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Review

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Transcriptional memory and response to adverse temperatures in plants

Wei XIE[1,2], Qianqian TANG[1,2], Fei YAN[1,2], Zeng TAO[1,2]✉

[1]*State Key Laboratory of Rice Biology, Zhejiang University, Hangzhou 310058, China*
[2]*Ministry of Agriculture Key Laboratory of Molecular Biology of Crop Pathogens and Insects, Institute of Biotechnology, Zhejiang University, Hangzhou 310058, China*

Abstract: Temperature is one of the major environmental signals controlling plant development, geographical distribution, and seasonal behavior. Plants perceive adverse temperatures, such as high, low, and freezing temperatures, as stressful signals that can cause physiological defects and even death. As sessile organisms, plants have evolved sophisticated mechanisms to adapt to recurring stressful environments through changing gene expression or transcriptional reprogramming. Transcriptional memory refers to the ability of primed plants to remember previously experienced stress and acquire enhanced tolerance to similar or different stresses. Epigenetic modifications mediate transcriptional memory and play a key role in adapting to adverse temperatures. Understanding the mechanisms of the formation, maintenance, and resetting of stress-induced transcriptional memory will not only enable us to understand why there is a trade-off between plant defense and growth, but also provide a theoretical basis for generating stress-tolerant crops optimized for future climate change. In this review, we summarize recent advances in dissecting the mechanisms of plant transcriptional memory in response to adverse temperatures, based mainly on studies of the model plant *Arabidopsis thaliana*. We also discuss remaining questions that are important for further understanding the mechanisms of transcriptional memory during the adverse temperature response.

Key words: Transcriptional memory; Temperature stress; Vernalization; Cold acclimation; Thermomorphogenesis; Heat stress

1 Introduction

Plant growth and crop production are deeply affected by environmental conditions (Lobell et al., 2011). Climate trends show that the temperature on earth is tending to increase every year, which will be a continuous challenge to food supply (Alexander et al., 2006; Lobell and Gourdji, 2012). As the seasons change and the global temperature fluctuates, extreme weather conditions, like intense heat and freezing, recur worldwide from time to time. These adverse temperatures not only trigger various physiological and biochemical changes in plants, but also cause negative impacts on plant growth and crop production (Lobell et al., 2011; Tack et al., 2015).

✉ Zeng TAO, taozeng@zju.edu.cn
Zeng TAO, https://orcid.org/0000-0003-3981-6675

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Plants have evolved a series of sophisticated mechanisms to withstand adverse stresses and optimize their growth and development. Moreover, they can remember the first stress stimulus and acquire the ability to become more resistant to recurring exposures (Bruce et al., 2007; Conrath et al., 2015). Except for extreme cold stress, many species in temperate climates acquire competence to flower after experiencing a prolonged cold exposure in winter, through a process termed vernalization (Amasino, 2010; Andrés and Coupland, 2012).

Relatively warm temperature has been found to promote plant flowering and elongation, which is known as thermomorphogenesis (Quint et al., 2016). Accumulating research evidence, especially from the model plant *Arabidopsis thaliana*, has revealed that plants as sessile organisms respond quickly to environmental temperature changes and acquire transcriptional memory to balance their growth and survival through multiple transcriptional machineries (Vriet et al., 2015; Crisp et al., 2016; Hilker et al., 2016).

Transcriptional regulation is a major mechanism to modulate gene expression. In eukaryotes, the repeating subunit of chromatin is the nucleosome, formed by 147 bp DNA wrapped around a histone octamer containing two copies each of histones H2A, H2B, H3, and H4 (Luger et al., 1997; Wang et al., 2018). The chromatin state of target locus influences the accessibility of transcriptional machinery and is closely associated with their transcriptional activity, which can be heritable and stably maintained between cell generations. Epigenetics refers to the study of heritable changes to gene expression without changes to the underlying DNA sequence. Epigenetic modification usually includes DNA methylation and posttranslational histone modifications (PTMs), chromatin remodeling, histone variants, and noncoding RNAs (Deans and Maggert, 2015). Plenty of histone modifications have been identified, including histone acetylation, methylation, phosphorylation, ubiquitination, sumoylation, carbonylation, and glycosylation (Kouzarides, 2007; Tan et al., 2011). Epigenetic modifications not only play key roles in various chromatin-templated activities, including DNA replication, DNA repair, and RNA transcription (Gong and Miller, 2013; Zentner and Henikoff, 2013; Zhong, 2016), but also are involved in such biological processes from development to environmental responses, including transcriptional memory in response to adverse temperatures (Gong and Miller, 2013; Zentner and Henikoff, 2013; Zhong, 2016).

Plants evolve to adapt to different stressful environments by transcriptional reprogramming. They can acquire an enhanced or hypersensitive stress response after previous stress exposure, which indicates that primed plants can remember recurring stresses (Kinoshita and Seki, 2014; Avramova, 2015; Martinez-Medina et al., 2016). In this review, environmental memory achieved through altered gene expression is termed transcriptional memory. According to the duration of gene activation and inheritance in the life cycle of a plant, transcriptional memories can be categorized as somatic, intergenerational, or transgenerational (Sani et al., 2013). Somatic memory is limited to the current life cycle, while intergenerational memory extends to the next generation and transgenerational memory is maintained in the next two or more stress-free generations. Recent studies found that regulation of transcriptional memory during cold and heat stresses is tightly associated with epigenetic modifications (Nishad and Nandi, 2021). Furthermore, environment-triggered epigenetic modifications at some loci can be passed on to the next generation, while some are reprogrammed at the stage of sexual reproduction or early embryogenesis to maintain normal growth and development (Choi et al., 2009). DNA and histone methylation are chemically stable during DNA replication. They can also be used as templates to bind methylation to newly synthesized strands (Bannister et al., 2002), which could explain how chromatin modifications regulate plant memory. Dynamic regulation of chromatin is achieved not only by enzymes setting and removing chemical modifications of DNA or histones, but also by replacing the canonical histones with histone variants, therefore, resulting in an immediate loss of histone modifications and a resetting of epigenetic changes (Spiker, 1982).

In this review, we summarize recent progress in understanding transcriptional memory under adverse temperatures, mainly in the model plant *Arabidopsis*. Furthermore, we provide new insights into understanding the molecular mechanisms of transcriptional memory in plant adapting to adverse temperatures, and we also propose potential strategies for future application of epigenetically modified crops in dealing with climate changes.

2 Transcriptional memory and response to adverse temperatures in plants

2.1 Vernalization

In nature, plants have to endure the temperature and day-length fluctuations and activate inner signaling pathways. As a classical genetic model, vernalization refers to the process by which plants can reprogram expression and acquire the ability to flower in the subsequent warm growth conditions after prolonged winter exposure. Recently, epigenetic regulation of vernalization has been well explored in *Arabidopsis*. Transcriptional memory has been elegantly elucidated in the transcriptional reprogramming of FLOWERING LOCUS C (*FLC*), the main floral repressor gene, under vernalization in *Arabidopsis*, which has shed light on how vernalization-responsive crucifers synchronize their growth and development with seasonal changes (Fig. 1a).

FLC, a MADS-box transcription factor, is the main floral repressor that perceives and responds to

seasonal cues. The expression of *FLC* is tightly associated with the control of flowering time from the vegetative to the reproductive stage, which is regulated at diverse levels, including chromatin, transcription, co-transcription, and RNA metabolism (He, 2012; Whittaker and Dean, 2017). The expression of *FLC* during vernalization depends mainly on the crosstalk among different histone modifications of *FLC* chromatin. Hence, the expression status of *FLC* acts as a molecular switch to "memorize" the temperature signal during vernalization.

In the winter annual *Arabidopsis*, the expression of *FLC* is activated by the dominant alleles of FRIGIDA (*FRI*) and is maintained at a relatively high level to inhibit flowering in the vegetative stage of seedling development. During this period, the chromatin of *FLC* is occupied by histone H3 lysine 4 tri-methylation (H3K4me3) and histone H3 lysine 36 tri-methylation (H3K36me3), which are associated with active transcription mediated mainly through the *FRI* super-complex and *FRI-FLC* regulatory module (Li et al., 2018).

When winter begins, plants sense the temperature signal and set up the vernalization response. The expression of *FLC* is stably and transcriptionally silenced by the deposition of the repressive histone H3 lysine 27 tri-methylation (H3K27me3) modification in the chromatin, contributed by Polycomb repressive complex 2 (PRC2). Polycomb silencing of *FLC* has two distinct mechanistical steps (Yang et al., 2017). First, a subset of PLANT HOMEODOMAIN (PHD)-PRC2 components, including VERNALIZATION 2 (VRN2), the plant-homeodomain proteins VERNALIZATION INSENSITIVE 3 (VIN3), VRN5, and the PRC2 accessory protein INCURVATA 11 (ICU11) (Gendall et al., 2001; Sung and Amasino, 2004; Greb et al., 2007; Bloomer et al., 2020), are required to silence *FLC* by increasing the level of H3K27me3 in a Polycomb response element (PRE)-like region close to the *FLC* transcription start site during cold exposure (Yang et al., 2017). Second, the H3K27me3 methyltransferases CURLY LEAF (CLF) and the H3K27me3-binding protein LIKE HETEROCHROMATIN PROTEIN 1 (LHP1) bind to the first metastable locus to increase the enrichment of H3K27me3 when plants are returned to a warm environment (de Lucia et al., 2008). Therefore, the enrichment of repressive chromatin and the silenced expression of *FLC* establish the "vernalized memory" in the plant.

During vernalization, a pair of B3 transcriptional factors VIVIPAROUS1/ABSCISIC ACID INSENSITIVE 3 (ABI3)-LIKE 1 (*VAL1*) and *VAL2* play key roles in mediating silencing at *FLC* in *Arabidopsis* (Qüesta et al., 2016; Yuan et al., 2016). The sequence-specific readers of *VAL1*/*VAL2* not only directly bind to the *cis*-element which named Cold Memory Element (CME) at the nucleation region of *FLC* chromatin, but also can recognize the H3K27me3 repressive marker. Furthermore, VAL1 not only directly associates with LHP1 (PRC1 component) and the histone deacetylation complex, but also interacts with the apoptosis- and splicing-associated protein complex, resulting in stable silencing of *FLC* (Qüesta et al., 2016; Yuan et al., 2016). Importantly, three kinds of long noncoding RNAs (lncRNAs), including COOLAIR, COLDAIR, and COLDWRAP, function as key regulators of *FLC* silencing during vernalization (Swiezewski et al., 2009; Heo and Sung, 2011; Kim and Sung, 2017). Nevertheless, how the lncRNAs and VAL proteins act coordinately or separately to maintain a high level of H3K27me3 in *FLC* chromatin during vernalization is still unknown. However, *Lov-1*, a Northern Swedish *Arabidopsis* accession, due to its specific single nucleotide polymorphisms (SNPs) at the *FLC* loci, evolves an unstable epigenetic memory even after extremely long cold exposure and full spreading of H3K27me3 across the locus (Qüesta et al., 2020). This is similar to the situation in *Drosophila*. The loss of PRE in the *Drosophila* genome results in unstable H3K27me3 inheritance and *HOX* repression in the subsequent replication cycle (Coleman and Struhl, 2017; Laprell et al., 2017). Taken together, a high level of H3K27me3 is deposited on the nucleation region of *FLC*, and the expression level of *FLC* decreases as the cold exposure continues.

After returning to a warm environment, H3K27me3 spreads to the entire *FLC* chromatin through cell division and DNA replication, leading to the stable maintenance of the repressive state of *FLC*. In a warm environment, the level of H3K27me3 at *FLC* is maintained through a DNA replication-coupled mechanism, in which LHP1 plays a critical role in maintaining and spreading H3K27me3 at the *FLC* locus (Sung et al., 2006; Jiang and Berger, 2017; Yang et al., 2017). Therefore, the vernalized seedlings can remember the previous cold experience, endowing plants with the ability to flower properly in late spring (Michaels and Amasino, 1999). However, the silenced chromatin

state at the *FLC* locus must be "erased" and reprogrammed to the active state, so that the expression of *FLC* can be reactivated in the offspring and the memory can be transmitted to the next generation. The chromatin remodeling from paternity is always accompanied by the removal of H3K27me3 methyltransferase subunits, the activation of histone demethylation, and the deposition of H3 variants (Ingouff et al., 2010), subsequently resulting in decreased enrichment of H3K27me3 in sperm cells (Borg et al., 2020). The silenced *FLC* is maintained in the egg cells, but not in the sperm cells (Borg et al., 2020; Luo et al., 2020). Therefore, the memory of winter cold is inherited maternally and is meiotically stable in the process of the formation of female gametes (Borg et al., 2020; Luo et al., 2020).

Shortly after fertilization, the silenced *FLC* is reactivated in the proembryo by an embryo-specific transcriptional factor LEAFY COTYLEDON 1 (LEC1) (Tao et al., 2017). First, LEC1 specifically binds to the *CCAAT cis*-element in the promoter region of *FLC*. Second, *LEC1* engages with EARLY FLOWERING IN SHORT DAYS (EFS, an H3K36me3 methyltransferase) and SWR1c (the chromatin remodeling complex, also known as the PIE1 complex) to establish the active chromatin environment at the *FLC* locus (Tao et al., 2017). The active state enhances chromatin accessibility and promotes the recruitment of more factors to activate *FLC* expression in concert with *LEC1* in subsequent embryo development. Therefore, *LEC1* functions as a pioneer transcription factor and initiates *FLC* reactivation in embryogenesis (Kwon et al., 2009; Tao et al., 2017). Another two embryo-specific B3 transcriptional factors, LEAFY COTYLEDON 2 (*LEC2*) and FUSCA3 (*FUS3*), are also necessary for *FLC* activation in early embryogenesis (Tao et al., 2019). LEC2 and FUS3 bind to *CME* at the *FLC* locus and compete against *VAL1* and *VAL2*, which results in "diluted" H3K27me3 occupancy of the *FLC* chromatin. LEC2 and FUS3 specifically interact with FRI and recruit the active modifications to stably maintain *FLC* activation throughout the whole process of embryogenesis (Tao et al., 2019). During embryogenesis, demethylation of H3K27me3 by EARLY FLOWERING 6 (*ELF6*) is also necessary for *FLC* activation (Crevillén et al., 2014). When the transition from embryo to seedling is set up, the active H3K36me3 modification on the *FLC* chromatin is transmitted through mitotic cell division (Tao et al., 2017). Finally, the epigenetic memory of winter cold exposure is reactivated in the next generation.

2.2 Cold acclimation and deacclimation

Cold stress including chilling (0–15 °C) and freezing (<0 °C) can inhibit growth and leaf expansion, and even kill plants (Thomashow, 1999; Xin and Browse, 2000). Plants have evolved to bear cold by activating expression of cold responsive genes and by "memorizing" those signals in their daughter cells through cell division, thereby providing them with stronger tolerance to the next exposure (Byun et al., 2014; Zuther et al., 2019). This adaptive response is termed as cold acclimation, by which plants remember the first so-called priming in non-freezing temperatures and respond more effectively to the next freezing stimulus (Thomashow, 1999) (Fig. 1b).

Cold acclimation helps plants to survive better during long cold exposure, especially in the winters of cold zones. In *Arabidopsis*, plants usually need at least 7-d exposure at 4 °C to acquire their fully-primed competence, and this competence exists only in the true leaves of seedlings (Wanner and Junttila, 1999). In 7-d-old seedlings without true leaves, the induction of cold responsive genes does not induce significant freeze resistance (Leuendorf et al., 2020). The duration of cold memory in plants is associated with their physiological state and the duration of priming (Leuendorf et al., 2020). When the freezing resistance (an index determined by measuring the temperature that causes 50% electron leakage) of the plant is restored to the level before cold treatment in the primed plants, the cold memory disappears as that of in the non-primed plants (Leuendorf et al., 2020).

Cold acclimation refers to the process of training plants under non-freezing temperatures to make them more tolerant of the next freezing temperature, while the process of deacclimation always occurs after cold exposure. Deacclimation reduces the freezing tolerance acquired during acclimation, so that the plants can resume growth and development in the warm spring (Xin and Browse, 2000; Vitasse et al., 2014). Studies of cold acclimation and deacclimation have received increasing attention in recent years (Pagter et al., 2017; Vyse et al., 2020). It has been demonstrated that cold acclimation involving transcriptional memory can greatly improve subsequent freezing tolerance,

which is mediated by activating lipid metabolism, secondary metabolism, and the stress response (Zuther et al., 2019). A large set of genes is induced rapidly during cold acclimation, but most of these genes quickly restore their initial transcriptional levels when deacclimation begins (Pagter et al., 2017). Most such genes usually maintain at a high expression level after 12 h of deacclimation, but significantly down-regulate 24 h later (Vyse et al., 2020). Studies have revealed that epigenetic regulators such as members of the Polycomb group and Trithorax group are differentially expressed during cold acclimation and deacclimation (Pagter et al., 2017). This implies that epigenetic modifications may be involved in the regulation of transcriptional memory under cold acclimation and deacclimation.

C-REPEAT-BINDING FACTORS (*CBF*s) or DEHYDRATION-RESPONSIVE ELEMENT-BINDING FACTOR 1 (*DREB1*) genes are the master regulators in cold stress and cold acclimation (Stockinger et al., 1997; Liu et al., 1998). CBFs are highly and promptly induced by cold stress, and subsequently activate the expression of cold-regulated genes (*COR*s). This results in the accumulation of protective substances during cold acclimation and freezing stress (Jia et al., 2016). Post-translational modification is tightly associated with cold response and enriched in the chromatin of a large number of CORs such as *COR15A* and *COR47* (Zhu et al., 2008; Pavangadkar et al., 2010). When exposed to cold temperatures (4 °C), occupancy of H3K27me3 in the promoters of the freezing-induced gene *COR15A* and stress-responsive gene *ATGOLS3* decreases gradually (Lin and Thomashow, 1992; Taji et al., 2002). The level of H3K27me3 can be inherited through cell division (Kwon et al., 2009). However, the reduced H3K27me3 occupancy at *COR15A* and *ATGOLS3* during cold exposure is not accompanied by increased expression in a second cold exposure (Kwon et al., 2009), suggesting that H3K27me3 is not sufficient for such repression (Friedrich et al., 2019). In addition, the decreased level of H3K27me3 in *COR15A* is possibly caused by reduction in general occupancy of H3 (Vyse et al., 2020). Apparently, the detailed mechanisms of cold stress memory require further investigation.

Chilling and freezing are regarded as two distinct cold stresses for plants, but it is still largely unknown whether transcriptional regulation of the commonly activated genes like *COR*s differs in response to each of the two stresses. HISTONE DEACETYLASE 6 (HDA6) is also required for cold acclimation and freezing tolerance in *Arabidopsis*. Cold-treated *hda6* mutant exhibits reduced freezing tolerance compared with cold-treated wild-type plants, while non-cold-treated *hda6 m*utant shows no significant difference (To et al., 2011). HIGH EXPRESSION OF OSMOTICALLY RESPONSIVE GENE 15 (HOS15), a WD40-repeat protein, is involved in cold tolerance and histone deacetylation. HISTONE DEACETYLASE 2C (HD2C), a HD2 family deacetylase, has been identified as a partner of HOS15, which is associated with histone deacetylation in the chromatin of *CORs*. Under cold treatment, HOS15 and HD2C are degraded by the CULLIN4-based ubiquitin E3 ligase complex (Zhu et al., 2008). This results in an increased level of histone acetylation and switches the chromatin status from repressive to active in the chromatin of *COR*s (Park et al., 2018). POWERDRESS (PWR) is predicted to be a homolog of NCoR1 in plants and involved in a chromatin-modifying complex with HOS15 and HD2C (Wang and Brendel, 2004; Lim et al., 2020). PWR epigenetically regulates the expression of *COR*s and freezing tolerance in plants (Lim et al., 2020), and the enrichment of histone acetylation in the target chromatin can be removed within the first 24 h after returning to normal growth conditions (To et al., 2011). In summary, transcriptional expression of *COR*s is regulated by epigenetic modifications, and the chromatin states of *COR*s are dynamic and can be reversed during cold acclimation and deacclimation.

2.3 Heat stress

Global warming increases environmental temperatures, which may result in irreversible damage to plant growth and development (Hasanuzzaman et al., 2013). Heat stress (HS) can cause protein misfolding and accumulation of reactive oxygen species in plant cells (To et al., 2011; Suzuki et al., 2012). Plants respond to extreme or prolonged HS and exhibit intergenerational inheritance, but the effect is limited to a few non-stressed progeny generations (Lang-Mladek et al., 2010; Waqas et al., 2015). More and more evidence indicates that plants can acquire HS memory after a non-lethal heat exposure, which enables plants to respond quickly to recurring HS in the future (Molinier et al., 2006; Ohama et al., 2017). This phenomenon is also known as priming (Molinier et al., 2006; Ohama et al.,

2017). The effects of priming can be maintained or memorized for a few days or weeks, suggesting that genetic changes can be stored after this period (Bäurle, 2018). Transcriptional regulation of heat shock responsive proteins (HSRs), including heat shock proteins (HSPs) and heat shock transcription factors (HSFs), which are highly induced by heat treatment, plays a critical role in the process of HS memory acquisition (Fig. 1c).

In prolonged heat treatment, repetitive elements which associate with posttranscriptional gene silencing (PTGS) are reactivated. Heat-induced PTGS exhibits transgenerational epigenetic inheritance, which can be observed in subsequent generations grown under normal conditions (Zhong et al., 2013). Furthermore, release of heat-induced PTGS contributes to the formation of double-stranded RNA (dsRNA), which is required for producing small interfering RNAs (siRNAs). SUPPRESSOR OF GENE SILENCING 3 (*SGS3*) is also required for dsRNA formation in this process (Zhong et al., 2013). However, a temperature increase from 22 °C to 30 °C results in a significant reduction in the abundance of many *trans*-acting siRNAs that require dsRNA for biogenesis, since increased temperature reduces the protein abundance of SGS3. Moreover, over-expression of *SGS3* releases the warmth-triggered inhibition of siRNA biogenesis and reduces the transgenerational memory. HEAT SHOCK TRANSCRIPTION FACTOR A2 (*HSFA2*) is an important transcriptional factor specifically involved in HS memory (Charng et al., 2007; Liu et al., 2018). It plays an essential role in preventing and repairing the damage caused by HS, and in extending the duration of acquired thermotolerance in *Arabidopsis*. Therefore, *HSFA2* confers stronger resistance against subsequent challenges, even against normally lethal HS (Charng et al., 2007). Moreover, HSFA2 is required for the sustained accumulation of H3K4 methylation and active memory of HS in plants (Charng et al., 2007; Lämke et al., 2016). The heritable feedback loops of *HSFA2* and H3K27me3 demethylase relative of RELATIVE OF EARLY FLOWERING 6 (*REF6*) are essential for the establishment and transmission of thermomemory (Liu et al., 2019). Furthermore, the HSFA2-REF6 module activates the SGS3-interacting protein, which in turn degrades SGS3 and inhibits the biosynthesis of siRNA. This finding elegantly elucidates the detailed molecular mechanism of transgenerational thermomemory which ensures reproductive success and heat adaptation of plants. This mechanism involves a coordinated epigenetic network including histone demethylase, transcriptional factors, and siRNAs (Liu et al., 2019).

HS changes the global levels of histone acetylation and methylation in plants, especially in the chromatin of some *HSR*s. Histone H3K4 methyltransferases SET DOMAIN PROTEIN 25 (SDG25) and ARABIDOPSIS HOMOLOG OF TRITHORAX 1 (ATX1) are required for HS tolerance and recovery. They regulate and maintain the expression of *HSR*s through increasing H3K4me3 and decreasing DNA methylation at the target chromatin during stress recovery (Song et al., 2021). Disassembled nucleosomes are required for RNA *Pol*II recruitment, and the accessibility of *trans*-factors and the density of nucleosomes are directly associated with the transcriptional activity of target genes. Forward genetic screening has uncovered the key role of FORGETTER 1 (FGT1), which interacts with chromatin remodelers of the SWI/SNF and ISWI components in sustained heat treatment. FGT1, together with the chromatin remodelers BRAHMA (BRM), CHR11, and CHR17, is required for physiological HS memory by modulating nucleosome occupancy at memory loci during stress recovery (Brzezinka et al., 2016). Furthermore, FGT1 is required for the maintenance of high *HSFA2* expression after HS, suggesting that it functions as a central regulator to coordinate these different chromatin remodelers to regulate nucleosome occupancy in HS memory. Chromatin remodeling seems to have broader roles in the regulation of abiotic stress memory, as CHROMATIN ASSEMBLY FACTOR-1 (CAF-1) is also required for defense priming (Mozgová et al., 2015; Ding et al., 2020).

MicroRNAs are small RNAs that repress the expression of their target genes at post-transcriptional levels (Bartel, 2004), which play important roles in plant development and HS memory (Stief et al., 2014). *MicroRNA156* (*miR156*) promotes the sustained expression of HS-responsive genes during recovery after HS through attenuating the level of SQUAMOSA PROMOTER BINDING PROTEIN-LIKE (*SPL*), which are master regulators in developmental transitions (Stief et al., 2014). *MiR824* gradually accumulates in response to heat treatment, and its accumulation depends on the transcriptional activity of HSFA1 and HSFA2 transcription factors. Subsequently, *miR824* decreases the expression of its target gene AGAMOUS LIKE 16 (*AGL16*), which encodes a MADS-box transcriptional

factor and negatively regulates flowering time. The miR824-AGL16 module acts as a "post-transcriptional memory factor" to balance recurring HS and plant growth fitness (Szaker et al., 2019).

Post-translational modifications such as phosphorylation and sumoylation also contribute to the regulation of *HSR* expression and HS memory (Yoo et al., 2006; Wiese et al., 2021). FGT2 encodes a TYPE-2C PROTEIN PHOSPHATASE (PP2C) and interacts with PHOSPHOLIPASE D α2 (PLDα2). PLDα2 may alter the lipid composition of the cell membrane and activate signaling molecules to induce HS memory (Bargmann and Munnik, 2006; Abd-El-Haliem et al., 2012). Mutations of *FGT2* are specifically defective in HS memory, indicating that *FGT2* and *PLDα2* are essential for HS memory (Urrea Castellanos et al., 2020).

2.4 Thermomorphogenesis

Thermomorphogenesis is an adaptive response and refers to the process by which warm ambient temperatures (22–30 °C) below HS induce the production of the phytohormone auxin and cause abnormal growth such as early flowering, hypocotyl and petiole elongation, and leaf hyponasty in plants (Gray et al., 1998; Quint et al., 2016). Thermomorphogenesis is regarded as an acclimation process, tightly regulated by epigenetic modifications, which endows plants with stress memory to conquer a secondary stimulus (Fig. 1d).

PHYTOCHROME INTERACTING FACTOR 4 (PIF4), a bHLH transcription factor, is the central regulator of thermomorphogenesis, highly induced under warm temperatures and loss of *PIF4* would greatly repress thermomorphogenesis-related defects. Epigenetic modifications are indicated to be involved in the transcriptional regulation of *PIF4*. Warm ambient temperature leads to auxin-mediated hypocotyl elongation by affecting the histone methylation level of auxin biosynthetic and responsive genes. During warm temperatures, *PIF4* directly binds to the promoter of YUCCA8 (*YUC8*), a rate-limiting enzyme in auxin biosynthesis, and activates its expression, promoting hypocotyl elongation in *Arabidopsis* (Sun et al., 2012). The RNA-binding protein FLOWERING CONTROL LOCUS A (FCA), which can interact with a histone demethylase, recruit H3K4 demethylation in the chromatin of *YUC8* during warm temperatures, and dissociates *PIF4* occupancy from *YUC8* (Lee et al., 2014). The SEUSS (SEU) transcriptional regulator coordinates with *PIF4* and positively regulates hypocotyl growth by promoting H3K4me3 in the chromatin of *YUC8*, INDOLE-3-ACETIC ACID INDUCIBLE 6 (*IAA6*), and *IAA19* under warm temperatures (Huai et al., 2018). PICKLE (PKL), an adenosine triphosphate (ATP)-dependent chromatin remodeling factor, negatively affects the level of H3K27me3 at loci of *IAA19* and *IAA29* (Zha et al., 2017), but the exact mechanisms are unknown.

In addition to histone methylation, histone acetylation/deacetylation and chromatin remodeling also have prominent roles in thermomorphogenesis. When exposed to high ambient temperatures, HDA15 represses the expression of warm temperature-responsive genes and the hypocotyl elongation through directly interacting with LONG HYPOCOTYL IN FAR-RED LIGHT 1 (HFR1) (Shen et al., 2019), an antagonistic regulator of *PIF*s in thermomorphogenesis (Duek et al., 2004). However, HDA9 plays an opposite role to HDA15 (Shen et al., 2019). HDA9 is stabilized in response to high temperature and mediates histone deacetylation at the *YUC8* locus at warm temperatures. Nucleosomes with histone variant H2A.Z wrap DNA more tightly than other H2A nucleosomes and modulate gene transcription in a temperature-dependent manner (Kumar and Wigge, 2010). HDA9 permits net eviction of the histone variant H2A.Z from nucleosomes associated with *YUC8*, which promotes the subsequent binding and transcriptional activation of PIF4, and causes auxin accumulation in thermomorphogenesis (van der Woude et al., 2019). Furthermore, histone variant H2A.Z is suggested to be a plant thermosensor essential for the correct perception of ambient temperature (Kumar and Wigge, 2010). Mutants deficient in incorporating H2A.Z into nucleosomes exhibit a constitutive thermomorphogenic response. H2A.Z-containing nucleosomes provide thermosensory information that is used to coordinate the ambient temperature transcriptome, as H2A.Z confers distinct DNA-unwrapping properties on nucleosomes. However, whether H2A.Z-nucleosome eviction is a direct temperature consequence or is mediated indirectly by a temperature-responsive chromatin remodeling factor is still unknown.

H3K36me3 is involved in the regulation of temperature-induced alternative splicing (Pajoro et al., 2017). Alternative splicing has been identified as a "molecular thermometer" in plants, by which plants integrate temperature cues into developmental programs (Capovilla et al., 2015). H3K36me3 was previously

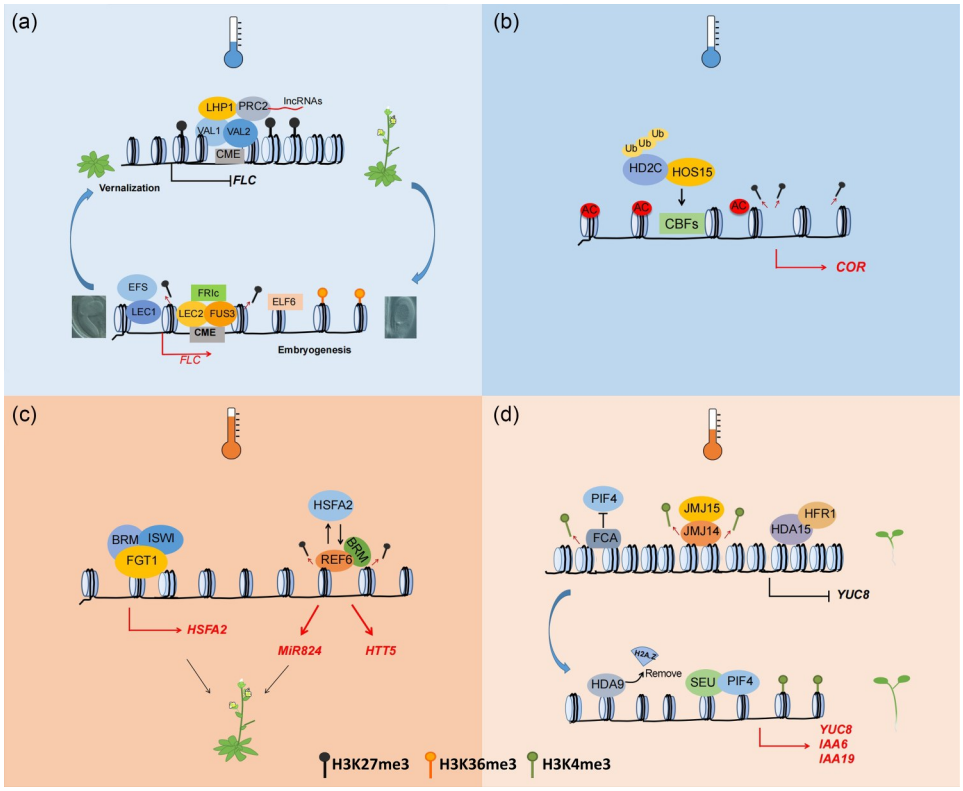

Fig. 1 Transcriptional memory and response to adverse temperatures in plants. (a) The establishment, maintenance, and reactivation of transcriptional memory during vernalization are regulated by *FLC* via a series of *cis*- and *trans*-factors, as well as coordination with active and repressive histone modifications. In the winter annual *Arabidopsis*, the expression of *FLC* is maintained at a high level to inhibit flowering in the vegetative stage. During vernalization, B3 transcriptional factors *VAL1*/*VAL2* and CME *cis*-element directly associate with LHP1, while lncRNA associates with PRC2 to mediate polycomb silencing at *FLC*. After returning to a warm environment, H3K27me3 is spread to the entire *FLC* locus through cell division and DNA replication, leading to the stable repression of *FLC*. During embryogenesis, the silenced *FLC* is sequentially reactivated by embryo-specific transcriptional factors *LEC1*, *LEC2*, *FUS3* and *ELF6*. Finally, the epigenetic memory of winter cold exposure is reactivated in the next generation. (b) Transcriptional memory of cold acclimation is associated with transcriptional expression of *COR*s and *CBF*s by histone methylation and acetylation. *CBF*s are the master regulators in cold stress and cold acclimation. *CBF*s are highly and promptly induced by cold stress, and subsequently activate the expression of *COR*s, resulting in the accumulation of protective substances during cold acclimation and freezing stress. Under cold treatment, HOS15 and HD2C are degraded by the E3 ubiquitin ligase complex, which results in an increasing level of histone acetylation and active expression of *COR*s. (c) Transgenerational thermomemory is regulated mainly by the *HSFA2-REF6*-siRNAs module and chromatin remodeler FGT1. *HSFA2* plays an important role in heat stress (HS) and acquired thermotolerance in *Arabidopsis*. The heritable feedback loops of *HSFA2* and H3K27me3 demethylase REF6 are essential for the establishment and transmission of thermomemory, which activates the SGS3-interacting protein to degrade SGS3 and inhibits the biosynthesis of siRNA. *FGT1*, together with the chromatin remodelers *BRM*, *CHR11*, and *CHR17*, is required for response to sustained heat treatment and physiological HS memory by modulating nucleosome occupancy on memory loci during stress recovery. (d) Transcriptional memory of thermomorphogenesis is associated with expression of the master transcriptional regulator PIF4 and auxin biosynthesis. During thermomorphogenesis, epigenetic modifications such as histone methylation/demethylation, histone acetylation/deacetylation, and chromatin remodelers contribute to the activity of *PIF4*, which directly binds to the promoters of *YUC8* and *IAA*s and provides plants with stress memory. *FLC*: FLOWERING LOCUS C; VAL1: VIVIPAROUS1/ABSCISIC ACID INSENSITIVE 3 (ABI3)-LIKE 1; CME: Cold Memory Element; LHP1: LIKE HETEROCHROMATIN PROTEIN 1; lncRNA: long noncoding RNA; PRC2: Polycomb repressive complex 2; H3K27me3: histone H3 lysine 27 tri-methylation; LEC1: LEAFY COTYLEDON 1; FUS3: FUSCA3; ELF6: EARLY FLOWERING 6; *COR*: cold-regulated gene; CBF: C-REPEAT-BINDING FACTOR; HOS15: HIGH EXPRESSION OF OSMOTICALLY RESPONSIVE GENE 15; HD2C: HISTONE DEACETYLASE 2C; *HSFA2*: HEAT SHOCK TRANSCRIPTION FACTOR A2; REF6: RELATIVE OF EARLY FLOWERING 6; siRNA: small interfering RNA; FGT1: FORGETTER 1; SGS3: SUPPRESSOR OF GENE SILENCING 3; BRM: BRAHMA; JMJ14: Jumonji C domain-containing protein 14; HDA15: HISTONE DEACETYLASE 15; PIF4: PHYTOCHROME INTERACTING FACTOR 4; *YUC8*: YUCCC8; SEU: SEUSS; *IAA*: INDOLE-3-ACETIC ACID INDUCIBLE; Ub: ubiquitin; AC: histone acetylation; FCA: FLOWERING CONTROL LOCUS A; HFR1: LONG HYPOCOTYL IN FAR-RED LIGHT 1.

assumed to promote opening of the chromatin, leading to a fast elongation rate that benefits splice site skipping (Zhou et al., 2014). H3K36me3 might serve as an anchor for the formation of the H3K36me3-MRG15 (MORF-RELATED GENE 15)-PTB (POLYPYRIMIDINE TRACT-BINDING PROTEIN) chromatin-adaptor system and recruit it to the nascent precursor messenger RNA (pre-mRNA) (Luco et al., 2010). Hence, temperature variation may be memorized in the chromatin landscape via H3K36me3 deposition, causing a specific splicing pattern (Pajoro et al., 2017). H3K4me3 demethylases are also involved in plant responses to elevated ambient temperature. The Jumonji C (JmjC) domain-containing protein 14 (JMJ14), as well as the other two H3K4me3 demethylases JMJ15 and JMJ18, regulates plant development and stress response redundantly (Yang et al., 2012). Mutation of *JMJ14* affects both the gene activation and repression programs of plant thermo-responses, which further indicates that H3K4 demethylases are involved in the plant response to elevated ambient temperatures (Cui et al., 2021).

3 Conclusions and perspectives

Climate change has widespread effects on the distribution and behavior of plant species, and extreme temperatures could markedly decrease global crop yields. Recent findings suggest that plants can respond quickly to changing temperatures through reprogramming gene expression and may even "memorize" recurring environmental events. The identification of genetic loci and molecular mechanisms involved in transcriptional memory may provide effective ways or strategies to breed temperature-tolerant crops. Understanding the mechanisms of the formation, maintenance, and resetting of stress-induced transcriptional memory will not only enable us to understand why there is a trade-off between plant defense and growth, but also enable the generation of stress-tolerant crops optimized for future climates.

Recent studies on the regulatory mechanisms of transcriptional memory of temperature changes have suggested the crucial role of complex epigenetic regulatory networks in these processes (Gong and Miller, 2013; Zentner and Henikoff, 2013; Zhong, 2016). Stress-induced transcription is precisely regulated by alterations to the chromatin to ensure proper expression in the given background. This regulation may be mediated by the dynamics of different kinds of epigenetic modifications in different developmental stages and cell types, and in response to environmental stimuli. To improve our knowledge of transcriptional memory, several opening questions are worthy of further investigation. Firstly, is the memory in plant cells gradual or digital? In individual seedlings, the transcriptional memory which plants use to respond to temperature signals is established gradually according to the duration of exposure, as illustrated by vernalization. However, what happens at the responsive loci in single cells of plants is still obscure. Using single-cell measurements and a digital paradigm, quantitative silencing of *FLC* under vernalization was shown to represent an ON/OFF switch in an increasing proportion of cells, which implies that the cells' autonomous digital switch and transcriptional memory are tightly correlated (Angel et al., 2011; Berry et al., 2015; Yang et al., 2017). Whether there are similar mechanisms affecting other memory events and genetic loci needs further elucidation. Secondly, how do treated or responsive plants perceive temperature signals, and how do they measure the length of treatment? These are two emerging issues in plant biology that remain to be explored. The establishment and duration of memory depend largely on activating transcriptional machineries such as histone acetylation, H3K4me3, and H3K36me3, while the mechanisms involved in maintaining such hyper-activation are less well understood. Whether the ability to activate priming is a constant feature available throughout the whole life cycle, or limited to specific developmental stages, organs, or tissues of plants, is unclear. As short-term and long-term memory transmissions may involve different mechanisms, further effort is needed to determine how environmental factors affect genomic flexibility, and whether and how acquired chromatin characteristics are inherited by the next generation to adapt to environmental changes. In the context of global climate change, studying whether and how stress memory is transmitted through cell divisions and across generations will be of interest for rationally breeding well-adapted crops to deal with unexpected stresses. Thirdly, many H3K27me3-targeted genes, which are stably repressed in non-stress conditions, are activated immediately after stress exposure, but the detailed mechanisms of activation and resetting epigenetic information during the temperature response

await further elaboration. Transcriptional reprogramming of *FLC* is tightly associated with the establishment and reactivation of vernalization in *Arabidopsis*. Whether there are similar reprogramming mechanisms after other temperature memory events needs further investigation. Finally, mechanisms of stress memory have been well established. For example, changes in signaling metabolites, alterations of primary metabolism, and the transmission of prions or prion-like proteins have also been found to associate with transcriptional memory (Zuther et al., 2019). Whether there are interactions between chromatin-dependent transcriptional memory and these chromatin-independent mechanisms is still unknown.

Understanding the underlying mechanisms in the model plant *Arabidopsis* will ultimately enable us to improve stress tolerance in crop species. However, it remains to be investigated whether the regulatory mechanisms are generally conserved between model plants and crop species. In conclusion, there remains a long way to go in gaining a comprehensive understanding of temperature response mechanisms in plants.

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Author contributions

Wei XIE, Qianqian TANG, and Fei YAN wrote the manuscript and prepared the figures. Zeng TAO contributed to the study design, writing and editing of the manuscript. All authors have read and approved the final manuscript and, therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Wei XIE, Qianqian TANG, Fei YAN, and Zeng TAO declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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