald, 2012). However, it remains to be determined how XA21 is cleavage by an unknown endopeptidase.

Another functionally known PRR involved in resistance against *Xoo* is XA3/XA26, originally identified from the *indica* variety Minghui 63 (Sun et al., 2004). XA3/XA26 interacts with OsSERK2 and OsTPI1.1 that are essential for XA3/XA26-mediated resistance (Chen et al., 2014c; Liu et al., 2018e). AvrXa3, the cognate avirulence protein to XA3/XA26, has been isolated. However, how it initiates XA3/XA26-mediated resistance remains unclear (Wu et al., 2007). *Xa4*, encoding a cell wall-associated kinase (WAK), also confers race-specific resistance to *Xoo* during the whole growth period (Hu et al., 2017a; Leach et al., 2001). XA4-mediated cell wall strengthening prevents bacterial infection, and also increases mechanical strength of the culm, which may improve lodging resistance of the rice plant. The XA4-triggered simultaneous improvement of multiple agronomic

traits promises XA4 as potential targets for rice breeding (Hu et al., 2017a).

ETI is a major determinant and breeding target of rice disease resistance

Identification of NLR genes and dissecting ETI signaling are the frontiers of plant biology, and are prerequisites of crop breeding. Utilization of NLR-mediated resistance is the main strategy for rice breeding to control diseases. Although the rice genome encodes more than 400 NLR-encoding genes dispersed in all 12 chromosomes (Baggs et al., 2017; Luo et al., 2012; Wang et al., 2019c), only a few of NLRs are functionally identified to execute resistance against pathogens and insects, especially fungal blast, bacterial blight, and brown planthoppers (Deng et al., 2020; Li et al., 2020a). Notably, blast resistance NLRs constitute the majority of the NLRs isolated in rice. So far, at least 37 blast *R* genes have been functionally identified in different cultivars, landraces, and wild rice. A majority of the isolated *R* genes encode NLR receptor proteins, except for *Pi-d2* encoding a lectin receptor kinase (Chen et al., 2006), *Ptr* encoding an ARM repeat domain containing protein with E3 ligase activity (Zhao et al., 2018a), *pi21* encoding a proline-rich protein with heavy metal-binding domain (Fukuoka et al., 2009), and *Bsr-d1* encoding a C_2H_2-type transcription factor (Li et al., 2017d). These genetic cues suggest that resistance against blast fungus is mostly controlled by ETI immune responses. Interestingly, however, resistance or susceptibility genes to *Xoo* encode diverse proteins, including RLK or WAK (XA21, XA3/XA26, and XA4), sugar transporter (XA13, XA25, and XA41), executor R proteins (XA10, XA23, XA7, and XA27), and a small subunit of a general transcription factor (XA5) (Chen et al., 2021b; Chu et al., 2006; Zhang et al., 2019e). Only the locus *Xa1* with additional alleles *Xa1-2*/*Xa2*/*Xa14*/*Xa31*/*Xa45* encodes NLR receptor protein (Ji et al., 2020; Yoshimura et al., 1998; Zhang et al., 2020a). A majority of *Xa* genes are usually activated by the *Xoo* T3SS transcription activator-like effectors (TALEs) that bind to specific promoter sequences of the *Xa* genes to elicit disease resistance or induce susceptibility to *Xoo*. However, no single AvrXa has been isolated that is perceived by the cognate XA NLRs. Therefore, the ETI pathways involved in *Xoo* resistance need to be recognized and established. On the other hand, the divergence of R proteins against fungal blast and bacterial blight suggests that rice have evolved differential immune machineries against different pathogens. It will be interesting to further investigate whether rice has been differentially domesticated on resistance against *M. oryzae* and *Xoo*.

The recognition of effectors by NLRs mainly is classified into four models, the direct Interaction, Guard, Decoy, and Integrated Decoy models (Jones et al., 2016; Kourelis and van der Hoorn, 2018). Along with isolation of many Pi NLRs, at least 11 *Avr* genes (*PWL1*, *PWL2*, *ACE1*, *AvrPi9*, *Avr1CO39*, *AvrPia*, *AvrPib*, *AvrPii*, *AvrPik*/*km*/*kp*, *AvrPita*, and *AvrPiz-t*) have been functionally characterized (Zhang et al., 2019e). Most of the *Avr* genes encode small secreted proteins except *ACE1* that encodes a putative hybrid between a polyketide synthase and a nonribosomal peptide synthetase, which is involved in microbial secondary metabolism (Böhnert et al., 2004). The Pita-AvrPita interaction is the first example of direct R and Avr interaction with the gene-for-gene mode in rice (Jia et al., 2000). AvrPita is a small secreted protein with a conserved metalloprotease domain, which directly binds to the C-terminal LRR domain of cognate NLR protein Pita. However, many NLR-Avr recongitions do not adopt the direct interaction model in rice. Instead, plants have evolved intracellular NLR surveillance system to monitor guardee(s) targeted by multiple pathogen effectors to activate immune responses indirectly (Kourelis and van der Hoorn, 2018). For example, AvrPiz-t interacts with various host targets, such as APIP6, APIP10, and APIP5, to suppress host ROS production and defense response (Figure 6) (Park et al., 2012; Park et al., 2016; Wang et al., 2016a); some of the AvrPiz-t targets were guarded by the NLR Piz-t, leading to robust and high resistance against blast fungus (Wang et al., 2021b). Interestingly, some rice NLR/Avr interactions adopt the integrated decoy model, which comprises two NLR receptor proteins, one NLR protein integrated with atypical decoy domains that can interact or recognize avirulence proteins to release another NLR protein to mediate resistance against *M. oryzae* (Cesari et al., 2014). These NLR pair-Avr interactions include Pik1/Pik2-AvrPik and RGA4/RGA5-Avr1CO39/AvrPia (Figure 6). The two NLRs, RGA4 and RGA5, form an NLR pair for the recognition of AvrPia and Avr1CO39. In the absence of *M. oryzae*, the function of RGA4 in cell death and disease resistance is repressed by RGA5 through physical interaction (Cesari et al., 2013). Upon challenged by *M. oryzae*, RGA5 interacts with the effector AvrPia as well as Avr1CO39 through the C-terminal integrated domain RATX1, leading to release of RGA4 that activates ETI (Cesari et al., 2013; Ortiz et al., 2017). Moreover, pairs of two adjacent and inversely oriented rice *R* genes, such as *Pik-1*/*Pik-2*, *Pikm-1*/*Pikm-2*, and *Pikp-1*/*Pikp-2*, are highly homologous and activate immune responses with similar mechanism.

Identification and application of broad-spectrum disease resistance in rice breeding

As most of NLR genes confer race-specific resistance to pathogens, resistant varieties often remain effective only for a few years after being commercially released due to the

advent of new dominant pathogenic races. Therefore, it is urgent to identify and deploy broad-spectrum resistance (BSR) genes in breeding programs. Several recessive *BSR* genes, such as *pi21*, *bsr-d1* conferring blast resistance, were functionally characterized (Fukuoka et al., 2009; Li et al., 2017d). *Pi21* encodes a proline-rich protein with a putative heavy metal-binding domain (HMA), which suppresses the defense responses. Loss-of-function mutation of *Pi21* relieves the inhibition of defense, leading to broad-spectrum resistance to *M. oryzae* (Fukuoka et al., 2009). Interestingly, HMA domain functions as a decoy to recognize various virulence effectors from different pathogenic fungi, thereby activating NLR-mediated immunity response (De la Concepcion et al., 2018; Maqbool et al., 2015). Moreover, *Pi21* does not affect grain yield, and is separable from a closely linked gene conferring poor flavor. The *pi21* allele has been applied to improve blast resistance of rice varieties (Fukuoka et al., 2009). Another recessive gene *bsr-d1* encodes a C2H2-type transcription factor (Li et al., 2017d). Due to a single nucleotide change in the promoter of *bsr-d1* resistance allele, a repressive MYB transcription factor can bind *bsr-d1* allele promoter to reduce its gene expression, further inhibiting H_2O_2 degradation and enhancing non-race specific blast disease resistance. Interestingly, *bsr-d1* confers broad-spectrum blast resistance without grain yield penalty, which suggests that this allele could be used to improve blast disease resistance in rice breeding (Li et al., 2017d).

Notably, plant immune activation often leads to fitness cost due to the trade-off between defense and growth (Karasov et al., 2017; van Schie and Takken, 2014; Yang et al., 2012b; Wang et al., 2020b). Given that many BSR genes enhance resistance against a variety of pathogens, fitness cost associated with them is a major concern in breeding design. With this scenario, important progress has been made in the balance of broad-spectrum disease resistance and grain yield in rice. For example, the rice *R* locus *Pigm* that confers durable and broad-spectrum blast resistance encodes two NLRs, PigmR and PigmS (Deng et al., 2017; Deng et al., 2006). Epigenetic control of PigmS expression not only attenuates the PigmS-derived inhibitory effect on PigmR-mediated blast resistance, but also compensates the negative effect of PigmR-induced broad-spectrum blast resistance on grain yield (Deng et al., 2017). Interestingly, translational control of the BSR gene *NON-EXPRESSOR OF PR 1* (*NPR1*) using the *TL1*-binding TF (TBF) uORF strategy achieved broad-spectrum resistance against *M. oryzae* and *Xoo*, without obvious negative effect on growth and grain yield in transgenic rice (Xu et al., 2017a). Similarly, the transcription factor IPA1 fine-tunes the balance between disease resistance and grain yield in rice, which is dependent on differential phosphorylation modification induced by pathogens (Wang et al., 2018c). Therefore, understanding of molecular mechanisms underlying fitness trade-off is essential for designing breeding strategies to achieve both high yield and disease resistance (Deng et al., 2020).

Key components of NLR signaling pathway in rice disease resistance

Dissecting the downstream signaling of ETI is the key to engineering crop disease resistance, which has emerged as the frontier of plant immunity. Recently, accumulating evidence documents that transcription factors play critical roles in NLR-mediated resistance, which may be directly associated with NLRs and govern transcriptional activation of immunity (Deng et al., 2020). OsWRKY45, which is activated by OsMPK6 through phosphorylation, is a key activator of defense response and SA signaling in rice (Ueno et al., 2017). The degradation of OsWRKY45 by the 26S ubiquitination system compromises defense response (Matsushita et al., 2013), while the NLR Pb1 directly interacts with OsWRKY45 to prevent its degradation, ensuring Pb1-mediated resistance to *M. oryzae* (Inoue et al., 2013; Matsushita et al., 2013). The bZIP type TF APIP5 also directly interacts with Piz-t, and the binding of Piz-t stabilizes APIP5 (Wang et al., 2016a). Conversely, APIP5 is also involved in Piz-t protein accumulation, enabling Piz-t-mediated resistance (Wang et al., 2016a). Most recently, it was reported that Piz-t physically interacts with the TFs OsVOZ1 and OsVOZ2. OsVOZ1 is a transcriptional repressor while OsVOZ2 is a transcriptional activator, both of which play negative roles in basal defense but positively regulate Piz-t-mediated immunity (Wang et al., 2021b). Importantly, a new plant-specific TF family, PIBP1 and its homologs containing the RRM domain, were recently recognized as new TF family which directly interact with the broad-spectrum resistance NLRs, PigmR, Piz-t, and Pi9 through their conserved CC domains, forming an immune complex that is transferred into the nuclei to activate defense gene expression through binding to AT-rich domains of defense genes, further shedding light on the molecular mechanisms underlying broad-spectrum resistance against *M. oryzae* (Zhai et al., 2019). Hence, NLRs often activate immune signaling pathways by recruiting specific TFs for defense transcriptional reprograming, likely providing a shortcut to activate plant immune response.

ROS are widely produced in different cellular compartments upon challenge of both biotic and abiotic stress in plants, which play a central role in plant signaling and regulate diverse cellular processes (Apel and Hirt, 2004; Lamb and Dixon, 1997; Mittler et al., 2004; Qi et al., 2017). Recent advances shed new light on sophisticated mechanisms controlling ROS biogenesis and signaling in plant immunity (Kachroo et al., 2021; Waszczak et al., 2018). In particular, ETI activation is usually associated with robust ROS burst (Cui et al., 2015; Jones and Dangl, 2006). The apoplastic

ROS, which are mainly produced by the NADPH oxidase machinery (respiratory burst oxidase homologs, RBOHs), cell wall peroxidases and amine oxidases, are involved in PTI and ETI (Figure 6) (Kadota et al., 2015). The rice homolog of mammalian Rac small GTPase (OsRac1) is a positive regulator of ROS biogenesis and modulates rice immunity including PTI and ETI (Oda et al., 2010; Wong et al., 2007). OsRac1 is activated by chitin signals from *M. oryzae* to form an OsCEBiP/OsCERK1-rice Rac GDP/GTP exchange factor 1 (OsRacGEF1)-OsRac1 module to trigger chitin-induced immunity (Akamatsu et al., 2013; Kawano and Shimamoto, 2013). The OsRac1 is activated by the phosphorylaed OsRacGEF1 through the guanine nucleotide exchange process, leading to ROS production by interaction with the NADPH oxidase OsRbohB and OsMT2 (Akamatsu et al., 2013; Kawasaki et al., 1999; Kosami et al., 2014; Wong et al., 2007; Wong et al., 2004). Moreover, OsRac1 is also activated by rice NLR protein Pit at the plasma membrane, which is required for Pit-mediated ROS production as well as disease resistance to *M. oryzae* in rice. Additional studies suggest that OsRac1 also interacts with NLR Pia and PID3 to regulate NLR-mediated blast resistance (Chen et al., 2010; Zhou et al., 2019). It is worthy of further investigating whether the Rac small GTPase plays conserved functions in ETI in other crops.

Autoimmunity control and broad-spectrum disease resistance in rice

The plant immune responses are tightly controlled by various negative and positive regulators to avoid the inappropriate defense activation in the absence of pathogens. Therefore, loss-of-function mutations in the negative regulators or guarded targets or gain-of-function mutations in plant receptors, such as NLRs and RLKs, could trigger inappropriate immune response activation, which leads to autoimmunity. Although many autoimmune mutants have been identified in *Arabidopsis*, a limited number of such mutants were investigated in detail (Chakraborty et al., 2018). In rice, at least 80 similar mutants were identified, which are named as lesion mimic mutants (*lmm*) or spotted lesion mutants (*spl*). These mutants usually exhibit features of activated immune responses, such as ROS burst, activated *PR* gene expression and elevated levels of defense hormones including SA, or JA under normal growth conditions. Moreover, most of these mutants were characterized in broad-spectrum resistance to *M. oryzae* and *Xoo*. Therefore, identification and dissection of molecular regulatory mechanism of autoimmunity in rice are helpful for deciphering key regulators of defense signaling, understanding the crosstalk between immunity and growth, and breeding elite rice varieties with high disease resistance (You et al., 2016; Zhu et al., 2020).

Several genes have been isolated underlying autoimmunity mutants, which function in transcriptional control, protein degradation, vesicular trafficking, catalyzation of metabolism, and cell death (Kang et al., 2021; Zhu et al., 2020). The rice *spotted leaf 11* (*spl11*) mutant confers the non-race-specific resistance to blast and bacterial blight (Yin et al., 2000). *SPL11* encodes a U-Box/Armadillo repeat protein with E3 ubiquitin ligase activity (Zeng et al., 2004). A single nucleotide mutation in *spl11* resulted in nonfunctional E3 ligase, which disrupts ROS homeostasis and the release of suppressed PCD. Moreover, SPL11-interacting Protein 6 (SPIN6) is a Rho GTPase-activating protein (RhoGAP), which is ubiquitinated and degraded by the 26S proteasome-dependent pathway (Liu et al., 2015a). The transgenic rice plants carrying knockout of *spin6* display PCD and increased resistance to *M. oryzae* and *Xoo*. Surprisingly, SPIN6 also interacts with OsRac1 to regulate ROS production. Therefore, E3 ligase-mediated ubiquitination actively cooperates with OsRac1-associated defensome system to regulate plant immunity by controlling ROS production. Similarly, a RING finger E3 ligase OsBBI1 positively regulates blast resistance through cell wall reinforcement (Li et al., 2011b). More importantly, a RING-type E3 ligase protein *EBR1* directly interacts with the rice Bcl-2-associated athanogene (BAG) OsBAG4, a positive regulator of cell death in rice, to elicit ubiquitination-mediated degradation to avoid cell death and growth arrest (You et al., 2016). The *ebr1* mutant plants and transgenic plants overexpressing *OsBAG4* confer broad-spectrum resistance to both *M. oryzae* and *Xoo*. It is worth further investigating if the EBR1-OsBAG4 module-mediated autoimmunity is conserved in other cereal species, and the molecular mechanisms of growth and immunity mediated by EBR1-OsBAG4 module may provide a new approach for precise molecular breeding for disease resistance improvement in crops (You et al., 2016).

Most recently, a Ca^{2+} sensor is reported to suppress immunity in rice (Gao et al., 2021). A natural broad-spectrum disease resistance germplasm *resistance of rice to diseases1* (*rod1*) with autoimmunity phenotype was identified from breeding population, which exhibits high resistance to multiple diseases, such as rice blast, sheath blight, and bacterial blight. *ROD1* encodes a C2 domain Ca^{2+} sensor, which promotes ROS scavenging by interacting with a catalase CatB and activating catalase activity to accelerate H_2O_2 degradation, resulting in immune suppression. The ROD1 protein stability is fine-tuned by a pair of E3 ligases, RIP1 and APIP6, through the 26S proteasome-dependent pathway. Surprisingly, a fungal effector AvrPiz-t secreted by *M. oryzae* adopts the same ROD1 protein surveillance cascade and also interacts with and is instabilized by APIP6 and RIP1 (Gao et al., 2021; Park et al., 2012). Besides, AvrPiz-t also interacts with CatB to promote catalase-mediated ROS scavenging, and similarly suppresses disease resistance. Therefore, AvrPiz-t and ROD1 share a common immune

suppression circuit. More importantly, the ROD1 C2 domain and AvrPiz-t share a similar β-strands structure, which contributes to their functional mimicry and exchangeability in host and fungus in immune suppression. ROD1 orthologues play conserved roles in monocot crops. Moreover, two haplotypes are present in ROD1 alleles, and natural variations of ROD1 have different effects on catalase activation and field disease resistance, suggesting that the allelic variation of *ROD1*-mediated fine-tuning of ROS homeostasis is likely responsible for subspecies-specific basal disease resistance. It is worthwhile to investigate the molecular mechanism triggered by ROD1-mediated subspecies-specific disease resistance in cereal plants (Gao et al., 2021). Gene editing would create elite alleles of ROD1 for improvement of disease resistance to multiple pathogens without disturbing yield performance in rice breeding.

Rice insect resistance: isolation of BPH resistance genes and their molecular mechanisms against BPH

Among the insect resistance genes identified in rice germplasm, 15 BPH resistance genes have been isolated and characterized via map-based cloning, shedding light on our understanding of the molecular mechanisms of insect resistance in plants (Figure 7). The first cloned BPH *R* gene *Bph14* encodes a typical coiled-coil, nucleotide binding site, leucine-rich repeat (CC-NB-LRR) protein, revealing similarity in the molecular mechanism of plant defense against pathogens and insects (Du et al., 2009). BPH14 can form homocomplexes and interact with transcription factors WRKY46 and WRKY72, enhancing its W-box binding activity and potentiating defense gene expressions, such as the receptor-like cytoplasmic kinase gene RLCK281 and the callose synthase gene (Hu et al., 2017b). This process induces callose deposition in the sieve tubes where BPHs insert their stylets, preventing the BPH from ingesting the phloem sap, thereby impairing the feeding, growth rate, and survival of BPH insects on *Bph14*-carrying plants (Hao et al., 2008).

Several BPH resistance genes also encode NLR proteins. Among the eight BPH resistance genes clustered on chromosome 12L, *Bph26* (identical to *Bph2*) and *Bph18* encode a CC-NB-NB-LRR protein containing two NB domains (Ji et al., 2016; Tamura et al., 2014). *Bph9* encodes a rare type of NLR proteins and could induce hypersensitivity response like cell death (Zhao et al., 2016b). BPH9 localizes to the endomembrane system (ES), highlighting ES as a prominent battlefield for rice-BPH interaction. Moreover, the results revealed that the eight BPH-resistance genes clustered on chromosome 12L are allelic with each other. These alleles are classified into four allele-types and confer varying resistance levels to different biotypes of BPH, demonstrating that allelic variation is an important strategy for rice to combat BPH biotype variation. The LRR domain of *Bph9* may specifically recognize BPH-derived signals, leading to multiple intramolecular interactions, triggering the self-association of CC domains and activation of downstream defense signaling and BPH resistance (Wang et al., 2021e).

Bph6 encodes a novel atypical LRR protein that colocalizes with the exocyst complex (Guo et al., 2018a). BPH6 interacts with exocyst subunit OsEXO70E1 and promotes the secretion of cytosolic proteins to the cell surface, providing protection by maintaining and reinforcing plant cell walls, thereby conferring a high and broad-spectrum resistance to planthoppers. Further analyses revealed that *Bph6* could enhance lipolysis of BPH insects (Zheng et al., 2020). Recently cloned *Bph30* also encodes a novel protein with two leucine-rich domains, which do not belong to any previously identified LRR consensus (Shi et al., 2021). *Bph30* is strongly expressed in sclerenchyma cells and enhances cellulose and hemicellulose deposition. The thicker and stiffer sclerenchyma prevents BPH stylets from penetrating the tissues and reaching phloem cells for feeding. *Bph40* is a *Bph30*-like resistance gene, and the mechanism is related to cell wall fortification in sclerenchyma. Both *Bph6* and *Bph30* confer broad-spectrum resistance to BPH and WBPH (white-backed planthopper).

BPH resistance genes *Bph3* and *Bph15* encode plasma membrane-localized lectin receptor-like kinases (LecRKs), which are supposed to function as receptors or as receptor-associated proteins in plant immunity. *Bph15* functions in both innate immunity and seed germination in the plant. Knocking down *Bph15* significantly reduced the resistance of rice plants to BPH (Cheng et al., 2013). *Bph3* comprises a cluster of three LecRKs (OsLecRK1–OsLecRK3), which belong to the G-type LecRK family, containing an extracellular bulb-type lectin domain, a plant PAN/APPLE-like domain, a transmembrane domain, and an intracellular serine/threonine kinase domain (Liu et al., 2015c). The cell surface localization of OsLecRK proteins suggests that they may play a critical role in priming PTI by perceiving BPH-derived herbivore-associated molecular patterns (HAMPs) or plant-derived damage-associated molecular patterns (DAMPs), conferring broad-spectrum and durable planthopper resistance. *Bph29* encodes a protein with a B3 DNA-binding domain and *Bph32* encodes a short consensus repeat (SCR) domain-containing protein (Ren et al., 2016; Wang et al., 2015). The mechanisms of these two genes remain unknown.

According to recent advances on BPH resistance genes in rice and aphid resistance genes in tomato and melon (Kaloshian and Walling, 2016), one can reasonably speculate that two branches of the plant immune system for recognizing and fending off pathogens are also applicable to plant-insect interactions. In this context, the cell surface receptor kinases LecRKs encoded by *Bph3* and *Bph15* function as putative PRRs to perceive unidentified HAMPs

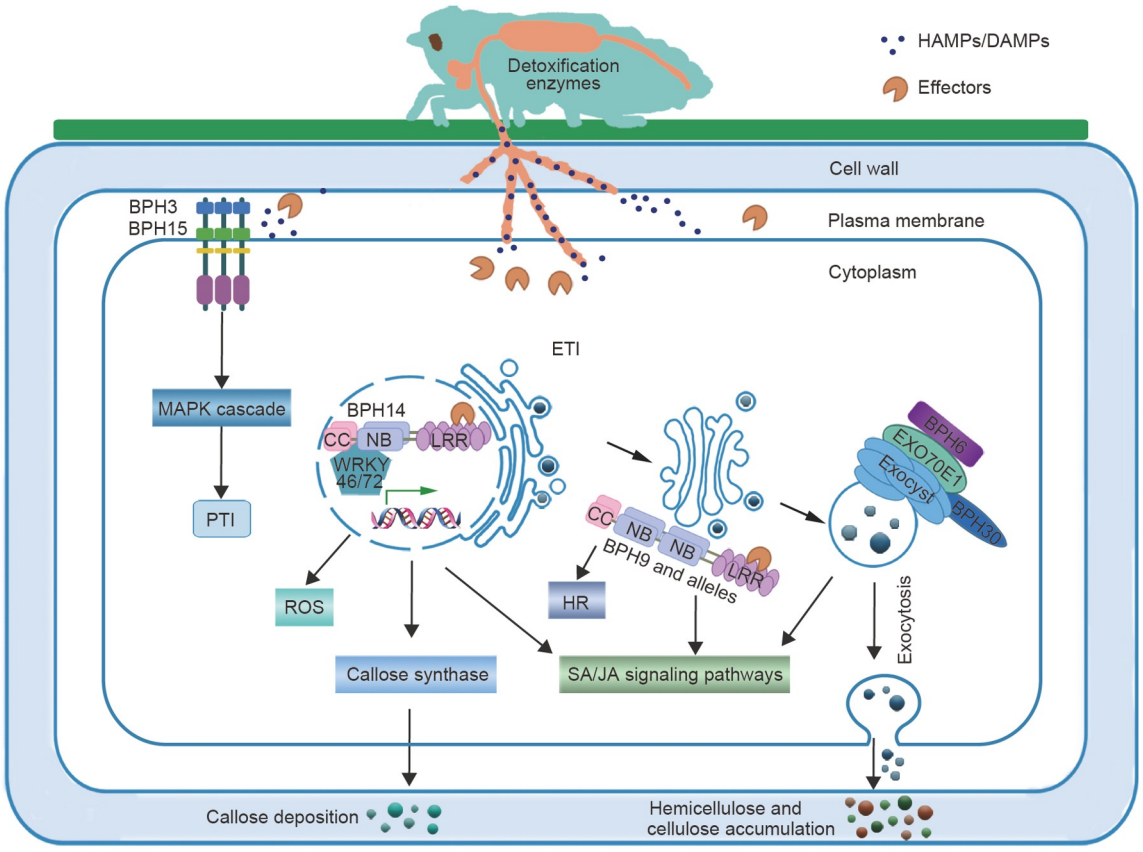

Figure 7 Molecular mechanisms of insect resistance in rice, modified from Zheng et al. (2021). BPH resistance genes *Bph3* and *Bph15* encode plasma membrane-localized LecRKs, recognize insect-derived herbivore-associated molecular patterns (HAMPs) or damage-associated molecular patterns (DAMPs), and activate the MAPK cascade and trigger PTI. Some insect resistance genes, such as *Bph14* and *Bph9*, encode classical NLR proteins to perceive specific effectors delivered to rice cells by BPH and elicit ETI. The process involves ROS generation, HR, phytohormone signaling networks, and callose deposition. *Bph6* and *Bph30* encode novel atypical LRR protein that colocalize with the exocyst complex, strengthen cell walls with enhanced cellulose and hemicellulose content, which prevents BPH stylets from penetrating the tissues and sucking sap.

or DAMPs (Liu et al., 2015c). Intracellular-localized NLR proteins, including *Bph14* and *Bph9*, perceive BPH derived effectors and elicit ETI (Du et al., 2009; Zhao et al., 2016b).

The diversity of BPH resistance genes is favorable for sustainable control of BPH. To further understand the evolutionary mechanisms driving the host plant to cope with BPH, the resistance of a core collection of 1,520 varieties and 17 accessions of wild rice to three BPH biotype populations was examined. GWAS identified 3,502 SNPs and 59 loci associated with BPH resistance in rice (Zhou et al., 2021a). The secondarily evolved Biotypes II and III were virulent to more rice varieties than that of Biotype I. In response, more loci resistant to BPH biotypes II and III were detected, revealing that the BPH resistance loci in rice exhibit high diversity and should have undergone balancing selection (Zhou et al., 2021a). A new BPH resistance gene *Bph37* was isolated and encoded a truncated protein containing the CC and NB domains but lacking the LRR domain due to premature translation termination (Zhou et al., 2021a).

Molecular understanding of rice-insect interactions

Diverse molecular processes regulate the interactions between rice and insects. Various approaches have been employed to identify genes, proteins, phytohormones, metabolites, and miRNA involved in rice-insect interactions. Characterization of a T-DNA insertion mutant revealed a deficiency of mitochondrial outer membrane protein 64 constitutively activated hydrogen peroxide (H_2O_2) signaling, hence conferred rice resistance to both BPH and striped stem borer (SSB) (Guo et al., 2020). OsMPK4 functions as a positive regulator of rice resistance to the SSB by regulating JA-, ET-, and SA-mediated signaling pathways (Liu et al., 2018d). OsMKK3 positively regulates rice resistance to BPH by means of herbivory-induced phytohormone dynamics (Zhou et al., 2019). A group D MAPK gene OsMAPK20-5 rapidly responds to infestation by gravid female BPH, likely resulting from oviposition. OsMAPK20-5 can reduce the resistance of rice plants to planthoppers, and also functions to prevent defense response-related autotoxicity (Li et al., 2019c). OsLRR-RLK1, an early responsive leucine-rich re-

peat receptor-like kinase, acts upstream of MPK cascades and positively regulates defense-related MPKs and WRKY transcription factors, as well as plant resistance towards SSB (Hu et al., 2018a). Suppression of OsLRR-RLK2 decreases BPH preference and performance by reducing the constitutive activity of OsMPK6 and transcript levels of defense-related WRKY transcription factors (Ye et al., 2020). OsERF3 affects early components of herbivore-induced defense responses by suppressing MAPK repressors and is a positive regulator of plant resistance to SSB and a susceptibility factor against BPH (Lu et al., 2011). Silencing of *OsWRKY45* increases both the levels of BPH-induced H_2O_2 and the extent of resistance in rice to BPH (Huangfu et al., 2016). OsWRKY53 functions as a negative feedback modulator of MPK3/MPK6, enabling rice plants to control the magnitude of defensive investment during early signaling (Hu et al., 2015c). Upon herbivore attack, OsMPK3 and OsMPK6 are activated and elicit OsWRKY70, which subsequently activates the JA- and ET-signaling pathways, resulting in the production of defense compounds and enhanced resistance against SSB. While the activation of OsWRKY70 decreases the production of GAs, which prioritizes defense over growth and leads to increased susceptibility to BPH (Li et al., 2015a).

Phytohormones and defense-related metabolites also play important roles in rice defense against pathogens and insects (Tong et al., 2012b; Yang et al., 2012b, 2013a). The SA pathway participates in *Bph9*-, *Bph14*-, and *Bph29*-mediated BPH resistance in rice, with the increased SA synthesis-related gene expression and SA levels upon BPH infestation (Du et al., 2009; Wang et al., 2015; Zhao et al., 2016b). The phenylalanine ammonia-lyase (PAL) pathway is the main route of SA biosynthesis in rice. Recent work demonstrated that OsPALs, regulated by OsMYB30, confer resistance to BPH by increasing the biosynthesis and accumulation of SA and lignin (He et al., 2020). Rice cytochrome P450 gene CYP71A1 catalyzes the conversion of tryptamine to serotonin. Inactivation of CYP71A1 suppresses serotonin biosynthesis, resulting in higher SA levels and enhanced resistance to planthoppers and stem borers (Lu et al., 2018). GA signaling also plays a positive role in mediating the resistance of rice to BPH as silencing of *OsSLR1*, a negative regulator of GA pathway, and overexpression of the GA receptor *OsGID1* enhances the resistance of rice to BPH (Chen et al., 2018b; Zhang et al., 2017a). The JA pathway plays a central role in plant defense against chewing insects (Browse and Howe, 2008). Silencing of JA biosynthesis and signal transduction genes decreases herbivore-induced JA levels, makes rice more susceptible to chewing herbivores SSB and rice leaf folder (LF), but enhances (or at least not adversely affects) resistance to piercing-sucking BPH correlated with higher levels of BPH-induced SA and H_2O_2 (Qi et al., 2011; Wang et al., 2013c; Ye et al., 2012a; Zeng et al., 2021; Zhou et al., 2009; Zhou et al., 2014a). It has been demonstrated that miR156 negatively regulates BPH resistance by increasing JA level in rice (Ge et al., 2018). Recent work supports that JA signaling also positively regulates BPH resistance in rice. JA pathway genes are significantly upregulated and JA concentrations were significantly induced in rice under BPH attack. Mutations of AOC and MYC2 genes that blocked JA biosynthesis and signal transduction rendered rice more susceptible to BPH (Xu et al., 2021). Isopentylamine functions as a new type of plant defense metabolite against BPH. Its rapid accumulation in rice under herbivore attack is completely dependent on JA signaling (Aboshi et al., 2021).

BRs negatively regulate resistance to BPH by modulating the SA and JA pathways in rice (Pan et al., 2018). Ethylene acts as a negative regulator in BPH resistance. Suppression of ET biosynthetic gene OsACS2 reduces elicited ET emission, decreases the resistance to SSB, while enhances the resistance to BPH, demonstrating the contrasting effects of ET signaling on rice herbivore resistance (Lu et al., 2014b). A recent study revealed that the crosstalk between ET and JA pathway, as exemplified by the OsEIL1-OsLOX9 module, synergistically and negatively modulates rice resistance to BPH (Ma et al., 2020). Flavonoid schaftoside could interact with NICDK1 and result in a significant lethal effect on BPH (Hao et al., 2018). It has been found that OsF3H positively mediates both the flavonoid contents and BPH resistance under modulation of miR396/OsGRF8 (Dai et al., 2019). Knockout of naringenin O-glucosyltransferase leads to a higher accumulation of naringenin and sakuranetin, and increases pest resistance in rice (Yang et al., 2021).

Rice insect effectors

Piercing-sucking insects have developed a specialized mouthpart, the stylet, to access the phloem sap. Insects secrete both gelling and watery saliva from their salivary glands into plant cells during the feeding process. Plant responses to insect attacks may be elicited or suppressed by compounds in insect saliva (Jiang et al., 2019a). Broadly, insect effectors are proteins or other molecules that alter host structures and functions (Erb and Reymond, 2019). Many putative BPH effectors have been identified through transcriptome, proteome, and secretome analyses (Huang et al., 2016a; 2020; Ji et al., 2013; Liu et al., 2016a; Rao et al., 2019). The predicted secretome of BPH contains 1,140 potential secreted proteins. *In planta* transient expression of 64 secreted proteins identified six that induced cell death, chlorosis, or dwarf phenotype in *N. benthamiana*, suggesting a potential extensive effector repertoire in BPH (Rao et al., 2019). The salivary sheath protein NlMLP (mucin-like protein) is required for feeding and elicits immunity response in rice, including cell death, the expression of defense-related

genes, and callose deposition (Huang et al., 2017; Shangguan et al., 2018). NlSP1 is essential for BPH feeding and survival. *In planta* expression of NlSP1 could trigger plant defense and cell death. NlSP1 can interact with an unknown rice partner (Huang et al., 2020).

Several insect proteins function to suppress host defense to facilitate feeding. NlFAR is essential for cuticular hydrocarbons production and cuticle waterproofing, enabling BPH to jump between rice plants (Li et al., 2019a). NlEG1 functions as an endo-β-1,4-glucanase to degrade plant cell wall celluloses, enabling the BPH's stylet to reach the phloem of rice (Ji et al., 2017). EF-hand calcium-binding protein NlSEF1 can capture Ca^{2+} and decrease rice cytosolic Ca^{2+} accumulation in rice cells, allowing BPH to suck from rice phloem continuously (Ye et al., 2017). The small brown planthopper (*Laodelphax striatellus*, SBPH) secreted salivary DNase II participates in degradation of extracellular DNA released from damaged plant cells, and prevents the surrounding cells from "seeing" the "danger signal," thereby suppressing the defense system in rice (Huang et al., 2019). When secreted into the host rice plant, Vitellogenin (Vg), regulated by NlFoxO (Dong et al., 2021), can directly interact with the rice transcription factor OsWRKY71, thus effectively attenuating H_2O_2-mediated plant defense and improving insect feeding performance (Ji et al., 2021). Nevertheless, the effector perceived by NLRs or PRRs has not been identified in insects.

Perspective of disease and insect resistance research and breeding in rice

During co-evolution with pathogens and insects, rice has developed complex and specific resistance against pathogens and insects. Rice-pathogens and rice-insects have been engaged in endless cycles of arms race. Great progress has been achieved on our understanding of rice-insect and rice-pathogen interactions at the molecular level. Evidence is accumulating that supports the idea that two branches of the plant immune system recognizing and fending off pathogens are also applicable for insect resistance. Future research may focus on the following questions: (1) How to quickly identify new BSR PRRs or NLRs from rice and elucidate their functions? (2) How do environmental factors, such as temperature, humidity, and light, affect rice immunity against pathogen or insect attacks? (3) How does the environmental microbiome, including rhizosphere microbiome and foliar microbiome, affect the interaction between rice and pathogens? (4) How are insects-derived molecular signatures recognized by rice immune receptors to activate immunity? (5) How do rice R proteins perceive different effectors and trigger ETI response? (6) How does variation in virulence occur in insect and pathogen populations and enable insects and pathogens to break down resistance? A comprehensive understanding of rice-pathogen and rice-insect interactions is crucial for the development of innovative long-term methods to cope with evolving pathogen and insect populations with new virulence variation. A more durable resistance may be achieved by taking advantage of the (allelic) diversity of *R* genes against pathogens and insects from rice germplasms and pyramiding multiple *R* genes. Genome-editing technology can also be used to edit effector targets or susceptibility genes, thus converting susceptible alleles to resistant ones, providing the potential to design rice combating evolving pathogens and pests.

Photoperiodic flowering

Heading date is a key agronomic trait that determines the adaptation of rice cultivars to different geographical regions and cropping seasons. Suitable heading date is able to make rice plants fully utilize light and temperature resources in the cultivation regions to maximize the yield production. Suitable heading date of rice is positively correlated with grain yield: the longer the heading date is, the more biomass and the higher productivity are obtained (Zhang et al., 2019a). The genetic divergence affecting flowering time is also a major factor of reproductive isolation between *Oryza* species (Xu et al., 2020).

Heading date is controlled not only by certain genes but also by some external factors such as photoperiod and temperature. Photoperiodic response refers to the flowering time regulated by changes in day-length. Plants can be classified as long day (LD) and short day (SD) species whose flowering is promoted by LD and SD, respectively, and day-neutral plants whose flowering is not sensitive to day-length. Rice is a SD species, and its heading date is mainly determined by three factors: basic vegetative growth (BVG), photoperiod sensitivity (PS), and temperature sensitivity (TS). Rice originates in the tropical and subtropical regions; its life cycle does not involve vernalization. Moreover, its BVG is relatively stable, around 25 days (Yoshitake et al., 2015). Therefore, PS is the key factor determining heading date in rice. Original rice cultivars were domesticated from the wild rice (*Oryza rufipogon*) with very strong PS. After long-term domestication and artificial selection, diverse rice cultivars with different PS and heading dates have been generated, making rice extend to higher-latitude geographical regions of long day-length such as Heilongjiang Province in China, Japan, and Italy.

Over the last two decades, much attention has been paid to unveil the genetic and molecular mechanism of rice photoperiodic flowering and much important progress has been made particularly in constructing photoperiodic flowering pathways. Such achievements provide great values for designing heading date as follows: (1) establish the primary

theory for breeding by design to develop varieties with optimal heading date in broad regions to achieve a high yield; (2) design hybrid parental lines with similar heading date; (3) avoid breeding too-late heading of hybrid rice varieties by diagnosing parental heading date gene combinations. These great advances attracted many scientists to review this topic in rice (Brambilla et al., 2017a; Hori et al., 2016; Zhou et al., 2021b). In this section, we focus on the recent advancements in the genetic and molecular basis of rice photoperiodic flowering, identify foundational gaps between pathways, and discuss their applications in rice breeding.

A glimpse into the regulatory network of rice heading

As compared to those in LD plant *Arabidopsis*, rice heading has some interesting characteristics: (1) less genes are involved in SD regulation than that in LD; (2) genes involved in SD regulation promote heading in both SD and LD, suggesting that they are necessary for flowering; (3) many genes specifically suppress heading in LD at multiple levels, including expression regulations, protein interactions and modifications; (4) different upstream regulating signals integrate to *Early heading date 1* (*Ehd1*), and finally control the expression of the two florigen genes *Hd3a* and *RICE FLOWERING LOCUS T 1* (*RFT1*), and heading (Figure 8A).

Besides the rice *OsGI-Hd1-Hd3a/RFT1* flowering-promotion pathway that is conserved to the *GI-CO-FT* pathway in *Arabidopsis*, rice has evolved a specific LD flowering-suppression pathway, *Ghd7-Ehd1-Hd3a/RFT1*. *Ehd1* is a rice unique heading gene without homologs in *Arabidopsis*. It encodes a B-type response regulator, which functions as a transcription factor by formation of homodimers (Cho et al., 2016; Doi et al., 2004). *Ehd1* promotes heading by upregulating the expression of *Hd3a* and *RFT1* in both LD and SD, forming *Ehd1-Hd3a/RFT1* module. Multiple upstream genes such as *Heading Date 1* (*Hd1*), *Ghd7*, *COL4*, and *DTH8* (also named *Ghd8* or *Hd5*) negatively regulate *Ehd1* (Lee et al., 2010; Wei et al., 2010; Xue et al., 2008; Yano et al., 2000), while *RID1/Ehd2/OsID1*, *SE5*, *OsMADS51*, etc. promote *Ehd1* expression (Andrés et al., 2009; Kim et al.,

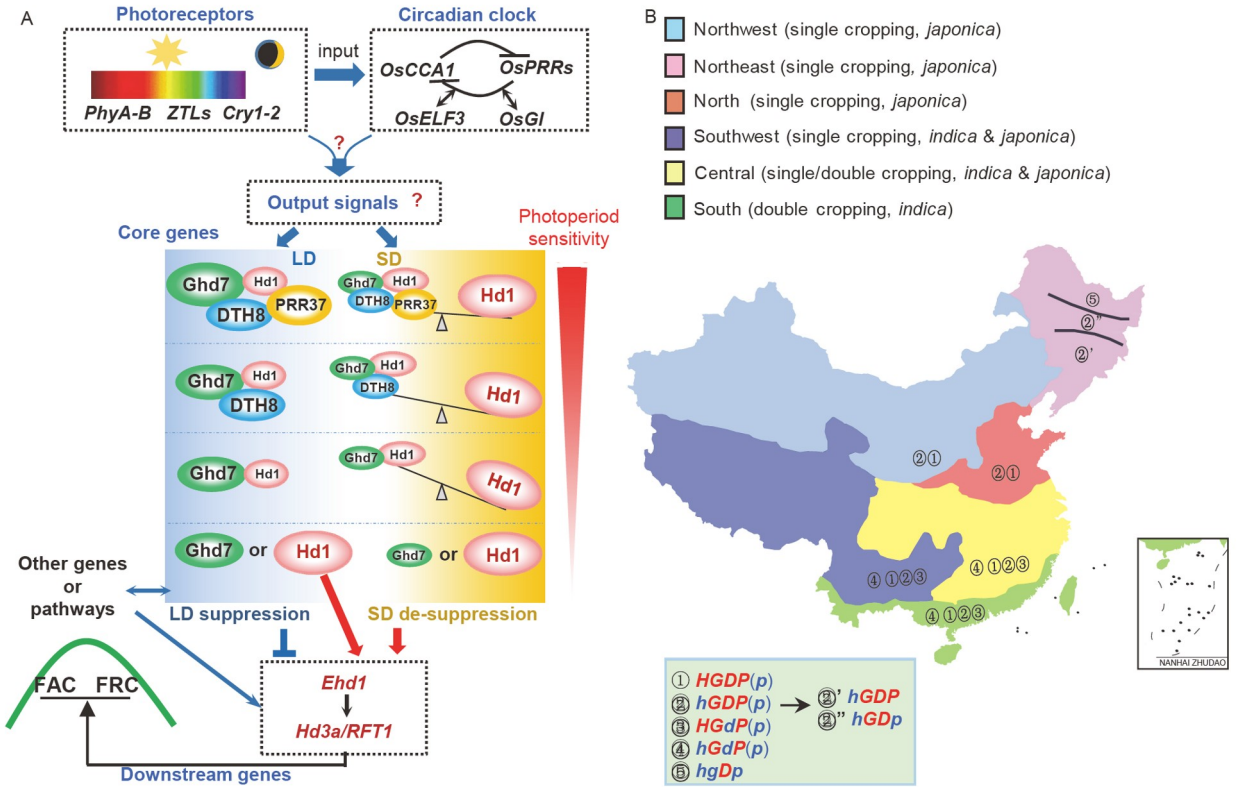

Figure 8 The rice photoperiodic flowering pathway and main genotype combinations in rice cultivation regions in China. A, The control of photoperiodic flowering in rice includes hierarchical regulatory steps: photoreceptors receiving light; signals processing into the circadian clock; day-length measurement by complicated interactions among photoreceptors and circadian clock then converge to forming the output signals that specifically regulate the expression of the core flowering regulatory genes. B, The rice cultivation areas in China are divided into six cropping regions (Mei et al., 1988), where single or/and double cropping systems are adopted as indicated. Different cropping regions are highlighted by different colors. The map is based on the standard map (review number GS (2019) 1683), with no modifications to the base map. Rice varieties of *japonica* and *indica* subspecies planting in different regions have their suitable heading date and PS characteristics governed by the haplotypes of the core heading date genes. In the double cropping regions (South and Central China areas), varieties carry ①, ②, ③, ④ haplotypes, of which varieties for early-season mainly carry haplotype ④ with weak PS, while those for late-season carry haplotypes ①, ②, ③ with moderate or strong PS. In the single cropping regions (Central, North, and Northwest China areas), varieties mainly carry haplotypes ① and ② with strong and moderate PS. In the Northeast region, varieties mainly carrying haplotypes ② and ②′/②″ with weak PS, and ⑤ without PS (with very early heading). *H*, *Hd1*; *h*, *hd1*; *G*, *Ghd7*; *g*, *ghd7*; *D*, *DTH8*; *d*, *dth8*; *P*, *OsPRR37*; *p*, *Osprr37*.

2007; Wu et al., 2008). The ectopically expressed transcription factor OsLFL1 represses *Ehd1* expression by binding the RY element (CATGCATG) within its promoter region (Peng et al., 2007). Recombinant protein Ghd7-GFP in transgenic rice binds to the upstream sequence of *Ehd1* promoter and represses its expression (Nemoto et al., 2016). However, it is not clear how different signals integrate to *Ehd1*, and what is the molecular mechanism of *Ehd1* on promoting the expression of *Hd3a* and *RFT1*.

The florigen genes in plants function at the downstream of the photoperiodic and other flowering regulatory pathways. The rice florigen genes *Hd3a* and *RFT1* are homologs of *FT* in *Arabidopsis*, and they all belong to *FT-like* subfamily of the phosphatidyl ethanolamine-binding protein (PEBP) gene family (also including *TFL-like* and *MFT-like* subfamily). *Hd3a* and *RFT1* are the essential genes for rice flowering, and their silencing leads to no heading (Komiya et al., 2008). These florigen proteins are produced in leaves, transported along phloem to SAM, and formed a "florigen activation complex" (FAC) with the 14-3-3 proteins and bZIP transcription factor OsFD1. FAC directly activates the floral meristem identity genes and floral organ identity genes, such as *OsMADS14*/*15* (homologs of *Arabidopsis FUL*, *AP1*, all belonging to the MADS-box gene family), to promote the vegetative-to-reproductive transition (Corbesier et al., 2007; Tamaki et al., 2007; Taoka et al., 2011).

FAC is required for heading, and there are some factors fine-tuning its amount. Hd3a binds to the bZIPs-like proteins HBF1 and HBF2 in leaves, which down-regulates the expression of *Hd3a* and *RFT1* by a feedback repression of *Ehd1* transcription (Brambilla et al., 2017b). The TFL-like proteins RCN1–RCN4 are transported from leaves to SAM and competitively bind 14-3-3, forming a "florigen repression complex" (FRC) that antagonizes FAC. The balance between FAC and FRC coordinately and delicately controls rice panicle development (Kaneko-Suzuki et al., 2018; Liu et al., 2020b). DTH4 also competes with OsFD1 to bind 14-3-3, attenuating the FAC function (Cai et al., 2021a). Moreover, phosphorylation of the S192 site of OsFD1 by OsCIPK3 is a critical step in FAC formation (Peng et al., 2021).

Photoperiodic flowering in rice

The control of photoperiodic flowering in rice includes four hierarchical regulatory steps: (1) photoreceptors sensing light signals with different wavelength in leaves; (2) signals processing into the circadian clock; (3) measurement of the relative changes of day (light) and night (dark) by photoreceptors and circadian clock that converge to the output signals that specifically regulate the expression of the core flowering regulatory genes (In *Arabidopsis*, CO specifically accumulated at dusk in LD. Thus *CO* is the core gene within the photoperiodic flowering pathway); (4) the core genes determining the expression of the downstream genes and finally the florigen genes. At present, steps 1–3 are still poorly understood, while much progress on step 4 has been made. In general, these core genes constitute the two regulatory pathways: (*Hd1*, *Ghd7*, *DTH8*, *OsPRR37*)–*Ehd1*–*H3da*/*RFT1* LD-suppression pathway and *Hd1*–*Hd3a*/*RFT1* SD-promotion pathway.

Complicated interactions among the core flowering regulatory genes

In rice, *Hd1*, *Ghd7*, *DTH8*, and *OsPRR37* are regarded as the core flowering regulatory genes in controlling photoperiodic flowering. Because defective mutation of any one of these genes leads to great weakening of PS, and different combinations of the four genes show a diverse PS variation from strong PS to complete insensitivity, which are tightly associated with the latitude adaptability of different rice populations.

Hd1, the CO homolog, contains the B-box and CCT domains. Hd1 has dual effects on suppressing heading in LD and promoting heading in SD. It is speculated that day-length regulates Hd1 at the protein level because the transcript levels of *Hd1* are similar in LD and SD (Yano et al., 2000). *Grain number*, *plant height and heading date 7* (*Ghd7*), also named as *Hd4*, encodes a CCT-domain-containing protein. Recent studies revealed that Hd1 is a flowering promoter in LD and SD conditions, while its functional conversion from promoting to inhibiting in LD is dependent on the status of other core flowering regulatory genes *Ghd7*, *OsPRR37*, and *DTH8* (Zhang et al., 2017b; Zhang et al., 2019g; Zong et al., 2021). Except for the role of suppressing heading, *Ghd7* also has pleiotropic effects on increasing plant height and spikelets per panicle (Xue et al., 2008). *Days to heading date 8* (*DTH8*) encoding the NF-YB/HAP3 subunit of the CCAAT-Box-binding transcription factor complex functions in LD on suppressing heading and increasing plant height and spikelets per panicle, but these effects are dependent on the active *Ghd7* (Fujino et al., 2013; Wei et al., 2010; Yan et al., 2011). *Oryza sativa Pseudo-Response Regulator 37* (*OsPRR37*), also named as *Ghd7.1*, *DTH7*, or *Hd2*, encodes a pseudo-response regulator-like protein with the CCT domain, which significantly represses heading and increases grain yield under LD conditions (Gao et al., 2014; Koo et al., 2013; Liu et al., 2013; Yan et al., 2013;). Functions of the four genes are modified at the transcriptional and post-transcriptional levels (Zhou et al., 2021c). Recent studies have uncovered that *Hd1*, *Ghd7*, *DTH8*, and *OsPRR37* synergistically or antagonistically regulate heading date and PS. Here we highlight advancements of the genetic and molecular interactions among the four genes (Figure 8A).

(1) In the *ghd7*/*dth8* background, Hd1 promotes heading

regardless of day-length by up-regulating the expressions of *Ehd1-Hd3a*/*RFT1*, suggesting that Hd1 primarily functions on accelerating flowering, like CO does (Du et al., 2017; Zhang et al., 2017b; Zhang et al., 2019g; Zong et al., 2021). In the *hd1*/*dth8* background, the expression of *Ghd7* is increased under LD to suppress the *Ehd1-Hd3a*/*RFT1* pathway, leading to a slightly delayed heading. Thus, Hd1 functions as a heading promoter in LD/SD when lacking Ghd7, and Ghd7 functions as a heading repressor in LD. Plants carrying *Hd1* or *Ghd7* alone (when the other three core genes are defective) have very weak PS (Zong et al., 2021).

(2) However, the Hd1 and Ghd7 proteins form a functional complex to strongly suppress the *Ehd1-Hd3a*/*RFT1* module in LD conditions. Therefore, rice lines carrying functional *Hd1* and *Ghd7* have largely delayed heading dates in LD, where the Hd1 effect on heading-promotion is converted to heading-suppression. But in SD, the decreased expression of *Ghd7* releases the heading-promotion role of Hd1, and Hd1 competes with the weakened Hd1-Ghd7 complex to promote the florigen gene expression. Thus, plants with *Ghd7*/*Hd1* genotype show a stronger PS, which is confirmed in some *indica* cultivars (Zong et al., 2021). These findings show that *Hd1* and *Ghd7* collaborate and compete to regulate the florigen genes in LD and SD, respectively, forming the primary genetic basis of rice PS (Zhang et al., 2017b; Zhang et al., 2019g; Zong et al., 2021).

(3) The genetic effects of *Hd1* or/and *Ghd7* are affected by *DTH8* and *OsPRR37*. First, rice lines with *DTH8* or *OsPRR37* alone (*hd1*/*ghd7*/*DTH8*/*osprr37* or *hd1*/*ghd7*/*dth8*/*OsPRR37*, abbreviated as *hgDp* or *hgdP*) have a weak effect on heading suppression in LD. Second, those lines carrying the two-gene combinations *Hd1*/*DTH8* or *Hd1*/*OsPRR37* show later heading than those with *Hd1*/*ghd7*/*dth8*/*osprr37* (*Hgdp*) regardless of day-length, indicating that *DTH8* or *OsPRR37* interferes with the primary heading-promotion function of *Hd1* (Zhang et al., 2017b; Zhang et al., 2019g; Zong et al., 2021). Third, the *Ghd7*/*DTH8* combination enhances the suppression effect of *Ghd7* on heading by protein interaction that suppresses the *Ehd1-Hd3a*/*RFT1* pathway in LD and SD (Zong et al., 2021).

(4) The three-gene and four-gene combinations among *Hd1*, *Ghd7*, *DTH8*, and *OsPRR37* attenuate the heading-promotion role of *Hd1* under SD at different levels, or incrementally enhance their LD-suppression role, till completely inhibit the *Ehd1-Hd3a*/*RFT1* module in LD, leading to no heading (Du et al., 2017; Fujino et al., 2019; Goretti et al., 2017; Nemoto et al, 2016; Wang et al., 2019e; Zhang et al., 2017b; 2019a; 2019g; 2019h; Zong et al., 2021) (Figure 8A).

Hd1, Ghd7, OsPRR37, and DTH8 forming different CCT/NF-Y complexes

Hd1, Ghd7, and OsPRR37 are CCT domain-containing proteins. They interact with the NF-YB (DTH8 is a member of the NF-YB family)/NF-YC dimer through their CCT domains to specifically target a conserved "CCACA" motif within the promoters of *Hd3a* (Shen et al., 2020). Other members in the NF-YB and NF-YC family can also interact with Hd1, Ghd7, and OsPRR37 (Goretti et al., 2017; Zhu et al., 2017). These CCT family proteins may form diverse and dynamic complexes with different NF-YB/YC components, and may have higher-order interactions among these complexes. The four genes have plenty of natural variations that could lead to the complex with different interaction intensities even variant identities. Their complicated genetic and intricate molecular interactions might have fine-tuning functions in regulating heading date in various day-length conditions, and confer rice varieties with abundant PS variations adapting to diverse environmental conditions.

In summary, the strong PS of ancient rice is regulated by a complicated and sequential process, including LD-suppression (*Hd1*, *Ghd7*, *DTH8*, *OsPRR37–Ehd1–H3da*/*RFT1* module) and SD-desuppression (*Hd1–Hd3a*/*RFT1* module), which ensure full vegetative growth in LD and rapid flowering in SD. This indicates the genetic divergence of photoperiod flowering mechanisms between LD and SD plants. It is speculated that there are at least two roles of the output signals generated by the upstream regulators, one is to confer Hd1 with dual roles depending on day-length and other heading-related proteins, the other is to mediate the specific expression of *Ghd7* in LD.

The Ghd7 gate opening in LD by light quality and day-length

Currently, we only understand that the switch from the LD to SD pathway is achieved by downregulating the expression of *Ghd7* depending on the *Ghd7* gate and light quality (Itoh et al., 2010). The rhythmic gene expression set by the circadian clock has a sensitive phase in response to a given stimulus, such as external light, which is called the "gate." Studies have showed that the *Ghd7* gate is at dawn in LD. At this time, opening the gate needs exogenous red light that increases the *Ghd7* expression, and thereafter inhibits *Ehd1-Hd3a*/*RFT1* and delays heading. When the day-length is gradually shortened to SD conditions, the gating phase of *Ghd7* is shifted to the middle of night, and *Ghd7* is expressed at a very low level. Whether in LD or SD, the gate of *Ehd1* is at dawn and the gate opening is induced by blue light. In SD, the expression of *Ehd1* is released because of the *Ghd7* silencing (Itoh et al., 2010). Therefore, cultivars carrying *Ghd7* show a strict critical day-length response, in which the day-lengths longer than 13.5 h significantly promote *Ghd7* expression and result in suppression of *Hd3a* (Qiu et al., 2021). Probably, light quality perceived by the photoreceptors and *Ghd7* gate set by circadian clock participate in measuring day-length.

Effects of photoreceptor genes on heading

Sensing the sunlight is the first step in rice photoperiodic flowering pathway. Plants sense and transmit light signals by photoreceptor proteins. The photoreceptors in *Arabidopsis* include phytochromes (PHYA-PHYE, red/far-red light receptors), cryptochromes (CRY1 and CRY2), and a ZTLs protein family (ZTL, FKF1, and LKP2) (blue light receptors), phototropins (PHOT1 and PHOT2), and UV-B receptor (UVR8). Mutations of most photoreceptor genes affect flowering time. PHYA, PHYB, CRY2, and FKF1 regulate photoperiodic flowering by controlling the transcript stability of the core gene *CO* and its encoding protein (Song et al., 2015).

There are three phytochromes in rice, OsPHYA, OsPHYB, and OsPHYC. All the double mutants of Nipponbare have a very weak PS and headed early regardless of the day-length. The two-gene combinations of *OsPHYA*/*OsPHYB* or *OsPHYA*/*OsPHYC* promote the *Ghd7* transcription and delay heading in LD (Andrés et al., 2009; Takano et al., 2005). OsPHYA and OsPHYB also stabilize the Ghd7 protein (Zheng et al., 2019). A short exposure to light in the middle of night causes delay of flowering in SD plants, which is called night break (NB). This suggests that the night length is the important factor determining plant flowering time and PS. In rice, a single NB is sufficient to delay flowering in SD via the PHYB-mediated transcriptional promotion of *Ghd7* and then repressing *Hd3a* expression (Ishikawa et al., 2005; Ishikawa et al., 2009; Itoh et al., 2010). Thus, phytochromes are required for generating the output signals that control the *Ghd7* gate.

The phytochromes contain a chromophore essential for their functions. *SE5* and *SE13* encode different enzymes in the chromophore biosynthesis. They promote the expressions of *Hd1* and *Ghd7*, and consequently repress the transcriptions of *Ehd1* and *Hd3a* in LD (Andrés et al., 2009; Yoshitake et al., 2015). The phenotypes of the *se5* and *se13* mutants are similar to the *phya*/*phyb*/*phyc* mutants, with early heading but without PS (Takano et al., 2009). Rice has three ZTLs blue light receptor genes *OsFKF1*, *OsZTL1*, and *OsZTL2* (*OsLKP2*). However, only the expression of *OsFKF1* shows circadian rhythm. OsFKF1 promotes heading by repressing the *Ghd7* expression in LD and upregulating the transcription of *Ehd2* (a flowering promotion gene) in SD (Han et al., 2015). HAL3, a highly conserved flavin mononucleotide (FMN)-binding protein, interacts with Hd1 only in the dark. This HAL3-Hd1 complex binds the promoter region of *Hd3a* to induce its expression in SD, thus accelerating heading (Su et al., 2016). Among the three cryptochrome genes (*OsCRY1a*, *OsCRY1b*, and *OsCRY2*), only *OsCRY2* promotes heading in both LD and SD (Hirose et al., 2006).

Effects of circadian clock genes on heading

The circadian clock controls many biological processes of plant growth and development. In *Arabidopsis*, the circadian clock consists of multiple interlocked transcription–translation feedback loops. In the early morning, the MYB family genes *CCA1* and *LHY* are induced to be expressed. In midday, *RVE4*, *RVE6*, and *RVE8*, together with the transcriptional coactivators *LNK1* and *LNK2*, are expressed. The PRR family genes, *PRR9*, *PRR7*, *PRR5*, *PRR3*, and *PRR1*/*TOC1*, are transcribed after the *CCA1* and *LHY* expression with a sequential pattern. In the night, *GI* and evening complex (EC) genes, including *ELF3*, *ELF4*, and *LUX*, are expressed. CCA1 and LHY directly repress the *TOC1* expression, while TOC1 represses the expression of *CCA1* and *LHY*, which comprise the core feedback loop (Greenham and McClung, 2015; Sanchez et al., 2020). Mutations of the circadian clock genes affect flowering time and other traits. Of them, *CCA1*, *PRR5*, and *GI* regulate the transcription of *CO* (Song et al., 2015).

The mechanism of circadian clock is conservative in plants. In recent years, several important circadian clock genes have been cloned in rice. Genes in each feedback loop control photoperiodic flowering mainly by regulating *Hd1* and *Ghd7*. *OsCCA1* (or named *OsLHY* or *Nhd1*) has a wide impact on the expression of circadian clock genes. *OsCCA1* promotes heading in LD and delays heading in SD by regulating the circadian rhythm expression of *OsGI* and inhibiting the transcription of *Hd1* in both LD and SD (Sun et al., 2021). OsCCA1 directly binds the promoter region of *Hd3a* to accelerate heading under low nitrogen conditions (Zhang et al., 2021b). In addition, OsCCA1 positively promotes tiller growth and panicle development by the strigolactone signaling and sugar sensing (Wang et al., 2020a).

OsPRR37 and *OsPRR73* are homologs of *PRR7* in rice. *OsPRR37* is a flowering suppressor in LD in the PS network, acting in a heterotrimer with DTH8 and NF-YCs (Koo et al., 2013; Liu et al., 2018b; Yan et al., 2013; Zhang et al., 2019a). OsPRR73 suppresses the expression of *OsCCA1* and *Ehd1* by binding to their promoter regions in LD (Liang et al., 2021). In addition, OsPRR73 also positively promotes salt tolerance (Wei et al., 2021a).

OsGI delays heading in LD by promoting *Hd1* expression and inhibiting *Hd3a* transcription, which establishes the *OsGI-Hd1-Hd3a* regulatory pathway (Hayama et al., 2003). OsGI is also involved in *Ghd7* regulation by interacting with Ghd7 and promoting its degradation at daytime (Zheng et al., 2019). *OsELF3* (or named *OsELF3-1*, *Hd17*, or *Ef7*) encodes a component of the EC complex, which positively regulates the expression of *OsCCA1* and negatively controls the transcriptions of the *OsPRR* genes, affecting the circadian rhythm in rice. OsELF3 promotes heading by repressing the expression of *OsGI* and *Ghd7* in LD, and promoting the expression of *Ehd1* in SD. OsELF3 represses the phytochrome signaling pathways by blocking the gated *Ghd7* expression under LD conditions (Itoh et al., 2019; Yang et

al., 2013b; Zhao et al., 2012). The *haf1* mutant delays heading in LD and SD. *HAF1* encodes an E3 ubiquitin ligase, which is essential for modulating the degradation of Hd1 under SD conditions and mediating the ubiquitination of OsELF3 in LD (Yang et al., 2015b; Zhu et al., 2018).

Evolution and application of rice photoperiodic flowering

The ancient rice landraces with strong PS were initially cultivated in tropical and subtropical regions of Asia. After the long-term natural and artificial selections, rice varieties possess abundant variations of heading date and PS. Nowadays, rice cultivars with diverse genetic constitutions (e.g., different heading date gene combinations) have been planted in a broad region from north latitude 45° (45°N) to south latitude 35° (35°S) (Chen et al., 2019; Monfreda et al., 2008).

Abundant variations of the genes involved in the whole photoperiodic flowering pathway lead to a diverse heading date and PS in rice. Therefore, it is not surprising that more than 600 QTLs have been mapped and nearly 100 heading date genes have been cloned in rice (Hori et al., 2015; Itoh et al., 2018; Khush, 1997; Yonemaru et al., 2010; Youens-Clark et al., 2011). Based on the adaptability of rice materials to latitude regions, variations of flowering genes are roughly divided into two categories: (1) variations such as non-functional or weak-functional mutations of *Hd1*, *Ghd7*, *DTH8*, and *OsPRR37*, which lead to increased LD-heading effect (de-suppression) and reduced PS, enabling rice cultivation in higher latitude regions; (2) variations that do not affect PS but retain strong-functional alleles that are necessary for flowering, such as *DTH2*, *Ehd4*, and *RFT1* (Gao et al., 2013; Wu et al., 2013; Zhao et al., 2015b). Among them, the master genes include *OsPHYB*, *OsGI*, *OsELF3*, *Hd1*, *Ghd7*, *OsPRR37*, *DTH8*, *Hd3a*/*RFT1*, *Hd16*, *Hd6*, and *RCN1*, which have abundant natural variations (Han et al., 2016; Huang et al., 2011; 2016a).

The single gene variations only explain a limited part of PS change. Analysis of multiple gene combinations of the functional and non-functional alleles among the core regulatory genes can better address the genetic basis of PS and regional adaptability. The wild rice *O. rufipogon* contains functional alleles of *Hd1*, *Ghd7*, *DTH8*, and *OsPRR37*, and thus possesses strong or very strong PS. The evolution of rice PS from very strong in the wild rice and landraces to different PS levels in the improved varieties is mainly contributed by the natural variations of these core genes and their genetic interactions. Sixteen 4-gene homozygous combinations are divided into three categories according to their PS. The first category includes the varieties with strong or very strong PS. They include the 4-gene combination of functional alleles (*HGDP*), all kinds of the three-gene combinations of functional alleles and *Hd1Ghd7* combinations, which have a strong effect on *Hd1* (conversion) and/or *Ghd7* (great enhancement). The second category has no PS including the genotypes with single *Hd1* alleles or the 4-gene combination of non-functional alleles (*Hgdp* type or *hgdp* type). The third includes varieties with moderate PS, containing the remaining eight genotypes, which have relatively small effects on *Hd1* (weakening) and/or *Ghd7* (minor enhancement). For example, many modern *indica* varieties have been bred to have the genotypes of *hd1*/*Ghd7*/*dth8* and *hd1*/*Ghd7*/*DTH8*, which produce moderate PS, thus are suitable for cultivation in South and Central China areas with both LD and SD conditions. While the modern *japonica* varieties with strong or moderate levels of PS (mainly possessing the *Hd1*/*Ghd7*/*DTH8* genotype) are suitable for cultivation in mid-season in Central China areas (Zhang et al., 2015; Zong et al., 2021) (Figure 8B).

Similar geographic distribution of the heading date gene haplotypes in inbred rice was also detected in hybrid rice (Zhou et al., 2021d). The three-line hybrids in the middle and lower reaches of the Yangtze River mainly carry the functional *Ghd7* and *Hd1*. *DTH8* was recently introduced into newly bred CMS/maintainer lines Quan9311A/B, which increased the yield potential in the hybrids. The two-line rice hybrids mainly carry functional *Ghd7* and *DTH8*. Very few hybrid rice varieties were found to carry the combination of *Hd1*/*Ghd7*/*DTH8*, because this haplotype produces strong PS (Zhou et al., 2021d).

In Northeast China, rice cultivars with weak PS have been bred. In Liaoning and Jilin provinces, rice varieties mainly carry the non-functional *hd1*, weak-functional alleles of *Ghd7* and *DTH8*, and strong-functional allele of *OsPRR37*. While in Heilongjiang Province (locating at higher latitudes), rice varieties carry the weak-functional *Ghd7*/*DTH8* alleles and non-functional *hd1*/*osprr37*, or possess the weak-functional *DTH8* and non-functional *hd1*/*ghd7*/*osprr37*. These haplotypes are suitable to the gradual changes of day-length and temperature in these regions. The higher the latitude and the lower the accumulated temperature are, the earlier the heading date of the varieties needs (Li et al., 2015c; Ye et al., 2018) (Figure 8B). In addition, an amino acid mutation (L558S) in the OsELF3 domain, which interacts with HAF1, has a great contribution to the diversified heading in *japonica*. Varieties carrying the *OsELF3*-L allele (the protein interacts with HAF1) are suitable cultivation in higher latitude regions because of early heading, while those carrying the *OsELF3*-S allele (the mutant protein does not interact with HAF1) are cultivated in lower latitude regions (Zhu et al., 2018).

In short, the application of the photoperiod flowering mechanisms in breeding rice cultivars should comply with two principles. First, cultivars with strong PS can be grown in the areas with longer growth time for the single-cropping rice in the middle area or late-season rice in Southern China. These kinds of cultivars make full use of light and heat resources via possessing a long vegetative growth phase in LD.

Second, cultivars with moderate PS can be developed for the areas which provide a limited time for rice growth, for example, single-cropping rice in Northeast China and early-season rice in Southern China. Because *Ghd7* also contributes largely to high yield, this gene is usually selected in high-yield varieties (Figure 8B).

Although much important progress has been made, the mechanisms of circadian formation, rice day-length sensation, and the association between growth phase transition and panicle development remain largely unclear. Basic research in the future should focus on elucidating these molecular mechanisms using genetic, biological, and biochemical tools. It is easy to accept the positive correlation between heading date and grain yield that cultivars with long heading date often have high grain yield. However, it is not yet clear why and how this relation occurs. Unveiling the mechanism underlying the relation will benefit developing the high yielding cultivars for local regions. In addition, more studies have revealed that some flowering genes are responsive to abiotic stress. Heading date genes may link the cell development to stress tolerance, which gives us the chance to optimize the balance between growth-control and stress-response pathways.

Fertility and sterility control

The control of male fertility and sterility is the key for hybrid rice breeding, which mainly relies on application of cytoplasmic male sterility (CMS) and photo/thermo genic male sterility (P/TGMS) in three-line and two-line systems, respectively. In 1970, Longping Yuan's group found the wild-abortive type cytoplasmic male sterility (CMS-WA) from a wild rice, and successfully explored this cytoplasm to the breeding of three-line hybrid rice (Chen and Liu, 2016). In 1985, Mingsong Shi discovered a spontaneous rice mutant Nongken 58S (NK58S) showing PGMS, which has been used in two-line hybrid rice breeding (Shi, 1985). These innovative findings have provided foundational materials for hybrid breeding and have opened a prelude to the utilization of heterosis in rice.

At present, the utilization of hybrid rice heterosis mainly depends on the use of intra-specific crossing, but the yield potential has reached a plateau (Yuan, 2008). Therefore, exploration of interspecific and sub-interspecific heterosis based on farther genetic distance is in urgent need to improve the grain yield. However, distant rice hybrids suffer from serious hybrid sterility (HS) because of reproductive isolation, which seriously hinders the use of the strong heterosis (Zhang, 2020b).

In this section, we summarize molecular genetic bases of fertility regulations for hybrid rice, including CMS and fertility restoration, P/TGMS and fertility transition, and interspecific and sub-interspecific HS in hybrid rice breeding.

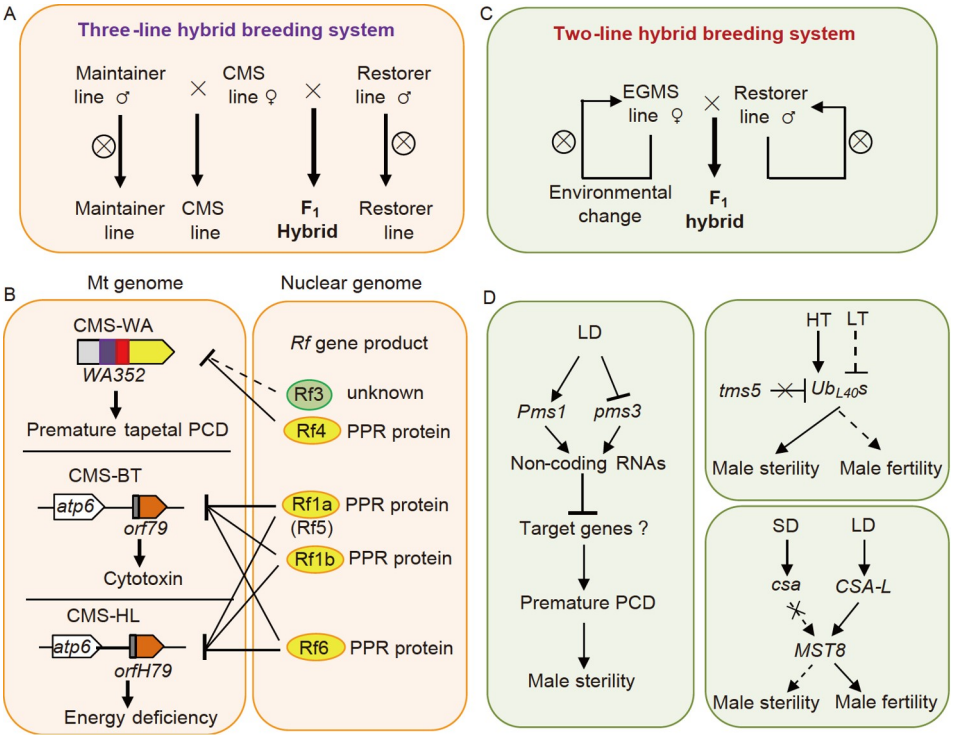

Figure 9 Three-line and two-line hybrid rice systems based on CMS/restoration and environment-sensitive genic male sterility. A, Three-line hybrid rice breeding system. B, Three major CMS/restoration systems used for hybrid rice breeding. The mitochondrial genes *WA352*, *orf79*, and *orfH79* are expressed in CMS lines to impair the anther and pollen development, and they are suppressed in hybrids by the corresponding nuclear *Rf* genes, thus restoring the male fertility. C, Two-line hybrid rice breeding system. D, Working models of three representative photo genic male sterility (PGMS) and thermogenic male sterility (TGMS) systems. LD, SD, HT, and LT represent long day, short day, high and low temperatures, respectively.

CMS and fertility restoration in three-line hybrid rice

Three-line hybrid rice system comprises CMS line, CMS maintainer line, and CMS restorer line (Chen and Liu, 2014). A CMS line harbors a mitochondrial CMS gene, which is inherited maternally, but lacks functional nuclear restorer gene(s), thus causing male sterility (Figure 9A). A maintainer line carries an identical nuclear background of the corresponding CMS line but a normal cytoplasm lacking the CMS gene, which can cross with the CMS line for CMS line propagation. A restorer line contains functional nuclear restorer gene(s), thus can restore the male fertility of F_1 hybrid. Therefore, understanding of molecular basis of CMS and fertility restoration is helpful for improving breeding of three-line hybrid rice.

Cytoplasmic male sterility systems used in hybrid rice breeding

At present, three major CMS systems, i.e., Boro II CMS (CMS-BT) derived from an *indica* rice cultivar Chinsurah Boro II, Wild Abortive CMS (CMS-WA), and Hong-Lian CMS (CMS-HL) from wild rice, are used in three-line hybrid rice breeding (Guo and Liu, 2009). These CMS systems have been discovered and commercially applied more than a half century, but their molecular bases of fertility control have been elucidated only in recent years. Three mechanistic models have been proposed to explain the CMS induction, including premature tapetal programmed cell death (PCD) hypothesis, cytoplasmic protein toxicity hypothesis, and mitochondrial energy deficiency hypothesis (Figure 9B).

The premature tapetal PCD in CMS-WA

The normal development of tapetum is very important for pollen development; early or delayed tapetal degradation causes pollen sterility (Li et al., 2006). The phenomenon that a CMS gene causes premature tapetal PCD was first observed in sunflower (Balk and Leaver, 2001). Later, it was found that the rice CMS-WA cytoplasm also causes pollen abortion by inducing premature tapetal PCD (Luo et al., 2013).

By comparison of the mitochondrial genomic sequences and the transcript patterns between a CMS-WA line and its normal male fertility lines, Liu et al. (2007) found two differentially expressed transcripts in the CMS-WA line. Further studies showed that a chimeric open reading frame (ORF) encoding a protein containing 352 amino acids, thus named *WA352*, was the CMS-WA causal gene (Luo et al., 2013). *WA352* (later renamed as *WA352c*) originated from multiple recombination events among mitochondrial genomic sequences, followed by functionalization, in wild rice species (Tang et al., 2017). The expression of *WA352* is constitutive, but the WA352 protein specifically accumulates in the anther tapetum at the microspore mother cell stage. WA352 is a typical transmembrane protein, which produces toxicity to *Escherichia coli*, but this region is independent from male sterility induction (Luo et al., 2013). WA352 interacts with the nucleus-encoded mitochondrial protein COX11 to cause the excessive accumulation of ROS in the tapetum at the microspore mother cell stage, thus leading to the premature tapetal PCD and resultant male sterility.

CMS protein cytotoxicity in CMS-BT

In 1988, It was found that cytotoxin encoded by a CMS gene in maize could cause pollen abortion, and thus proposed the hypothesis of cytotoxin encoded by abnormal mitochondrial genes (Dewey et al., 1988). Later, Wang et al. (2006b) found that the mitochondrial ORF *ORF79* in CMS-BT lines encodes a cytotoxic protein of 79 amino acids that has a lethal effect on bacteria. Similarly, specific accumulation of ORF79 in microspores of CMS-BT plants causes gametophytic sterility.

Mitochondrial energy deficiency in CMS-HL

In 2003, Sabar et al. (2003) found that the mitochondrial abnormal ORF leads to disorder of energy supply in CMS lines of sunflower. The CMS-HL line carries *orfH79* that is highly homologous to *orf79* (Yi et al., 2002). ORFH79 interacts with P61, a subunit of the electron transport chain (ETC) complex Ⅲ, to affect the enzyme activity of the ETC complex, thus causing mitochondrial energy deficiency and ROS outbreak, and ultimately leading to pollen abortion (Wang et al., 2013b).

Fertility restoration for CMS

In general, nucleus-encoded *Restorer of fertility* (*Rf*) genes produce mitochondria-targeting proteins, which disrupt the functions of CMS genes to restore male fertility of CMS plants via different levels of nuclear-cytoplasmic interactions.

CMS-BT line carries two *Rf* genes *Rf1a* and *Ra1b* encoding PPR proteins, which suppress the *orf79* function at the post-transcriptional level (Wang et al., 2006b). RF1A mediates cleavage of the *orf79* transcript into two fragments, while RF1B functions on complete degradation of the *orf79* transcript in the absence of RF1A. In the co-existence of RF1A and RF1B, RF1A has an epistatic effect on cleaving the *orf79* transcript. In the CMS-HL system, the fertility restoration is controlled by two PPR genes *Rf5* (the same gene *Rf1a* for CMS-BT) and *Rf6* (Figure 9B). RF5 associates with the cofactors GRP162 to form a fertility restoration complex (RFC) and bind to the *atp6-orfH79* transcript for cleavage processing and restoration of pollen fertility (Hu et al., 2012). In addition, the PPR protein RF6 interacts with the cofactor OSHXK6 to cleave the *atp6-orfH79* transcript at another site (Huang et al., 2015b). In addition, RF6 also has

effect on the fertility restoration of CMS-BT.

Fertility restoration of CMS-WA is controlled by two dominant nuclear loci, *Rf3* on chromosome 1 and *Rf4* on chromosome 10. *Rf4* encodes a P-type PPR protein and suppresses *WA352* expression by mediating *WA352* RNA degradation, while the currently uncloned *Rf3* restores the fertility of CMS-WA by decreasing WA352 protein accumulation (Luo et al., 2013; Tang et al., 2014) (Figure 9B). These studies have revealed that plant CMS/restoration genetic systems are involved in different levels of nuclear-cytoplasmic interactions.

Environment-sensitive genic male sterility and fertility conversion in two-line hybrid rice

Environment-sensitive genic male sterility (EGMS) is an important type of germplasm for two-line hybrid rice breeding. The two-line breeding system consists of two types of lines: EGMS lines and restorer lines (Figure 9C). The male fertility of an EGMS line is co-regulated by certain genetic locus/loci and environmental factor(s), including temperature, photoperiod, or humidity (Chen and Liu, 2014). Therefore, the EGMS lines are used as male sterility lines and as maintainer lines under different environmental conditions. Most normal varieties can be used as restorer lines. The two-line hybrid system further expands the yield potential and improves the genetic diversity for hybrid rice breeding.

In 1973, Mingsong Shi (1985) discovered a *japonica* PGMS line Nongken 58, which showed male sterility under long day conditions and normal male fertility under short day conditions. Subsequently, Chinese breeder Fenghua Deng (1999) developed an *indica* thermo-sensitive genic male sterility (TGMS) line, Annong S, which was male sterile under low temperature conditions and becomes fertile under high temperature conditions. In recent years, the molecular mechanisms underlying these two major EGMSs have been elucidated (Ding et al., 2012; Zhou et al., 2012; 2014b).

Non-coding RNA-mediated P/TGMS

The PGMS trait of Nongken 58S is regulated by two loci, semi-dominant *Pms1* located on chromosome 7 and recessive *pms3* located on chromosome 12 (Mei et al., 1999). Further studies have showed that *Pms1* and *pms3* encode long non-coding RNAs (lncRNAs) (Figure 9D). The lincRNA encoded by *pms3* has only one SNP (C>G) between the PGMS lines and wild type rice (Ding et al., 2012). This mutation increases methylation level of the locus, leading to lower transcript level and the male sterility. Interestingly, the same *pms3* (named *P/TMS12-1*) derived from Nongken 58S in the *indica* rice Peiai 64S exhibits a TGMS trait (Zhou et al., 2012). *P/TMS12-1* produces a 21-nt small RNA osa-smR5864, in which the C>G SNP site is located. It was assumed that the wild-type osa-smR5864W could inhibit the expression of downstream genes, while the mutant osa-smR5864M lost its inhibition function, thus eventually leading to TGMS. *Pms1* encodes a lncRNA in Nongken 58S and controls the PGMS trait in a semi-dominant manner (Fan et al., 2016b). The lncRNA is recognized and processed by the 22-nt microRNA mi2118 into 18 pairs of 21-nt phasiRNAs. Although how these phasiRNAs regulate the PGMS trait is still unclear, these findings indicate that lncRNAs and the derivative phasiRNAs are important players for male fertility control in plants.

Protein-controlled P/TGMS

In addition to non-coding RNA, some protein-coding genes are also involved in P/TGMS by different mechanisms.

(1) Environmental factor-induced accumulation of harmful proteins. The TGMS line Anong S-1 is widely used in *indica* two-line hybrid breeding, and its TGMS trait is controlled by a single locus *tms5* (Deng et al., 1999). Further, it was found that *tms5* is a loss-of-function mutant allele due to two base variations resulting in a premature stop codon (Zhou et al., 2014b). The wild type *TMS5* gene is temperature-insensitive, which encodes a ribonuclease Z (RNase Z^{s1}). RNase Z^{s1} degrades the transcripts of the ubiquitin-60s ribosomal protein L40 family (Ub_{L40}) genes that are highly expressed at high temperatures, thus eliminating the harmful effect of over-accumulated Ub_{L40} proteins for anther development. Under high temperature conditions (>25°C), the Ub_{L40} genes in the *tms5* plants are over-expressed, leading to excessive accumulation of Ub_{L40} proteins and resultant male sterility. Whereas, under lower temperatures (23–24°C), the Ub_{L40} genes of the *tms5* (and wild type) plants are expressed at low levels, thus the anthers develop normally and convert to male fertility.

(2) Compensation effect of P/TGMS-homologous genes induced by environmental factors. Two other P/TGMS-related genes, *CSA* and *TMS10*, have been cloned in recent years (Yu et al., 2017a; Zhang et al., 2013). *CSA* encodes a R2R3 MYB transcription factor, and the *csa* mutant exhibits male sterility under short day condition and male fertility under long day. *TMS10* encodes a leucine-rich kinase receptor, and the *tms10* mutant shows male sterility at high temperatures and fertility at low temperatures. Both genes restore fertility through inducing accumulation of homologous genes. *CSA* gene is highly expressed under short day but low expressed under long day. However, the homologous genes *OsMYB5* and *OsMYB8* of *CSA* are highly expressed under long day, and these three genes are functionally redundant for pollen development, thus *OsMYB5* and *OsMYB8* compensate the defective function of *csa* under long day. The expression of *TMS10* is not induced by high temperature, but its homologous gene *TMS10L* is highly expressed at low temperature and can compensate the defective function of

tms10, thus restoring the pollen fertility at low temperature.

Reproductive barrier in inter-(sub)specific hybrids

Cultivated rice includes two species, Asian cultivated rice (*O. sativa*) and African cultivated rice (*O. glaberrima*). *O. sativa* is further divided into *indica* and *japonica* subspecies. The yield potential of inter-(sub)specific hybrid rice is estimated to be 15%–30% higher than that of the *indica* intraspecific hybrid rice. However, inter-(sub)specific hybrid rice shows a serious postzygotic reproductive barrier due to HS, and thus hindering the use of distant heterosis (Li et al., 2019b). Therefore, studies on the cloning and molecular genetic basis of HS genes will benefit breaking the reproductive barrier and exploiting the heterosis of distant hybrid rice. About 50 HS loci have been identified in *Oryza* species (Ouyang and Zhang, 2013; Ouyang, 2016), but only 11 of these loci (*Sa*, *S5*, *HSA1*, *S7*, *S1*, *Sc*, *qHMS7*, *ESA1*, *DPL1*/*DPL2*, *S27*/*S28*, *DGS1*/*DGS2*) are cloned (Chen et al., 2008; Hou et al., 2019; Koide et al., 2018; Kubo et al., 2016; Long et al., 2008; Mizuta et al., 2010; Nguyen et al., 2017; Shen et al., 2017; Xie et al., 2017a; 2019b; Yamagata et al., 2010; Yang et al., 2012c; Yu et al., 2016; 2018).

Molecular genetic mechanisms of HS

Based on the current understanding of these HS loci, three working models have been proposed for HS molecular mechanisms, including the killer-target system, killer-protector system, and duplicate gametic lethal system (Figure 10).

(1) Killer-target systems. The Killer-target system refers to a molecular mechanism by which the HS allele-encoded gamete killer (a single component or multi-component complex) can specifically act on the target gene of the corresponding allele to kill the gametes containing this allele in the hybrids (Figure 10).

Since the first finding in the *indica-japonica* HS locus *Sa* (Long et al., 2008), it becomes clear that a majority of the isolated HS loci in *Oryza* species are complex loci composed of multiple closely linked genes that control the HS traits together. Two adjacent genes *SaF* and *SaM*, which encode an F-box/FBD protein and a small ubiquitin-like modifier E3 ligase-like protein respectively, are critical components of the *Sa* complex locus . In *indica-japonica* hybrids, SaF^{+} and SaM^{+} expressed from the *indica* allele *Sa-i* may form a pollen-killer complex to selectively kill pollen grains carrying the *japonica* allele *Sa-j* (with SaF^{-}/SaM^{-}). In another *indica-japonica* male HS locus *Sc* that encodes a DUF1618 protein essential for pollen development, genomic structural variations (including promoter-CDS recombination and copy number variation of 28-kb fragments) occurred in the *indica Sc-i* alleles (Shen et al., 2017). Pollen grains harboring *Sc-j* are selectively aborted due to the targeted repression of *Sc-j* by a Sc-i-containing complex in male gametes.

(2) Killer-protector systems. A killer-protector system refers to a molecular mechanism in which a gamete killer triggers a sterile signal to all gametes in hybrids, but the gametes carrying an allele expressing the gamete protector can selectively protect the gametes from the sterile effect for survival. Thus, those gametes lacking the protector allele are selectively aborted. The HS traits caused by *S5*, *qHMS7*, and *S1* are conferred by this type of killer-protector systems.

In *indica-japonica* hybrids, the killer system in *S5* (conferring female HS) is composed of *ORF5+* from the *indica* allele and *ORF4+* from the *japonica* allele, and the genetic interaction of these two genes can indiscriminately trigger ER stress signal to kill gametes. The *indica* type female gametes carrying a protector gene *ORF3+* are selectively protected by inhibition of the ER stress signal. However, the *japonica* type female gametes carry non-functional *ORF3–* are abortive (Chen et al., 2008; Yang et al., 2012c). Similarly,

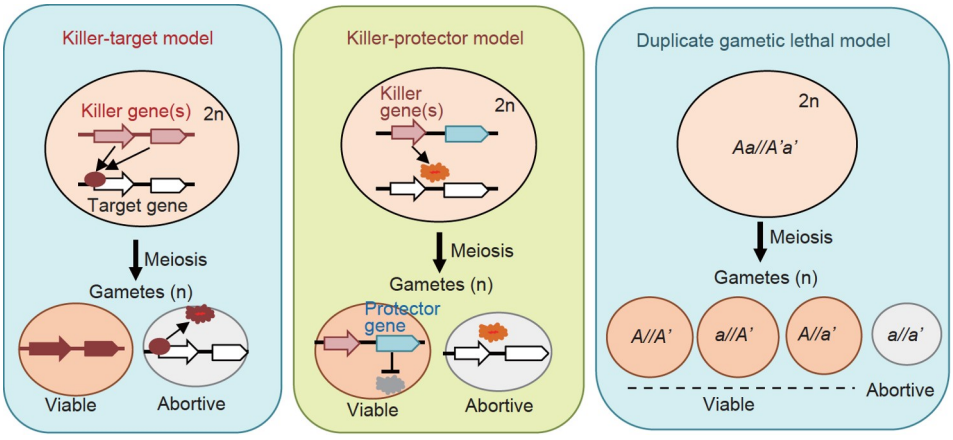

Figure 10 Genetic models of representative hybrid sterility systems in rice. In the killer-target model, the killer gene-expressed product (or a complex) in sporophytic (2*n*) cells of a hybrid acts on the allele-specific target gene to cause selective gamete abortion. In the killer-protector model, the killer gene product induces a sterile signal, but the gametes carrying a functional protector gene are rescued to fertile, and those lacking the functional protector gene are aborted. In the duplicate gametic lethal model, meiosis of a hybrid produces recombination between the non-allelic functional (*A*, *A*′) and defective (*a*, *a*′) gametophytic genes. Therefore, parts (25%) of gametes with *a*/*a*′ are sterile.

in the inter-specific rice hybrids, the killer gene $ORF2^D$ of *qHMS7* locus from *japonica* rice expresses a toxin causing male gamete abortion, but a closely linked protector gene $ORF3^D$ in the *japonica* allele acts as an antidote to protect the gametes from toxin of $ORF2^D$. Thus, only the male gametes carrying the wild rice allele of *qHMS7* are abortive (Yu et al., 2018).

S1 locus controls male and female HS in *O. sativa*-*O. glaberrima* interspecific hybrids. There are three genes *S1A4*, *S1TPR*, and *S1A6* at the African rice allele *S1*-g; proteins encoded by these genes form a killer complex, which induces indiscriminate sterile signals for gamete abortion (Xie et al., 2019b). Meanwhile, *S1TPR* has dual functions and can solely protect gametes. Thus, gametes with *S1*-g (carrying *S1TPR*) survive selectively, while gametes with Asian rice allele (*S1*-*s*) are abortive due to lack of the functional *S1TPR*. Different from *Sa* and *S5* in which the HS depends on parental allele interaction, *S1*- and *qHMS7*-mediated HS represents a new type model of asymmetric genetic interaction that completely depends on genes derived from the uniparental allele. In addition, the dual functional feature of *S1TPR* at *S1*-*g* also differs from the *S5*- and *qHMS7*-mediated HS, in which the killer and protector function independently.

(3) Duplicate gametic lethal systems.The mechanism of duplicate gametic lethal systems is based on that an essential gene for pollen development is duplicated on another chromosome, producing a new non-allelic functional locus. Then during evolution, one of the two genes lost its function in the divergent species, and thus in their F_1 plants, gametes with chromosomal recombination without any one of the duplicated essential genes for gamete development will be aborted. *DPL1*/*DPL2*, *S27*/*S28*, and *DGS1*/*DGS2* are such duplicate gametic lethal systems in rice (Mizuta et al., 2010; Nguyen et al., 2017; Yamagata et al., 2010). For example, *DPL1* and *DPL2* are highly conserved genes that encode a small plant-specific protein and are essential for gamete development (Yamagata et al., 2010). Functional *DPL1* locates on chromosome 1 of *japonica* rice but this gene is non-functional in *indica* rice. On the other hand, functional *DPL2* locates on chromosome 6 of *indica* rice, but it is non-functional in *japonica* rice. In *indica*-*japonica* hybrids, gametes carrying both *indica* non-functional *dpl1* and *japonica dpl2* are aborted.

Approaches for overcoming of HS in rice breeding

The final goal of studying the molecular mechanisms of HS systems is to overcome HS for hybrid breeding. At present, there are three main strategies for HS overcoming in rice. The first strategy depends on wide-compatible lines carrying neutral alleles in natural populations. This concept was first proposed by a Japanese scientist (Kitamura, 1962). Through extensive cross breeding and test crossing, he found that *indica*-*japonica* F_1 hybrids derived from crosses between some *indica* varieties and *japonica* varieties or between some *japonica* varieties and *indica* varieties are highly fertile, thus defined them as wide-compatible lines. However, it is difficult to identify such germplasm resources in distant populations, such as Asian and African rice. The second approach is the development of *indica*-compatible *japonica* lines. The concept was firstly proposed by Chinese scientists (Zhang and Lu, 2007). They found that HS between *indica* and *japonica* rice are mainly regulated by six major hybrid male sterility loci, *Sa*–*Sf*. Therefore, they introgressed the *indica* alleles of the HS loci into *japonica* rice by crossing and backcrossing, to breed *indica*-compatible *japonica* lines. In hybrids between the *indica*-compatible *japonica* lines and normal *indica* varieties, these HS loci are homozygotes of the *indica* alleles, which do not produce HS, and thus the heterosis of *indica*-*japonica* can be utilized. Indeed, this approach was used to breed *indica*-compatible *japonica* CMS lines (Guo et al., 2016; Ma et al., 2010). However, this approach is very time- and labor-consuming. The third approach is to create artificial compatible line using gene editing. In recent years, more and more genes related to HS loci have been cloned and functionally studied, by which it has been revealed that HS is generally induced by active roles of the HS genes. Therefore, it is possible to create engineered hybrid-compatible lines by knocking out or knocking down of the active HS genes. For example, knockout of *Sa*- and *S1*-mediated HS genes created *Sa*- and *S1*-neutral lines (Xie et al., 2017a; 2017b; 2019b). Similarly, *Sc*-neutral lines also were developed by deleting two of the duplicated three genomic copies of *Sc*-*i* that acts in a dosage manner (Shen et al., 2017).

In the inter-(sub)specific rice hybrids, multiple HS loci are present that cause very low fertility by their additive HS effects. Therefore, for complete overcoming of the reproductive barrier in these distant crosses, it is a big challenge to identify and characterize more rice HS genes in the future, and explore or create neutral alleles of the HS loci in rice breeding programs.

Perspective

It is estimated that the world population will rise to more than 9 billion by 2050 (Alexandratos, 1999), and then we will need about 60% more total food production to maintain the sustainable development according to the 2018 Global Agricultural Productivity Index. How to feed the increasing population in the context of limited farmlands and climate changes is a serious challenge we are facing now. Rice, one of the world's most important crops, plays an indispensible role in agriculture and economy, especially in China. Over the past decades, tremendous progress has been made in

understanding the complex agronomic traits of rice, dissecting how these traits are regulated and coordinated, and developing powerful breeding approaches to develop elite rice varieties. In 2002, a draft sequence of the rice *indica* variety 93-11 genome and a fine sequence analysis of rice chromosomes 1 and 4 from the *japonica* variety Nipponbare represented great breakthroughs in the rice genome sequencing, which set the basis for functional research in rice (Feng et al., 2002; Sasaki et al., 2002b; Yu et al., 2002). Shortly afterwards, the map-based cloning and functional analysis of MOC1 set an example for cloning and functional studies of genes controlling important agronomic traits (Li et al., 2003), and rapid and impressive progress in almost every aspect of rice biology has been made using genetics-based strategies in combination with multidisciplinary approaches over the past decades (Zuo and Li, 2014). Discovery of the semi-dwarf *sd1* mutant and exploitation of heterosis by introduction of hybrid rice have led to two quantum leaps in rice yield in China and have made great contribution to ensuring the national food security (Qian et al., 2016).

However, it is still a time- and labor-consuming process at present in improving yield-, quality-, stress- and NUE-related traits by traditional breeding approaches. To meet the challenge of improving grain yield while maintaining environmental sustainability, it is necessary to develop and breed future crops with maximal net production and minimal effect on ecology through new breeding technologies that facilitate pyramid of any known beneficial alleles into desirable combinations rapidly, rationally, and precisely (Tian et al., 2021). To achieve this goal, it is essential to further elucidate molecular mechanism and coordination of complex agronomic traits, especially the relationship and balance among grain yield, grain quality, immunity, NUE, and stress tolerance. Understanding the fitness trade-off between defense and growth, the identification and functional analysis of nutrient and stress sensors, and the regulatory networks controlling grain yield, grain quality, heading data, and fertility will provide powerful tools to achieve high yield, superior quality, strong disease resistance and robust stress tolerance in different geographical regions and soil environments.

The developments of sequencing technologies have greatly facilitated the genome sequencing of various rice germplasm resources and high throughout genotyping with high accuracy and low cost. But the plant phenotyping technologies still lag behind and have become one of the major bottlenecks in functional genomics and crop breeding. Recently, massive progress has been made in developing high-throughput phenotyping techniques and phenotyping platforms across different scales. For instance, the high-throughput rice phenotyping facility equipped with visible light imaging, X-ray CT, fluorescence imaging, automatic controls, and the image analysis pipeline have been developed and used in functional genomics. Remote sensing and robotic vehicles equipped with various sensors have been used in field conditions. In addition, the high-throughput phenotyping has been successfully integrated with GWAS for dissecting genetic architecture of complex agronomic traits in rice (Xiao et al., 2021). In the near future, with the development of crop phenomics, it is promising to meet the challenges and needs for root phenotyping in the field, dark morphogenesis of crops, 2D and 3D phenotypes under abiotic stress, and the wearable phenotyping tools with relatively low cost. These efforts will make important contributions to bridging the gap between genotypes and phenotypes.

Genome editing is a revolutionary technology in life science and is essential for crop improvement and future agriculture. Emerging genome editing technologies have been developed to introduce precise and predictable genome modifications into plants. These genome engineering technologies could target desired agronomic traits with high efficiency and realize precise crop breeding without introduction of exogenous DNA fragments. Genetic modifications generated by genome editing mainly include the small random insertions/deletions (indels), point mutations or base substitutions, targeted insertions, targeted deletions, and chromosomal rearrangements. Another advantage of genome editing is its capability to target multiple sites simultaneously and this feature is rather useful to obtain breeding materials with multiple elite alleles of important traits. Thus genome editing has provided a new toolbox to accelerate crop breeding at an unprecedented pace and to make crop breeding with higher efficiency and lower cost (Gao, 2021). Based on molecular mechanisms of major agronomic traits in model plants, complex traits in various crops could be directly improved using appropriate genome editing technologies.

Based on great advances in genome sequencing and genome editing technologies, the strategy of *de novo* domestication of wild or semi-wild plants through genetic modification has offered new opportunities to develop future crops. For example, *de novo* domestication of wild allotetraploid rice *Oryza alta* through editing of multiple genes has improved six major agricultural traits of the wild rice and meanwhile maintained the agriculturally beneficial traits such as extreme salt resistance, thus enabling rapid crop domestication (Yu et al., 2021). The domestication practices of wild plants (tomato, groundcherry, and allotetraploid rice) shed light on the potential of rapidly creating novel crops from wild plants using the frontier technologies.

The environmental microbiome, including rhizosphere and foliar microbiome, is also important for crop growth and health in natural environments. The root and foliar microbiome can influence phenotypes of host plants by

regulating their genomic and metabolic capabilities, for instance, through influencing the nutrient utilization and hormone signaling of host plants. Meanwhile, the composition of the root and foliar microbiota is regulated by host genetics in turn (Zhang et al., 2019d). However, the diversity, function, and contribution of microbiome to plant phenotypes and its interactions with plant genotype in regulating agronomical traits remain largely unknown. In addition, synthetic biology is a new interdisciplinary field that uses engineering principles and biology knowledge to optimize or even *de novo* design metabolic pathways. Recently, a chemical-biochemical hybrid pathway for starch synthesis from carbon dioxide (CO_2) and hydrogen has been developed in a cell-free system through computational pathway design, modular assembly and substitution, and protein engineering (Cai et al., 2021b). Undoubtedly, development and application of metabolic engineering tools will pave the way for designing future crops with a superior CO_2 conversion rate, balanced nutrition, enriched beneficial metabolites, drugs or even vaccine.

Sustainable breeding of new crop varieties with stable high yield, superior grain quality, robust stress tolerance, and nutrient use efficiency is of great importance for ensuring food security and sustainable agriculture. Utilizing the strong hybrid vigor of interspecific and sub-interspecific heterosis through exploitation of wide-cross compatibility is important for improving grain yield. Furthermore, because the agronomic trait is usually controlled by multiple quantitative loci and different agronomic traits often show mutual regulation, it is difficult and less effective to breed super crop varieties with elite comprehensive characters through traditional breeding based on hybridization and phenotypic selection. Thus it is urgent to develop crops with desired traits through rational design, which is mainly based on the ever growing knowledge about molecular mechanisms and master regulators of agronomic traits, the identification of beneficial alleles responsible for desirable variations, high-throughput and low-cost molecular detection systems, and precise genome editing tools. In summary, cutting-edge technologies such as genome sequencing pipelines, high-throughput phenotyping platform, precise genome-editing technology, environmental microbiome optimization, and synthetic techniques are emerging to promote the deep integration of basic research with breeding methodologies. The knowledge, genetic resources and technologies are now in place to drive another breakthrough in crop production.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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SUPPORTING INFORMATION

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