Introduction

The global climate change has created conditions that are harmful environments to plants. Such environmental change can significantly impede plant growth and reduce crop yield worldwide. In particular, plants growing in altered environment often encounter abiotic stresses, such as drought, high salinity and extreme temperatures, as well as biotic stresses, such as insects, microorganisms and viruses. Being sessile, plants have evolved multitude of strategies to cope with the potentially destructive effects of these stressors and to survive in harmful environment. For instance, the expression of genes involved in stress responses is precisely reprogrammed at the transcriptional and post-transcriptional levels. An efficient pathway of post-transcriptional gene regulation is the rapid modulation of the transcription and post-transcriptional levels. An efficient pathway of post-transcriptional gene regulation via mRNA modifications and transcript abundances in plants under stress (Anderson et al., 2018; Cheng et al., 2021; He et al., 2021; Hou et al., 2022; Hu et al., 2021; Liu et al., 2020; Mao et al., 2021; Wang et al., 2022a; Yang et al., 2021; Zhang et al., 2021a, 2021b, 2021c). However, the precise mechanism underlying post-transcriptional gene regulation via mRNA modification under stress awaits further investigation.

Among over 160 diverse RNA modifications identified to date, N6-methyladenosine (m6A), N7-methylguanosine (m7G) and 5-methylcytidine (m5C) are common and abundant internal modifications found in coding RNAs. Among these, m6A is the most prevalent and the best-eliculated modification of eukaryotic mRNAs (Dominissini et al., 2012; Ke et al., 2015; Lence et al., 2016; Li et al., 2019; Linder et al., 2015; Luo et al., 2014; Meyer et al., 2012; Schwartz et al., 2013; Zhao et al., 2017). The cellular components involved in these modifications include methyltransferases (referred to as ‘writers’) and demethylases (referred to as ‘erasers’), which introduce and remove methylation marks, respectively, as well as RNA-binding proteins (referred to as ‘readers’), which recognize and interpret the methylation marks (Davalos et al., 2018; Zaccara et al., 2019, Shi et al., 2019a; Figure 1). In particular, writer components responsible for m6A instalment on mRNA have been well characterized. MTA and MTB form heterodimers that are core elements displaying m6A methyltransferase activity, and three additional factors, including FIP37, VIR and HAKAI, form writer complexes that are either fully or partly required for m6A deposition (Rüžička et al., 2017; Figure 1). Two additional m6A writers, FIONA1 and enhanced downy mildew2 (EDM2) that...
deposit m\(^6\)A marks on a small group of mRNA, have recently been characterized (Figure 1; Ma et al., 2021; Wang et al., 2022b; Xu et al., 2022). Although a few m\(^6\)A erasers and readers have been characterized so far (Figure 1), a recent genome-wide analysis of m\(^6\)A writers, erasers and readers in 22 plant species revealed that multiple family members of m\(^6\)A writers, erasers and readers exist in plants and m\(^6\)A machineries are highly conserved across plant species (Yue et al., 2019). However, the functions of these effectors are yet to be characterized. In both animals and plants, disruption of any of these cellular components results in abnormal development and altered stress responses (Jiang et al., 2021; Shao et al., 2021; Wilkinson et al., 2021). In animals, the roles of m\(^5\)A, m\(^5\)C and m\(^1\)A in response to various stresses, including hypoxia, oxidative stress and UV radiation, have been demonstrated (Wilkinson et al., 2021). Moreover, transcriptome-wide m\(^6\)A and m\(^5\)C profiling has been performed in diverse plant species under various abiotic and biotic stresses (Table 1). However, the functions and significance of these modifications in plant stress responses remain largely unexplored. Therefore, the key questions are why RNA modification patterns vary under specific stress conditions and how RNA modifications are associated with altered transcript and protein levels and cellular localization in response to stresses. The re-localization of readers is associated with the stability and translation of transcripts under stress conditions. For instance, YTHDF2—a well-characterized m\(^6\)A reader in animals—is re-localized from the cytoplasm to the nucleus under heat stress, which helps preserve m\(^6\)A marks in the 5’-untranslated region (UTR) by blocking the binding of the m\(^6\)A eraser fat mass- and obesity-associated protein (FTO) and promoting the initiation of m\(^6\)A-mediated cap-independent translation (Zhou et al., 2015). Furthermore, ECT2 (YTH9), a well-characterized m\(^6\)A reader in plants, is re-localized from the cytoplasm to the stress granules (SGs) under heat shock (Scutenaire et al., 2018). Other interesting phenomena include the shift of m\(^6\)A marks within the same transcript and the redistribution of m\(^6\)A on new transcripts under stress. For instance, under salt stress, the abundance of global m\(^6\)A modifications in the 5’- and 3’-UTRs increases, and the introduction of m\(^6\)A marks in the 5’-UTR under salt stress is linked to the secondary structure and stability of mRNAs (Kramer et al., 2020). Therefore, the installation and interpretation of methylation marks on RNAs are crucial for stress adaptation in plants.

In this review, we summarize recent progresses in our understanding of mRNA modifications, particularly m\(^6\)A methylation, in plants under stress. Further, we discuss the stress-induced dynamics, stress-mediated distribution and roles of m\(^6\)A modification in mRNA metabolism and the related mechanistic links with plant stress response. Finally, we suggest potential strategies for breeding stress-tolerant crops by engineering mRNA modifications and propose future directions for research to gain a much deeper understanding of mRNA modifications in plant stress biology.

Occurrence of mRNA modifications in plant stress response

Two mRNA modifications, namely m\(^6\)A and m\(^5\)C, have been mapped in plants under abiotic and biotic stresses (Table 1). In mammals, m\(^1\)A, in addition to m\(^6\)A and m\(^5\)C, has been mapped and functionally characterized under stress (Alriquet et al., 2021). In Arabidopsis, m\(^5\)C levels, as measured by liquid chromatography-mass spectrometry, decrease following exposure to drought or heat (Cui et al., 2017). Conversely, in rice, the global level of m\(^5\)C, which regulates chloroplast function and reactive oxygen species (ROS) formation, increases under heat stress (Tang et al., 2020b). Bioinformatics analyses have revealed that several enzymes modifying RNA bases, including m\(^6\)A, m\(^5\)A, m\(^5\)G, Am and Cm, are potentially involved in stress response (Wang et al., 2017b). Further, Trm9/61 is responsible for the deposition of m\(^1\)A on both tRNAs and mRNAs (Tang et al., 2020a; Yang et al., 2020). Similarly, m\(^5\)G is installed on both tRNAs and mRNAs in plants (Chu et al., 2018). Notably, the levels of m\(^1\)A and m\(^5\)G changed differentially in Arabidopsis and rice under stress (Wang et al., 2017b). In the present review, we will focus on mRNA modifications associated with plant stress response through their effects on the base-pairing capacity and stability of mRNAs. A previous study on mRNA modifications and turnover in Arabidopsis revealed that modifications were enriched in mRNAs responsive to various abiotic and biotic stresses (Vandivier et al., 2015). As such, these modifications were primarily enriched in uncapped and easily degrading mRNAs. The possible reasons for extensive deposition of modification marks on stress-responsive mRNAs are as follows: (i) to maintain these stress-responsive transcripts at a basal level during normal growth and development and (ii) to initiate alternative translation to rapidly respond to stresses. For instance, m\(^1\)A is deposited around the start codon and affects Watson–Crick base pairing, which is positively correlated with alternative translation in response to stress in humans (Dominissini et al., 2016). These results imply a potential role of many other unidentified and uncharacterized mRNA modifications in plant stress response. However, mapping and characterization of these modifications are challenging due to their low abundance. Among the mRNA modifications listed above, m\(^6\)A is the best-elucidated one and the primary focus of the present review.

Landscape and dynamics of m\(^6\)A in plant response to diverse stresses

The mapping of mRNA modifications is a fundamental part of understanding how these modifications are dynamically regulated to modulate gene expression in stress response. At present, transcriptome-wide mapping of mRNA modifications in plant stress response is at the initial stage, with m\(^6\)A being the best-characterized mRNA modification, followed by m\(^5\)C. Recent advances in high-throughput sequencing technologies, including methylated RNA immunoprecipitation sequencing (MeRIP-seq), nanopore direct RNA sequencing, methylation individual-nucleotide-resolution cross-linking and immunoprecipitation (miCLIP), and m\(^6\)A-selective chemical labelling (m\(^6\)A-SEAL), have improved the mapping of m\(^6\)A landscape. Among these, MeRIP-seq is the most widely used to map m\(^6\)A in diverse plant species under various stresses (Table 1).

m\(^6\)A architecture in stress-mediated methylomes in plants

Similar to the observations under normal growth and development in plants (Luo et al., 2014; Wan et al., 2015; Shen et al., 2016; Duan et al., 2017; Wang et al., 2017c; Miao
et al., 2019; Parker et al., 2020; Hu et al., 2022) and other eukaryotes (Dominissini et al., 2012; Ke et al., 2015; Lence et al., 2016; Li et al., 2019; Linder et al., 2015; Meyer et al., 2012; Schwartz et al., 2013; Zhao et al., 2017), m6A is predominantly enriched at the 3′-UTR and the near-stop codon under stress (Anderson et al., 2018; Cheng et al., 2021; He et al., 2021; Hou et al., 2022; Hu et al., 2021; Liu et al., 2020; Mao et al., 2021; Wang et al., 2022a; Yang et al., 2021; Zhang et al., 2021a, 2021b, 2021c; Zheng et al., 2021). These findings indicate that m6A distribution on mRNAs is conserved across organisms under both normal and stress conditions. Analysis of the m6A sequence revealed an RR(m6A)CH (R = A/G; H = A/C/U) motif in all eukaryotes (Zhang et al., 2021b; Zheng et al., 2021) and a URU(m6A)Y (Y = C/U) motif unique to plants (Guo et al., 2021; Hu et al., 2021). Moreover, an AAACCV (V = U/A/G) motif in Pak-choi (Liu et al., 2020) and a WKUAH (W = U/A; K = G/U) motif in rice (Ma et al., 2021) were detected under heat stress. The presence of multiple plant-specific m6A motifs as well as the RR(m6A)CH motif conserved across all eukaryotes implies multifaceted functions of m6A modifications in plants. Notably, many stress-responsive transcripts, including mRNAs involved in response to water stress, disease and oxidative stress, are enriched in m6A. The key question is the necessity and importance of m6A in plant stress response, which will be discussed subsequently.

**m6A dynamics during plant response to diverse stresses**

Although the overall m6A patterns are conserved across plants, the global and individual m6A levels are dynamically regulated in response to diverse stresses. In fact, the global m6A levels increased under salt stress in *Arabidopsis* (Hu et al., 2021) and upon viral infection in rice (Zhang et al., 2021a) but decreased under drought stress in sea buckthorn (Zhang et al., 2021b), under moderate low-temperature stress in tomato (Yang et al., 2021) and upon cucumber green mottle mosaic virus (CGMMV) infection in watermelon (He et al., 2021). In contrast, global m6A levels remain unchanged in apples exposed to drought stress (Hou et al., 2022; Mao et al., 2021), Pak-choi exposed to heat stress (Liu et al., 2020), rice exposed to heavy metal (cadmium) stress (Cheng et al., 2021), and wheat infected by yellow mosaic virus (Zhang et al., 2021c). These findings indicate dynamic m6A modifications in a stress- or species-specific manner. In this context, a fundamental question is how various stresses differentially regulate m6A levels in plants, and the most plausible answer to this is the altered expression of m6A writers or erasers under stress. Salt stress induced the expression of several m6A writers (e.g. MTA, MTB and VIR), subsequently augmenting m6A levels in *Arabidopsis* (Hu et al., 2021). Moreover, drought stress induced the expression of the m6A eraser ALKBH10B.

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**Figure 1** Cellular components involved in m6A, m1A and m5C modifications in plants. Characterized writers, erasers and readers that install, remove and interpret methylation marks, respectively, are shown. The MTA, MTB, FIP37, VIR and HAKAI m6A writers and the TRM6 and TRM61 m1A writers form complexes. Question marks (?) denote unidentified components.
homologues, thereby suppressing m6A levels in sea buckthorn (Zhang et al., 2021b). In addition, cucumber green mottle mosaic virus infection increased the expression of CIALKBH4B, presumably reducing the global m6A levels in watermelon (He et al., 2021). These findings indicate the differential regulation of m6A effectors under various stresses.

Because the global m6A levels are determined by the expression level of m6A writers or erasers, it would be worth exploring whether specific stress regulates the expression of either writers or erasers or regulates the expression of both writers and erasers in a plant.

Although the global abundance of m6A remains unchanged in plants under the diverse stresses described above, transcriptome-wide analysis of stress-mediated m6A methylomes has revealed a dynamic feature of stress-induced redistribution of m6A on mRNAs. Salt stress increases m6A deposition in the 5'- and 3'-UTRs but not in the coding regions in Arabidopsis (Hu et al., 2021). Moreover, many transcripts with salt-specific m6A marks are linked to salt or osmotic stress (Anderson et al., 2018; Hu et al., 2021). The next key question is the biological significance of these salt stress-specific m6A marks in response to stress. A plausible hint can be obtained from recently reported m6A methylomes in salt-tolerant and salt-sensitive genotypes of sweet sorghum (Zhang et al., 2021b). As such, the salt-sensitive genotype presented considerable m6A redistribution in response to salt stress, while the salt-tolerant genotype exhibited little changes in m6A patterns (Zheng et al., 2021). Similarly, m6A patterns in the shoots and roots of a salt-tolerant rice cultivar remain unaltered under salt stress (Wang et al., 2022a). These findings suggest that m6A redistribution is an adaptive response of salt-sensitive plants to saline environment. Importantly, the comparison of m6A marks between salt-sensitive and salt-tolerant genotypes revealed m6A deposition in the former under salt stress, but not under normal conditions, was similar to that in the latter in the presence or absence of salt stress (Zheng et al., 2021). These observations suggest that the salt-induced m6A modifications in salt-sensitive genotype are resistant marks found in the salt-tolerant genotype during long-term salt acclimation, implying a functionally crucial role of these stress-induced m6A marks in salt stress response. Thus, the regulation of m6A dynamics appears to be an evolved regulatory strategy of plant adaptation to stress. This leads us to contemplate another interesting point of whether and how m6A modifications can serve as prime marks for the activation of stress-responsive genes, similar to the function of DNA methylation and histone modifications under stress. Additional comparative analyses of m6A patterns between stress-sensitive and stress-tolerant genotypes, particularly in crops, would be valuable to further understand the nature and roles of m6A dynamics in stress adaptation.

### Position- and transcript-specific m6A dynamics in response to stress

An important question is whether the m6A marks are installed in a position- and transcript-specific manner. Although every transcript contains many potential RRACH motifs throughout the sequence, transcriptome-wide m6A profiling has revealed that only one or two of these potential motifs are methylated in a vast majority of transcripts in both plants and other eukaryotes. As described above, various stresses can alter the m6A dynamics and distribution within the same or new transcripts, indicating that specific RRACH motifs are selected for m6A modification in a position- and transcript-specific manner depending on environmental cues and developmental stages. An intriguing question is what drives the selection of RRACH sites for m6A methylation under specific stress conditions. Several studies in mammals have implicated histone modifications, transcription factors, specific RNA-binding proteins and RNA polymerase II in selective m6A modification in a transcript (Zaccara et al., 2019). For instance, the histone modification H3K36me3 interacts with METTL14 to anchor the writer complex to a particular region of nascent RNA for m6A methylation (Huang et al., 2019), and the transcription factors, SMAD2/3, recruit the METTL3/14-WTAP complex to the promoter region for transcript methylation in response to transforming growth factor-beta signal (Bertero et al., 2018). Further, the RNA-binding motif protein 15 (RBM15) and RBM15B interact with the m6A methylation complex and guide the writer complex to a specific mRNA for m6A methylation (Patil et al., 2016), and RNA polymerase II interacts with METTL3 to mediate m6A modification in newly transcribed RNAs (Slobodin et al., 2017). H3K36me2, rather than H3K36me3, is crucial for m6A deposition in plants (Shim et al., 2020) and that MTA (plant
orthologue of METTL3) likely interacts with RNA polymerase II in Arabidopsis (Bhat et al., 2020). Although there is no evidence supporting the existence of similar mechanisms in plant response to stresses, histone modifications and transcription factors most likely regulate stress response through crosstalk with the m6A modification pathway. In addition to guiding the m6A writers to a specific site within the transcript, the possible involvement of m6A erasers cannot be overruled. As m6A methylation is processed co-transcriptionally, certain transcripts may be methylated at multiple sites in their nascent RNAs and some of these methylation marks may be selectively removed by m6A erasers depending on the developmental stage or stress conditions. Discovery of these mechanisms will help ascertain the significance of stress-induced m6A dynamics and the sequence context-specificity of m6A modifications in stress responses.

**Molecular roles of m6A in mRNA metabolism in plant stress response**

Numerous studies have demonstrated the vital roles of m6A modifications in mRNA metabolism, including mRNA stability (Anderson et al., 2018; Duan et al., 2017; Kramer et al., 2020; Wei et al., 2018), intron splicing (Ma et al., 2021), translation (Guo et al., 2021; Huang et al., 2021; Luo et al., 2020; Luo et al., 2021; Shao et al., 2021; Zhou et al., 2021), alternative polyadenylation (APA; Hou et al., 2021; Hu et al., 2021; Song et al., 2021), secondary structure formation (Kramer et al., 2020) and transcriptome integrity (Pontier et al., 2019). Typically, regulation of RNA metabolism of an individual transcript is associated with the location of m6A marks. For instance, m6A located in the 3′-UTR and near the stop codon is primarily involved in modulating transcript stability (Hou et al., 2021; Luo et al., 2020; Zhou et al., 2019, 2021) and transcriptome integrity (Pontier et al., 2019). m6A present in the 5′-UTR is involved in the regulation of translation (Hou et al., 2022), and m6A in the coding region affects the stability and splicing of mRNA (Ma et al., 2021; Zhou et al., 2021).

The location-specific m6A function on mRNA metabolism is associated with the binding of specific m6A readers. For instance, m6A located in the 3′-UTR can be recognized by a reader protein (e.g. YTHDF2) that recruits deadenylase complex (CCR4–NOT) to destabilize mRNA (Du et al., 2016), while m6A located in the 5′-UTR can be recognized by a reader protein (e.g. elf3) to facilitate translation (see below). Although our understanding of the roles of m6A in mRNA metabolism under stress is severely limited, its involvement in the regulation of mRNA stability and translation is relatively well-elucidated thus far (Figure 2) and is discussed in depth below.

**m6A regulates mRNA stability in plant response to abiotic and biotic stresses**

Integrated application of m6A-seq and RNA-seq is a reliable approach to explore the association of m6A levels with mRNA abundance in plants exposed to various stresses. In Arabidopsis, the deposition of m6A marks in salt-responsive genes under salt stress is associated with transcript stabilization, due presumably to the reduced endonucleolytic cleavage around the m6A site (Anderson et al., 2018). Moreover, salt-specific m6A deposition reduced mRNA secondary structures under salt stress, ultimately increasing mRNA stability and protein levels (Kramer et al., 2020). The m6A writer vir mutant with reduced m6A levels exhibited a lower abundance of mRNA under salt stress, suggesting that m6A marks protect transcripts from degradation (Hu et al., 2021). However, the abundance of other m6A-modified transcripts increased with decreased m6A levels in the vir mutant, suggesting a negative correlation between m6A and transcript stability under salt stress (Hu et al., 2021). Notably, the instability of m6A-modified transcripts is associated with APA (Hu et al., 2021). Contrary to either increased or decreased levels of mRNAs with reduced m6A marks under salt stress, the levels of m6A-modified transcripts were biasedly increased in both vir and fpa37 mutants during development (Hu et al., 2021; Shen et al., 2016). These findings suggest that the m6A-mediated control of mRNA stability is more complex during stress adaptation than during development. As m6A readers can modulate the degradation and stability of m6A-modified mRNAs, stress-specific m6A readers must be discovered and characterized to further elucidate the multifaceted roles of m6A marks in regulating mRNA stability under diverse stress conditions.

The correlation between m6A modification and transcript levels in crop species under stress has been recently explored. Interestingly, salt-induced m6A modification was associated with increased transcript levels in salt-sensitive but not salt-tolerant genotypes of sweet sorghum (Zheng et al., 2021), whereas m6A modification was not associated with increased transcript levels in the shoots and roots of a salt-tolerant rice genotype exposed to salt stress (Wang et al., 2022a). Furthermore, a positive correlation between m6A methylation and gene expression was observed in sea buckthorn under drought stress (Zhang et al., 2021b). In apple, the stability and abundance of transcripts encoding drought-, lignin biosynthesis- and H2O2 pathway-related genes increased under drought stress (Hou et al., 2022). Conversely, in tomato anther, low-temperature-induced m6A modification around the stop codon or in the 3′-UTR was negatively correlated with transcript abundance (Yang et al., 2021). Meanwhile, no clear correlation between m6A modification and mRNA abundance was noted in Pak-choi seedlings exposed to heat stress (Liu et al., 2020) and in rice subjected to heavy metal (cadmium) stress (Cheng et al., 2021). Notably, different effects of m6A modification on gene expression levels were observed in crops upon viral infection. For instance, a negative correlation between m6A methylation and transcript abundance was observed in watermelon infected with cucumber green mottle mosaic virus (He et al., 2021), but either positive or negative correlation between m6A methylation and gene abundance was noted in rice infected with rice stripe virus or rice black-streaked dwarf virus (RBSDV) depending on the location of m6A in the transcript (Zhang et al., 2021a). These observations suggest that the effects of m6A on transcript abundance in crops cannot be generalized and can vary in a stress-, species- or sequence-dependent manner. Notably, however, these studies were based on m6A methylomes obtained from mock- or stress-treated wild-type plants. Considering that transcript stability can be affected by other factors, such as RNA-binding proteins, microRNAs and transcription factors, the correlation between m6A and transcript abundance must be analysed in the mutants of m6A writers, erasers and readers to unveil the precise roles of m6A in the regulation of mRNA stability in plant response to abiotic and biotic stresses.

**m6A potentially regulates mRNA translation in plant response to stresses**

Although the effects of m6A on translational control under stress remain largely unexplored, some plausible evidence allows us to
speculate its potential role. For instance, in *Arabidopsis*, ECT2—a cytoplasm-localized m^6^A reader—is re-localized to SGs under heat stress (Scutenaire et al., 2018). As SGs are assembled under stress conditions and function to block translation by storing the mRNA-ribosome complexes, SG-localized ECTs may serve distinct functions in the regulation of translation under stress. ECT2 and
ECT4, but not ECT3, are re-localized to P-bodies under osmotic stress (Arribas-Hernández et al., 2018). P-body is a membraneless biomolecular condensate involved in RNA degradation. Increasing evidence in human studies indicates that YTHDF2 binds to the transcripts re-localized from translating pools to P-bodies (Lee et al., 2020), implying that re-localization of m6A readers from the cytosol to P-bodies might be associated with osmotic stress response. Of note, under heat stress, YTHDF2—a well-characterized m6A reader in humans—shows re-localization from the cytosol to the nucleus, during which the m6A mark in 5′-UTR is preserved through blocking the binding of the m6A eraser FTO, leading to the initiation of m6A-mediated cap-independent translation (Zhou et al., 2015). This distinct localization of YTH domain proteins in plants and humans indicates their functional diversity in different organisms under stress. Further, m6A modification in the 5′-UTR improves the translation efficiency of drought-related transcripts in apple, suggesting a positive role of m6A in the regulation of translation under drought stress (Hou et al., 2022). However, the mechanisms underlying m6A-mediated translational control under stress remain elusive. Several lines of evidence obtained from studies in humans indicate the pivotal functions of m6A readers. For instance, m6A methylation in the 5′-UTR serves as a selective mark for the binding of m6A readers, such as human YTHDF1, together with the eukaryotic translation initiation factor 3 (eIF3), to initiate cap-independent translation under stress (Wang et al., 2015). In addition, the m6A writer METTL3 facilitates cap-dependent translation through the recruitment of eIF3 to the translation initiation complex, with m6A marks serving as ribosome engagement sites, eventually promoting cap-independent translation (Wang et al., 2015). Furthermore, OsMTA2—a rice orthologue of human METTL3—interacts with eIF3 to modulate growth and pollen development in rice by affecting the global translation status (Huang et al., 2021). These reports suggest that m6A methylation plays a crucial role in translational control in plants and animals under both normal and stress conditions. Nonetheless, further in-depth mechanistic studies are warranted to identify the specific m6A readers or writers involved in translational control under different stress conditions.

### Biological roles of m6A in plant stress response

Following the identification and mapping of m6A methylomes in diverse plant species subjected to stress treatments, studies exploring the biological significance of m6A modifications in plant responses to abiotic and biotic stresses through the identification and characterization of m6A writers, readers and erasers in Arabidopsis and model crops are emerging (Figure 3), as discussed in detail below.

#### Significance of m6A in plant response to abiotic stresses

To date, the significance of m6A in abiotic stress response has primarily been evaluated in Arabidopsis. Several recent studies investigating m6A writer and eraser mutants have shown that m6A is positively correlated with salt tolerance. For instance, VIR—mediated m6A methylation regulates salt stress response by negatively modulating the abundance of transcripts encoding the negative effectors of salt stress (Hu et al., 2021), and knockout of ALKBH10B—an m6A eraser in Arabidopsis—promotes seed germination and seedling growth under salt or osmotic stress by down-regulating m6A-modified transcripts encoding the negative effectors of salt stress (Shoaib et al., 2021; Tang et al., 2021). Recently, ALKBH6 and ALKBH8—two putative RNA demethylases in Arabidopsis—were shown to contribute to salt, drought or heat tolerance (Huong et al., 2020, 2022). Collectively, these results indicate a positive role of m6A modifications in salt tolerance. Notably, bioinformatic analysis of m6A writer, eraser and reader expression levels revealed that m6A writer or eraser expression levels were altered only marginally following stress treatment, although m6A reader expression levels were altered markedly under different stresses (Hu et al., 2019), suggesting their important roles in stress response. Before the discovery of ECT family proteins as m6A writers, ECT1 and ECT2 were implicated in calcium signalling in response to various external stimuli through their interaction with the stress response protein Calcineurin B-Like-Interacting Protein Kinase1 (Ok et al., 2005). Re-localization of ECT2 to SGs under heat stress (Scutenaire et al., 2018) as well as of ECT2 and ECT4 to P-bodies under osmotic stress (Arribas-Hernández et al., 2018) strongly supported the notion that m6A is closely linked to abiotic stress response. Interestingly, ectopic expression of apple MhYTP2 in Arabidopsis enhanced tolerance to multiple abiotic stresses (Wang et al., 2017a), and MhYTP2 was recently identified as an m6A reader in apple (Guo et al., 2021).

Furthermore, biological roles of m6A modifications in abiotic stress response have been explored in several crop species. For instance, PrMTA overexpression enhanced the drought tolerance of Populus by altering trichome and root development (Lu et al., 2020). In apple, MdMTA played a positive role in drought tolerance by improving lignin deposition and ROS scavenging (Hou et al., 2022). In rice, the cadmium-induced abnormal root development was associated with differential m6A modifications in roots (Cheng et al., 2021). Comprehensive expression analysis of genes encoding YTH domain proteins in rice and wheat revealed that OsYTHs and TaYTHs were up-regulated under various abiotic stresses (Hu et al., 2019; Sun et al., 2020). Recent genome-wide sequence and expression analyses of ALKBH family proteins in sugar beet revealed that BvALKBH10B—an orthologue of Arabidopsis ATALKBH10B—was significantly induced by salt stress, suggesting its involvement in salt stress response (Cui et al., 2022). Although accumulating evidence clearly indicates the cruciality of m6A modifications in crop responses to abiotic stresses, the cellular and mechanistic roles of m6A writers, erasers and readers await further characterization.

#### Significance of m6A in plant response to biotic stresses

Unfortunately, only a few studies have demonstrated the involvement of m6A in biotic stress response in Arabidopsis. For instance, ALKBH9B affects the accumulation and systemic infection of alfalfa mosaic virus by interacting with its coat protein, thereby influencing the viral infection cycle (Martínez-Pérez et al., 2017, 2021). In Arabidopsis, the ENHANCED DOWNY MILDEW 2 (EDM2) has been characterized to be a specific gene conferring resistance against Hya1operonospora parasitica by regulating the expression of RECOGNITION OF PEROSONOSPARA PARASITICA 7 (Eulgem et al., 2007). Recently, EDM2 was identified as a novel mRNA m6A writer in rice (Ma et al., 2021). However, given the lack of a typical methyltransferase domain in its structure, whether Arabidopsis EDM2 regulates m6A methylation remains unclear. Cleavage and polyadenylation specificity factor 30 (CPSF30)—a newly confirmed YTH domain-containing m6A reader (Hou et al., 2021; Song et al., 2021)—confers resistance against Pseudomonas syringae through the basal and gene-mediated disease resistance pathways (Bruggeman et al., 2022).
et al., 2014); however, whether this defence response is m^6^A-dependent remains unknown.

Several lines of evidence link m^6^A abundance with biotic stress responses of crops. For instance, in *Nicotiana tabacum*, tobacco mosaic virus (TMV) infection suppresses the expression of m^6^A methylase and demethylase orthologous genes, thereby decreasing m^6^A levels (Li et al., 2018b). However, the precise roles of m^6^A modifications in TMV resistance and host–virus interactions warrant further verification. Moreover, rice stripe virus and RBSDV infection significantly increased the global levels of m^6^A and altered the transcription of genes encoding m^6^A machinery, suggesting the involvement of m^6^A modification in defence response (Zhang et al., 2021a). Moreover, decreasing m^6^A levels in small brown planthopper (SBPH)—a vector of RBSDV—through the interference of two m^6^A writers, namely LsMETTL3 and LsMETTL14, significantly increases the RBSDV titres in the midgut cells of SBPH, suggesting a negative correlation between global m^6^A levels and virus replication (Tian et al., 2021). In addition,
Epitranscriptomic mRNA modifications in stress responses

Potential strategies for engineering mRNA modification to develop stress-tolerant crops

Engineering mRNA modifications holds a great potential to improve plant tolerance of different environmental stresses due to their insignificant effects on plant genome integrity but high efficiency in the regulation of mRNA abundance. A recent study demonstrated an exciting and successful application of m6A modification to improve crop productivity and stress tolerance (Yu et al., 2021). Briefly, ectopic expression of FTO, an m6A demethylase in humans, in rice and potato not only considerably increased the biomass and yield by approximately 50% in the field trial but also enhanced plant tolerance of drought stress (Figure 3). Of note, however, although that study underscored the great potential of engineering m6A erasers for crop improvement, modification of overall m6A by engineering m6A writers or erasers may induce undesirable side effects, which should be closely monitored. Therefore, to overcome those seemingly undesirable side effects, more precise manipulation of m6A within a specific transcript is warranted. Here, we propose three potential approaches to engineer mRNA methylation for crop improvement (Figure 4). First, a specific adenosine (A) in the genomic DNA can be modified to guanosine (G) using CRISPR-Cas-derived base editors, such as the adenine base editor, generated by fusing the catalytically impaired Cas9 protein with signal-stranded DNA-specific adenosine deaminase (Gao, 2021). This A to G base editing system mimics the demethylase function to disrupt modification at a specific m6A site, eventually modulating the target mRNA abundance. This approach is particularly useful when the gene of interest is essential for plant development and its knockout can be lethal. Second, specific mRNA at a particular site can be modified using either a CRISPR-Cas9- or CRISPR-Cas13-based system targeting RNA methylation. This system is generated by fusing dCas9 or dCas13 with either methyltransferase or demethylase to directly add or remove modification marks in the target endogenous RNA molecules without altering the nucleotide sequence of genomic DNA (Li et al., 2020; Liu et al., 2019; Wilson et al., 2020). Third, the reader-mediated interpretation of modified mRNA can be regulated using the CRISPR-Cas13b-fused reader approach. For instance, the programmable dPspCas13b-m6A reader protein system, in which the human m6A reader proteins YTHDF1 and YTHDF2 are fused to a catalytically inactive PspCas13b protein, can target the reader to a specific m6A site within a specific mRNA using guide RNA complementarity (Rauch et al., 2018). To date, the first strategy has been successfully utilized in plants (Li et al., 2018a; Zong et al., 2017), while the last two techniques are yet to be optimized in plants. Further advances in these techniques for plants are expected to substantially boost the application of epitranscriptomics for crop improvement.

Concluding remarks and future perspectives

At present, the elucidation of mRNA modifications in plant responses to stress is only at the nascent stage. Except those of
m^6A, the biological functions of many mRNA modifications, such as m^6C and m^A, await further exploration. Although accumulating evidence has highlighted the involvement of m^6A modifications in stress-dependent manner and how m^6A differentially regulates the abundance of stress-responsive transcripts under different stress conditions, remain unresolved. In addition, majority of the m^6A maps reported thus far were created using antibody-based MeRIP-seq data, which do not specify the precise location of m^6A site in a transcript. Therefore, cutting-edge sequencing modalities, such as nanopore direct RNA-seq (Parker et al., 2020; Pratanwanich et al., 2021), MAZTER-seq (Garcia-Campos et al., 2019), m^6A-REF-seq (Zhang et al., 2019) and miCLIP-seq (Linder et al., 2015), should be applied to map m^6A modifications at a single-base resolution, which would enable the determination of the precise stoichiometry and dynamics of specific m^6A modifications under different stress conditions. Furthermore, analysis of stress-induced m^6A methylomes is crucial for distinguishing the ‘constitutive’ and ‘dynamic’ modulations associated with stress, which will provide valuable information to precisely engineer RNA modifications for crop improvement. With recent breakthroughs in CRISPR genome editing techniques in animals and plants, the application of base editing systems that can modify single bases and the CRISPR-Cas13-based targeting RNA methylation system is anticipated greatly accelerate epitranscriptomic studies aimed at improving crop yield and stress tolerance. Moreover, considering that writers, erasers and readers responsible for the installation, removal and interpretation of different RNA modifications in crops remain largely elusive, these components must be identified and characterized to aid the engineering of specific RNA modifications for improving agriculturally important traits of crops. In addition to elucidating the roles of m^6A in the regulation of mRNA metabolism, whether and how m^6A modifications regulate the fate of non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNA (lncRNAs), in plants under stress is of great interest. miRNAs are important players in plant stress responses, whether and how m^6A differentially regulates the expression of these ncRNAs will expand our repertoire of epitranscriptomic modulations related to plant stress tolerance.

In summary, a rapid progress in transcriptome-wide mapping has enabled the unveiling of the regulatory roles of m^6A modifications in plant responses to diverse abiotic and biotic stresses. Notwithstanding, many challenges remain in identifying and characterizing the cellular components of writers, readers and erasers in crops as well as establishing the molecular link between m^6A modifications and stress adaptation. Integrating these molecular insights on the regulatory roles of m^6A modifications in stress response with novel genome- and RNA-editing technologies will pave the way for a novel branch of plant stress biology, which will facilitate the breeding of stress-tolerant crops via precisely engineered RNA modifications.

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Conflict of interest
The authors declare no competing interests.

Authors’ contributions
H.K. and T.X. conceived the project; H.K., J.H., J.C. and T.X. wrote the paper. All authors read and approved the manuscript.

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