



Involvement of epigenetic factors in flavonoid accumulation during plant cold adaptation

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ARTICLE INFO

Keywords:

Flavonoids
Anthocyanins
Stress response
Cold acclimation
Chromatin modification
Stress memory

ABSTRACT

Plant responses to cold stress include either induction of flavonoid biosynthesis as part of defense responses or initially elevated levels of these substances to mitigate sudden temperature fluctuations. The role of chromatin modifying factors and, in general, epigenetic variability in these processes is not entirely clear. In this work, we review the literature to establish the relationship between flavonoids, cold and chromatin modifications. We demonstrate the relationship between cold acclimation and flavonoid accumulation, and then describe the cold adaptation signaling pathways and their relationship with chromatin modifying factors. Particular attention was paid to the cold signaling module OST1-HOS1-ICE1 and the novel function of the E3 ubiquitin protein ligase HOS1 (a protein involved in chromatin modification during cold stress) in flavonoid regulation.

1. Introduction

Cold stress is one of the most destructive factors determining crop loss (Thakur et al., 2010). Cold spells in April 2024 caused severe damage to fruit and vineyards in Europe, according to reports from multiple agencies. This year's damage is considered one of the most severe in the last century, causing significant financial losses. Crops such as soybeans, potatoes, rice, corn, tomatoes, and cotton are sensitive to cold, while temperate crops are better adapted to cold (Liu et al., 2022). Flavonoids are important factors for cold tolerance and freezing acclimation in plants, acting both at low temperatures above zero and at freezing temperatures below zero (Bruňáková et al., 2022; He et al., 2023).

Plants adapt to cold in one way or another, with varying degrees of success. Epigenetic factors play an important role in these processes, mainly through various chromatin modifications (Baier et al., 2019). However, the role of flavonoids in plant cold adaptation is not entirely clear in relation to chromatin-modifying effects. We have compiled literature data to establish whether such a connection exists. The relationship between flavonoids and cold stress is first discussed, followed by a discussion of cold adaptation signaling pathways involving chromatin-modifying factors, and then what is known about the

regulation of flavonoids in these pathways.

To distinguish the difference in the terms such as “acclimation” and “adaptation”, this article will be based on Gallusci et al. (2023) terminology, according to which **acclimation** is a non-heritable modification aimed at increasing the viability of a plant and **adaptation** is a heritable modification that allows a species to better adapt to its environment. In this review, we use also the term “memory”. An external stimulus puts the plant into a primed state, which is maintained even when the stimulus disappears. This condition allows the plant to respond to subsequent stressful events with a faster and stronger defensive response. **Memory** is defined as the ability to maintain a primed state caused by environmental stimuli, i.e. memory is the maintenance of a primed state over time (Charg et al., 2023). Thus, memory is part of plant adaptation strategy and an important component of natural epigenome plasticity (Lloyd and Lister, 2022).

While it is generally accepted that flavonoids play an important role in cold acclimation, their role in cold adaptation and cold memory is less clear. A recent review article summarized chromatin-modifying factors that could influence flavonoid biosynthesis associated with different stress conditions (Bulgakov, 2024). Surprisingly, there is little information about cold stress (Bulgakov, 2024), which prompts us to take a closer look at this factor, which has extremely damaging effects on crops

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<https://doi.org/10.1016/j.plaphy.2024.109096>

Received 13 June 2024; Received in revised form 26 August 2024; Accepted 3 September 2024

Available online 5 September 2024

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in both temperate and subtropical regions. If such mechanisms of plant resistance to cold as accumulation of carbohydrates and proline, membrane stabilization, maintenance of activity of the photosynthetic apparatus and normal redox balance are mobile, then accumulation of flavonoids (as secondary metabolites) would seem to be irreversible and cannot change under repeated stress. However, the life of a single plant and the long-term effects in the population must be considered. During the life of an individual plant, the content of flavonoids can change due to catabolic processes, which is typical for both anthocyanins (Zhao et al., 2021) and flavonol glycosides (Bozzo and Unterlander, 2021). In this case, flavonoid accumulation can be regulated by the so-called somatic stress memory representing a short-term memory, which duration is limited to one generation of organism (Lämke and Bäurle, 2017; Bäurle and Trindade, 2020; Gallusci et al., 2023). It is likely that when plant populations change over time, processes regulated by epigenetic factors may play an important role, providing a sustained increase (or decrease) in secondary metabolite levels (Li et al., 2024). Transgenerational stress memory represents a stress imprint that extends from one stressed generation of organisms to at least the second stress-free offspring generation (Liu et al., 2022). This type of memory is based on chromatin modifications stored during meiosis (Liu et al., 2022; Gallusci et al., 2023). Li et al. (2024) proposed that chromatin dynamics plays an integral role in the production of secondary metabolites by combining the effects of transcription factors and regulatory elements. They highlighted the role of DNA methylation and histone modification, the action of non-coding RNAs and processes of biomolecular condensation in the epigenetic regulation of secondary metabolism. Pioneer transcription factors (so-called “bookmarks”), which represent a special case of epigenetic inheritance, also perform an important function (Li et al., 2024). The names of the proteins used in this study are presented in accordance with the recommendations of the UniProtKB database.

2. Flavonoids and cold acclimation

The role of flavonoids in cold acclimation is currently being considered in terms of mitigating oxidative stress by ROS scavenging due to the presence of hydroxyl groups in the aglycone moiety (Nakabayashi et al., 2014) and maintaining photoprotection (Liu et al., 2020). The antioxidant properties of flavonoids are due to the presence of a catechol moiety in ring B, a C2–C3 double bond conjugated to a C4-oxo group in ring C, and a C3-hydroxyl group (Naróg and Sobkowiak, 2023). Flavonoids can complex metal ions, thus preventing the formation of reactive oxygen species (ROS), directly capture $^1\text{O}_2$ and inhibit lipid peroxidation by trapping lipid alkoxy radicals, and they are oxidized by peroxidase and function in the H_2O_2 -scavenging phenolic/AsA/POD system (Wang et al., 2024). Therefore, flavonoids, acting together with other non-enzymatic antioxidant substances, play an important role in stress acclimation (Wang et al., 2024). Leaves with higher anthocyanin content show relatively less degradation of chlorophyll and PSII reaction centers, which helps protect the photosynthetic apparatus and support carbohydrate metabolism necessary for increased cold tolerance (Liu et al., 2020). Flavonols regulate IAA signaling by inhibiting auxin transport proteins and regulate abscisic acid (ABA) signaling by counteracting ABA-induced stomatal closure (reviewed by Brunetti et al., 2018, 2019; Daryanavard et al., 2023). Brunetti et al. (2019) have proposed an interesting hypothesis that flavonols may modulate the activity of protein kinases (in particular, from the ABA pathway), similar to their activity in animals.

The biosynthesis and intracellular distribution of carbohydrates and proline, maintaining the activity of the photosynthetic apparatus and normal redox balance play an important role in cold tolerance (Hoermiller et al., 2017; Fürtauer et al., 2019; Liu et al., 2020). During acclimation to cold, extensive relocation of primary metabolites occurs inside the cell, with the movement of sugars into plastids, and ornithine and amino acids into the cytosol (Hoermiller et al., 2017). Flavonoids are synthesized in the cytosol and transported into the vacuole or to

other cell compartments (including cell-to-cell basipetal movement in epidermal layers), where they function as active molecules (Zhao, 2015). Flavonoid transport via vesicle trafficking is well studied and sequestration of flavonoids involves collaboration of vesicle trafficking with transporters and glutathione S-transferases (Petrucci et al., 2013; Zhao, 2015). However, it is unknown whether cold affects the intracellular sequestration of flavonoids, similar to the behavior of primary metabolites.

The relative contribution of flavonoids to cold tolerance appears to vary among plant species and is determined in each case by plant type and environmental conditions. Such specific case was described by Bruňáková et al. (2022) using cold-induced polyphenolic profiles of ten *Hypericum* species. The authors classified *Hypericum* plants to ‘freezing tolerant’ (FT) species, which tolerate the extracellular ice formation, and ‘freezing sensitive’ (FS) species. Ability of FT plants to tolerate ice crystallization was correlated with high basal levels of flavonols and flavonol glycosides, such as naringenin, amentoflavone, quercetin and its glycosides, and kaempferol-3-O-glucoside. In contrast, FS plants did not produce substantially elevated basal level of flavonoids and induced resistance to freezing by maintaining the functional photosynthetic apparatus and integrity of cell membranes.

3. Case studies in which flavonoid accumulation improved cold tolerance

Numerous reports indicate that flavonoids (anthocyanins, flavonols and their glycosides) accumulate in plants in response to cold stress and protect plants from cold. A detailed study by Schulz et al. (2016) used 19 mutant *Arabidopsis* lines in which various stages of flavonoid biosynthesis were disrupted. In mutant lines, resistance to freezing either decreased or remained the same. The authors found that flavonoids are induced in response to cold, and when one of the branches of biosynthesis leading to either anthocyanins or flavonols is blocked, flavonols compensate for the loss of anthocyanins, and *vice versa*. Freezing tolerance was increased in the line overexpressing *PAP1* (encoding the transcription factor MYB75). Mutations in the flavonoid biosynthetic pathway had little effect on primary metabolism (Schulz et al., 2016).

Bamboo leaves (*Phyllostachys edulis*) tolerate cold winters in south-east China (Wang et al., 2022). Unlike the cold-sensitive bamboo species *Bambusa ventricosa*, *Phyllostachys edulis* concentrates a larger pool of antioxidants, including flavonoids (mainly juglalin, i.e. kaempferol 3-O-arabinoside). The authors note that cold stress tolerance of *Phyllostachys edulis* leaves is based not only on flavonoids, but to a greater extent on increased levels of glutathione and trehalose (Wang et al., 2022). In plants of another species, called Ma bamboo (*Dendrocalamus latiflorus*), the biosynthesis of anthocyanins was activated by heterologous expression of the *Lc* gene encoding the transcriptional activator bHLH (Xiang et al., 2021). The cold resistance of bamboo plants transformed with the *Lc* gene increased due to the accumulation of cyanidin and peonidin derivatives; in addition, the plants became resistant to drought.

In red orange, anthocyanin content and expression of related genes were significantly higher in samples subjected to short-term cold induction than in control samples (Lo Piero et al., 2005; Crifò et al., 2012; Lo Piero, 2015). This group suggested different mechanisms of regulation of early flavonoid biosynthetic genes *CHS*, *CHI*, *F3H* and *FLS* and late genes (*F3'H* and *DFR*), as well as an important role of NAC transcription factors in anthocyanin regulation under cold conditions.

MYB transcription factors may combine cold acclimation processes and flavonoid biosynthesis. MYB88 and MYB124 positively regulated freezing tolerance and cold-responsive gene expression such as cold shock domain-containing protein 3 (CSP3) and protein CCA (protein CIRCADIAN CLOCK ASSOCIATED 1) in both apple and *Arabidopsis* (Xie et al., 2018). Accordingly, these MYB transcription factors promoted anthocyanin accumulation and H_2O_2 detoxification in response to cold (Xie et al., 2018). Transgenic apple calli and *Arabidopsis* plants with

overexpression of *MdMYB23* also exhibited increased cold resistance (An et al., 2018). Likewise, a MYB-related transcription factor from *Lilium lancifolium* was overexpressed in *Arabidopsis* and was shown to be responsible for cold resistance (Yong et al., 2019). The MYB transcription factors described above mainly activate anthocyanin biosynthesis in response to cold, and the same effect was noted for flavonols. For example, in Chinese cabbage (*Brassica campestris* ssp. *chinensis*), the content of flavonols (mainly quercetin and kaempferol) increased after cold stress due to the activation of the MYB transcription factor BcMYB111 (Chen et al., 2023). These authors identified a direct pathway in the formation of cold resistance, such as CBF → MYB → flavonoid biosynthetic enzymes.

Moderate cold treatment increased the levels of flavonoids cynaroside and graveobioside A in chili and bell pepper (*Capsicum* cultivars) leaves (Genzel et al., 2021). Sudheeran et al. (2018) compared the cold tolerance of mango fruits with green or red coloration. Red fruits contain more anthocyanins and flavonols and are therefore more resistant to cold stress compared to green fruits. Flavones and flavonols play an important role in cold tolerance in trees such as *Cryptomeria fortunei* (Zhang et al., 2022). It was also found that the increased cold tolerance of the turf grass *Zoysia japonica* (biotype YN-9) is due to the increased content of anthocyanins (Jin et al., 2022).

Is flavonoid accumulation a cause or a consequence of cold tolerance? By default, it is assumed that activation of flavonoid biosynthesis during cold stress is the cause of tolerance, similar to other processes of protective reactions (accumulation of carbohydrates, stabilization of membranes, etc.). Apparently, it can be both a cause and a consequence. If one plant species initially contains a large amount of flavonoids, and another contains a small amount, then the species with a high content could experience multiple stresses and thus prepare for new stresses over the years. Then this is a consequence. Such examples are described in this section (Wang et al., 2022; Sudheeran et al., 2018; An et al., 2018; Jin et al., 2022). Examples of flavonoid induction in response to cold or through genetic engineering have also been described, where increasing flavonoid content has resulted in increased cold resistance (Xiang et al., 2021; Xie et al., 2018; Yong et al., 2019; Chen et al., 2023). Thus, two strategies are implemented in parallel: a conservative one, costly for the plant due to high energy costs for flavonoid biosynthesis (consequence) and an inducible one (cause).

These examples show that flavonoids play an important role in protecting plants from low temperatures, both above and below zero. It is then necessary to discuss how flavonoids, cold, and chromatin modifications may be related. Below, we describe cold signaling systems important for epigenetic control, mediated primarily through chromatin modifications, and provide additional insight into the problem of memory.

3.1. Cold tolerance signaling pathways

3.1.1. OST1-HOS1-ICE1 module and CBFs

Cold tolerance signaling pathways include the best-known cold tolerance module SnRK2.6/OST1-HOS1-ICE1, which controls cold tolerance through the dehydration-responsive element-binding proteins (CBFs/DREBs), which drive the expression of cold-responsive (*COR*) genes, thereby ensuring the functioning of the CBF-*COR* cold signaling pathway (Ding et al., 2020; Guo et al., 2018; Kidokoro et al., 2022). In this module, OST1 activates ICE1 (inducer of CBP expression 1), and then ICE1 induces *CBF1*, *CBF2*, and *CBF3* by binding to gene promoters (Kim et al., 2015). The pleiotropic regulator HOS1 (E3 ubiquitin-protein ligase; synonym: high expression of osmotically responsive genes 1) is required for adaptation of plant development to both short-term cold stress and freezing through the regulation of ICE1 protein abundance (Dong et al., 2006; Ding et al., 2015; Ye et al., 2019). HOS1 is currently considered a key integrator of developmental processes and temperature information in response to acute signals (MacGregor and Penfield, 2015); its role in flavonoid biosynthesis is described below. The module

HOS1 –|| ICE1 ← OST1 is shown in Fig. 1.

The interaction of the signaling pathways based on the HOS1 –|| ICE1 ← OST1 module and the light-dependent cold signaling is of particular interest for plant bioengineering. We will consider this aspect in more detail in the next subsection; here we note one important issue about the possible cooperation of ICE1 and transcription factor HY5 (long hypocotyls 5), which is the main mediator of photosensitive cold adaptation.

It would seem that both ICE1-dependent and HY5-dependent pathways operate independently, since ICE1 and HY5 do not physically interact and do not have common interaction partners; at least, there are currently no reports of such interactions in databases and literature (Fig. 1). However, such interaction may be represented through the ABA signaling system, where HOS1 may be an important connecting component. Signaling through the ABA pathway is considered by many authors to be an essential component of cold resistance; partly this resistance is formed through flavonoids (Brunetti et al., 2018, 2019; He et al., 2023; Daryanavard et al., 2023). The intersection of ICE1 and HY5 in cold acclimation could occur via critical regulator of the ABA pathway ABI5 (protein abscisic acid-insensitive 5), which can serve as a concentrator of ICE1, PIF4, and HY5 signaling (Bulgakov and Koren, 2022). ABI5 receives signals from these proteins to regulate *RbohD* expression and H₂O₂ level to establish cold protection, as shown by Wang et al. (2018). ICE1 physically associates with ABI5 and antagonizes its transcriptional function by concurring with G-box type *cis* elements in promoters of responsive genes (Hu et al., 2019). Taken together, these data imply that ICE1 and HY5 may potentially overlap in regulating ROS balance to mediate cold protection. Currently, this is an intriguing hypothesis that consistently explains the complex interactions of cold acclimation pathways at the intersection of ABA, light, and ICE1 signaling (Fig. 1).

3.1.2. Cold-light signaling system and flavonoids

The light signaling system plays an important role in cold tolerance, mainly acting through phytochrome phyB, transcription factor HY5 and components of the circadian clock (Roerber et al., 2021), as shown in Fig. 2. Phytochrome-interacting factors (PIFs) also participate in these interactions, because CBF proteins interact with phyB and PIF3 causing degradation of PIF1, PIF4 and PIF5 which releases *COR* genes from PIF repression (Jiang et al., 2020a; Roerber et al., 2021). PhyB mediates shade avoidance and induces a classical red light (R)/FR-reversible response, and this light quality-dependent regulation is sufficient to increase *CBF* expression and confer freezing tolerance (Franklin and Whitelam, 2007). It has also been established that cold stress induces *CBF* gene expression, and accumulated CBF proteins interact with PIF3. This interaction prevents the degradation of PIF3 and phyB proteins (Jiang et al., 2020a). Cold-stabilized phyB promotes *COR* gene expression to enhance freezing tolerance (Jiang et al., 2020a).

HY5 plays a key role in the connection between anthocyanin biosynthesis and light (Bulgakov et al., 2017) and activates anthocyanin accumulation under cold conditions by inducing the expression of *CHS*, *CHI*, and *FLS* (Catalá et al., 2011). It was suggested that HY5 induces cold acclimation in *Arabidopsis* through CBF- and ABA-independent pathways, mediating the induction of about 10% of all *Arabidopsis* *COR* genes (Catalá et al., 2011). The author's model showing that HY5 couples cold and light signaling through the induction of anthocyanin biosynthesis to reduce the accumulation of reactive oxygen species (ROS) is now generally accepted. Subsequent studies revealed that ROS levels are regulated by HY5 during cold acclimation not only due to the accumulation of anthocyanins, but also due to the activation of NADPH oxidases at the transcriptional and posttranscriptional levels (Wang et al., 2018). Wang et al. (2018) showed the existence of a phytochrome-mediated HY5-ABA-ROS signaling pathway (more precisely the HY5-ABI5-RBOH1 pathway), which avoids cold-induced photoinhibition by inducing photoprotection. Cold-acclimated plants elevated ROS levels and showed increased expression of *Rboh1* and NADPH oxidase activity with concomitant upregulation of the

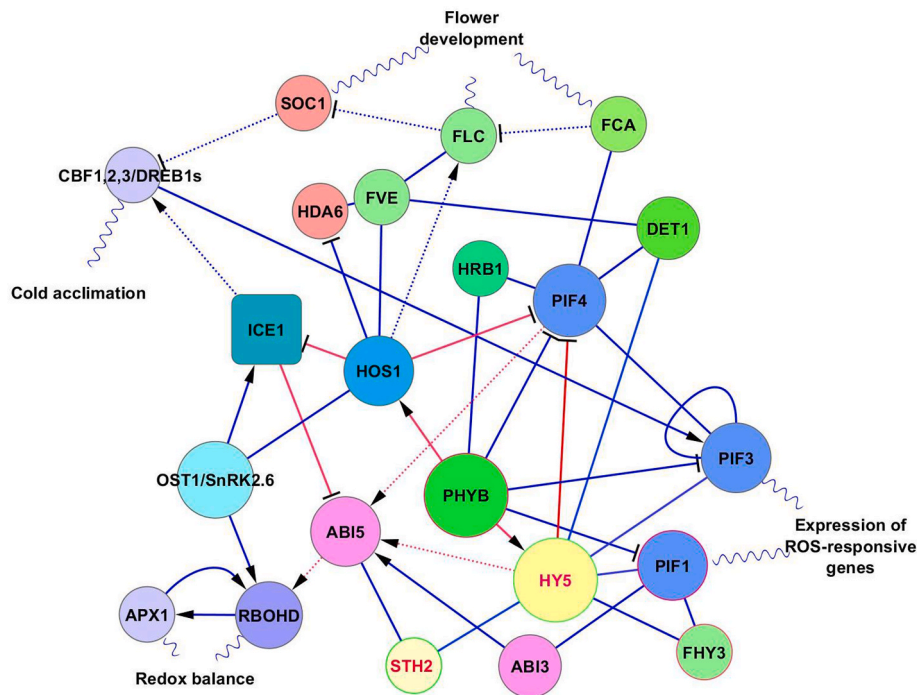


Fig. 1. HOS1 directly or indirectly influences numerous plant signaling modules. The interaction of HOS1 with ICE1, light signaling proteins, and *FLC* transcriptional activation is presented. The figure was built in the Cytoscape program based on the PAIR interactome database, as well as literature data. In the figure, solid lines show protein-protein interactions, and dotted lines show transcriptional activation of genes. Proteins of the light signaling system are highlighted in green or yellow (when they are involved in interaction with the signaling system of abscisic acid). PIF transcription factors are highlighted in blue. Wavy lines show which biological processes influences HOS1. PhyB activates HOS1, and HOS1 subsequently inhibits the transcriptional activity of the phytochrome-interacting transcription factor PIF4 (Kim et al., 2017). PIF4 itself also has a wide range of temperature- and ROS-sensitive targets and, when inhibited by HOS1, is involved in HOS1-mediated mechanisms. In addition, activated CBF/DREB activates PIF3, which may influence the functioning of antioxidant defense through the PIF1/PIF3-HY5/HYH module (Chen et al., 2013; Toledo-Ortiz et al., 2014). HOS1 binds to *FLC* chromatin and activates *FLC* transcription. HOS1 induces *FLC* expression by attenuating the effect of FVE by interacting with HDA6 (Jung et al., 2013). At this junction, FVE is required for the HOS1-mediated transcriptional activation of *FLC*. The link between flowering and cold resistance is due to the activation of the cold resistance module CBF/DREB-COR by the *FLC*-SOC1-CBF pathway. Flowering-independent cold resistance is provided by the HOS1-ICE1-CBF module. Abbreviations: ICE1, inducer of CBP expression 1; HOS1, E3 ubiquitin-protein ligase HOS1; ABI3/5, ABA insensitive 3/5; OST1/SnRK2.6, SNF1-related protein kinase 2.6; CBF1,2,3/DREB1s, dehydration-responsive element-binding proteins; PIFs, phytochrome-interacting transcription factors; PHYB, phytochrome phyB; HRB1, dehydration-induced 19 homolog 7 HRB1/DI19-7; HY5, transcription factor HY5 (protein long hypocotyls 5); FHY3, far-red elongated hypocotyls 3; STH2, B-box zinc finger protein 21/BBX21; RBOHD, respiratory burst oxidase homolog protein D (NADPH oxidase RbohD); APX1, ascorbate peroxidase 1; DET1, light-mediated development protein DET1; FVE, WD-40 repeat-containing protein MSI4; HDA6, histone deacetylase 6; FCA, flowering time control protein; FLC, MADS-box protein flowering locus C; SOC1, MADS-box protein SOC1.

expression and activity of antioxidant enzymes (Zhou et al., 2012), resembling the effect described as “RbohD ↔ APX1 loop” (Davletova et al., 2005) when the generation of ROS by NADPH oxidase is compensated by the activity of antioxidant enzymes. This process is necessary for stress acclimation (Davletova et al., 2005; Choudhury et al., 2017).

The cold-light signaling system is tightly connected with flavonoid biosynthesis. In particular, phytochromes generally regulate light-induced anthocyanin accumulation under different stress conditions. The most efficient increase in anthocyanins was observed with blue light irradiation and was mediated by cryptochromes (Bulgakov et al., 2017). HY5 physically interacts with transcription factors and directly affects the expression of numerous genes, including flavonoid-specific genes (Bulgakov et al., 2017; Xiao et al., 2022). PIF3 regulates anthocyanin biosynthesis in a HY5-dependent manner (Gangappa and Botto, 2016). A connection between flavonoids and circadian cycling is mediated by the CCA1 and other clock oscillators (Hildreth et al., 2022). RVE proteins (proteins REVEILLE) could enhance anthocyanin gene expression by directly binding to the promoters of anthocyanin biosynthesis genes (Pérez-García et al., 2015).

3.1.3. Heat shock factors

The role of heat shock factors (HSFs) under conditions of plant acclimation to cold is just beginning to be developed. Although HSFs

were originally attributed to thermal adaptation, certain genes have been found to respond to cold exposure (Andrási et al., 2021). These are *HSA4a*, *HSA6b*, *HSA8*, and *HSFC1* genes of *Arabidopsis*, of which *HSA6b* have the highest expression induced by osmotic and cold stress among *Arabidopsis* HSF genes (Swindell et al., 2007; Huang et al., 2016). In rice, seven of 25 HSF genes responded to cold (Andrási et al., 2021). Under cold conditions, HSA1 interacts with the regulatory protein NPR1 (known as the systemic acquired resistance regulator), leading to the induction of HSA1-regulated genes and cold acclimation (Olate et al., 2018). The current model for thermal adaptation suggests that the priming signal activates HSA1 proteins that increase the expression of the *HSA2* and *DREB2A* genes. *DREB2A*, in turn, promote *HSA3* expression, thereby integrating various signals into stress memory via *HSA3* (Friedrich et al., 2021). Freezing stress dramatically increased the expression of *HSF3* (Wang et al., 2020a), suggesting that HSF proteins may play similar role in cold adaptation. The involvement of HSF in flavonoid biosynthesis has recently been discovered (Wang et al., 2020b; Naik et al., 2023), and these factors are of interest because HSFs are classical pioneer factors in the generation of memory in both plants and animals (Friedrich et al., 2021). The HSF–DREB–MYB transcriptional regulatory module discovered by Naik et al. (2023) is particularly interesting because it couples the CBF/DREB cold response pathway and flavonoid biosynthesis.

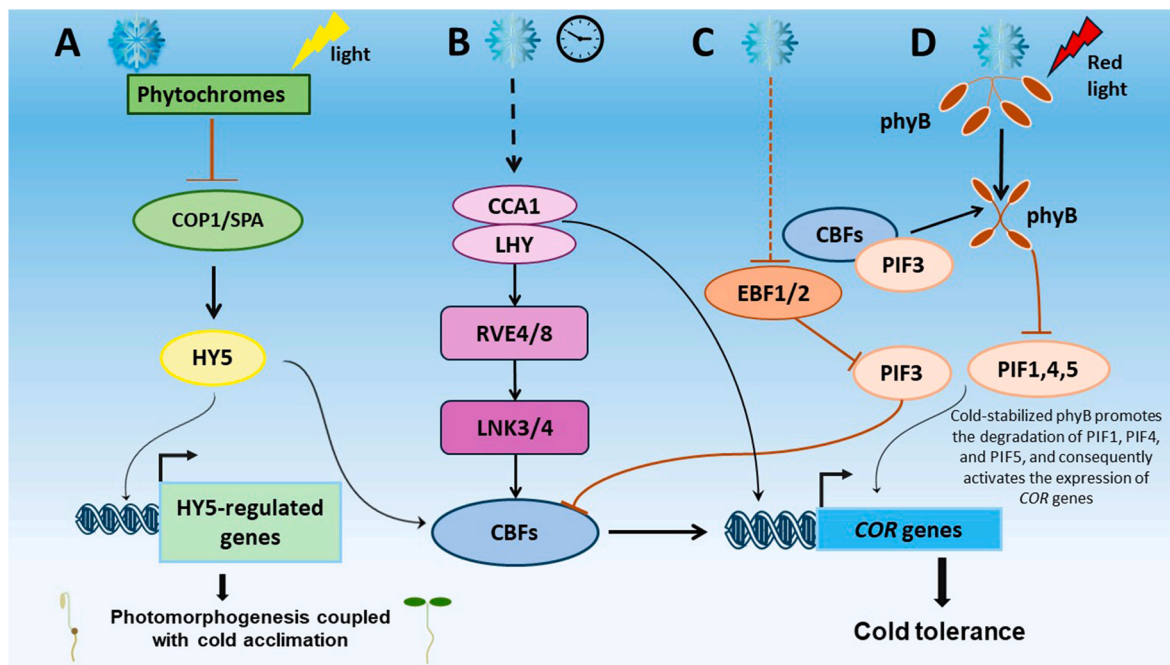


Fig. 2. A simplified model of the cold response during plant's response to light. **A.** Light signals are sensed by photoreceptors, which include the red and far-red light-sensing phytochromes (phyA to phyE), the blue/ultraviolet UV-A-perceiving cryptochromes (CRY1 and CRY2), and the UV-B-sensing photoreceptor UVR8. In response to light, phytochromes inactivate COP1-SPA complexes and induce degradation of negative regulators of photomorphogenesis, PIFs. These events promote photomorphogenesis by establishing the dynamic protein module PIF1-COP1/SPA1 and triggering HY5-mediated light signaling. **B.** The MYB-related transcription factors LHY/CCA1 serve as a link between the circadian clock and cold response. CCA1 and LHY suppress the expression of *CBF1/DREB1B*, *CBF2/DREB1C*, and *CBF3/DREB1A* under unstressed conditions and are rapidly degraded in the conditions of cold stress, acting indirectly as positive regulators of cold stress response. Under cold stress conditions, RVE4 and RVE8 accumulate in nuclei and activate the phosphorylation of proteins LNK3 and LNK4. This activates the expression of many cold-inducible genes, including *CBFs* (see also Kidokoro et al., 2021, 2023). **C.** At a normal temperature, PIF3 is degraded by EBF1/2 in the light, whereas EBF1/2 proteins are degraded and PIF3 protein is stabilized in darkness. Low temperatures negatively affect the degradation of PIF3 by EBF1/2 regardless of the light conditions, leading to the accumulation of PIF3, which directly binds to the promoters of *CBF* genes and suppresses their expression (Jiang et al., 2017). **D.** PIF3 generally is a negative regulator of the CBF pathway and freezing tolerance, but interactions in this pathway are more complex: the cold-induced CBF-PIF3 interaction enhances freezing tolerance by stabilizing phyB (Jiang et al., 2017, 2020a). Cold-stabilized phyB promotes the degradation of PIF1, PIF4, and PIF5, thus activating the expression of *COR* genes and enhancing freezing tolerance in *Arabidopsis*. Abbreviations: PIFs, phytochrome-interacting transcription factors; HY5, transcription factor HY5; LHY, protein late elongated hypocotyl; CCA1, circadian clock associated 1; LNK3 and LNK4 (night light-inducible and clock-regulated 3/4); SOC1, MADS-box protein SOC1; RVE4/8, proteins REVEILLE 4 and 8 (Myb transcription factors LHY/CCA1-like); EBF1/2, EIN3-binding F-box proteins 1 and 2.

3.2. E3 ubiquitin-protein ligase HOS1 regulates flavonoid biosynthesis

Then the *HOS1* gene was inhibited by T-DNA insertion mutagenesis (*hos1-3* plants; Lazaro et al., 2012) or via CRISPR/Cas9 technology (*hos1^{cas9}* plants; Shkryl et al., 2021), the resulting *hos1* mutant *Arabidopsis* plants showed increased resistance to cold treatment. Increased cold resistance was caused by increased abundance of ICE1 with subsequent activation of the CBF-COR cold acclimation pathway. At the same time, *hos1^{cas9}* plants accumulate greater amounts of flavonoids compared to control plants (Shkryl et al., 2021). The levels of total flavonoids were up-regulated by 1.2–4.2-fold in different *hos1^{cas9}* plant lines and this effect was mainly due to the rise in kaempferol derivatives content. In particular, the content of kaempferol hexose dideoxyhexose increased 7-fold. Levels of quercetin and isorhamnetin derivatives were also upregulated. The increase in flavonoid levels in the *hos1* mutants was caused by increased expression of genes encoding transcription factors such as *MYB12*, *TT8* and *PAP1*. The biosynthesis of aliphatic glucosinolates, especially methyl-thioalkyl and methyl-sulfinylalkyl derivatives was suppressed, mainly due to the repression of *MYB28* and *MYB76* (Shkryl et al., 2021).

These results are interesting, because despite the large amount of data on the effect of protein ligases on the biosynthesis of flavonoids (mainly anthocyanins), there is still little data on the relationship of ligases with cold and flavonoid biosynthesis. Post-translational regulation of transcription factors involved in flavonoid biosynthesis, controlled by E3 ubiquitin-protein ligases, is well known. For example, E3 ubiquitin-

protein ligases suppressed the accumulation of anthocyanins in the dark (E3 ubiquitin-protein ligase COP1; Maier et al., 2013), as well as regulate anthocyanin accumulation in response to auxin and ethylene signaling (Li et al., 2023) and promote gibberellin-activated anthocyanin biosynthesis (An et al., 2023). E3 ubiquitin-protein ligase RHA2b, which is involved in responses to salt and osmotic stresses, positively regulates anthocyanin biosynthesis in *Arabidopsis* (Zhou et al., 2024). Flavonols can also be regulated by ligases such as COP1 through the dark-dependent repression of *MYB12* (Bhatia et al., 2021). It should be noted that there were no data on the simultaneous regulation of flavonoids and cold response by E3 ubiquitin-protein ligases, so the report by Shkryl et al. (2021) is the first in this regard. Both cold tolerance and anthocyanin biosynthesis are also regulated by another class of ligases, namely the SUMO E3 ligase MdsIZ1, which helps stabilize MdMYB1, a key regulator of anthocyanin biosynthesis in apple (Zhou et al., 2017; Jiang et al., 2022).

HOS1 not only acts as ligase, but also acts as a transcriptional regulator (MacGregor and Penfield, 2015). It is unknown whether *HOS1* ubiquitin-protein ligase activity itself or the ability of *HOS1* to act as a transcriptional regulator might play a role in *HOS1*-mediated flavonoid regulation. The above data show how ligase activity can affect the biosynthesis of flavonoids, but there is also the possibility of regulation through mediating transcriptional activity of signaling components. The cold response and flavonoid biosynthesis could be activated through components of the light signaling system. As indicated above, *HOS1* is recruited to gene promoter regions via its interaction with DNA-binding

proteins by forming HOS1-PIF4 protein complex on the target gene locus, including loci for anthocyanin biosynthesis. By this mechanism, HOS1 inhibits the transcriptional activity of PIF4 (Kim et al., 2017). PIF4 regulates anthocyanin biosynthesis (Liu et al., 2021), and modulation of its transcriptional activity by HOS1 would lead to a change in anthocyanin content. Likewise, PIF4 is involved in cold stress response (Pan et al., 2021); in other words, both processes are regulated by HOS1-PIF4 interaction. The version of simultaneous regulation of cold response and flavonoid biosynthesis through ROS metabolism seems also promising, given that HY5 has a positive effect on both of these functions (Gangappa and Botto, 2016). Indeed, evidence suggests that HOS1 is

required to maintain ROS homeostasis under cold conditions as well as under intense light by preventing over-induction of ROS-mediated defense mechanisms (Gorpenchenko et al., 2023). The signaling components are currently unknown, as there is no direct interaction between HOS1 and ROS-generating or ROS-detoxifying enzymes (a hypothetical signal chain looks like the one shown in Fig. 1).

3.3. Chromatin modifications involved in plant response to cold

Heritable modifications include epigenetic mechanisms, which often result in memory to previous stress. Chromatin modifications under the

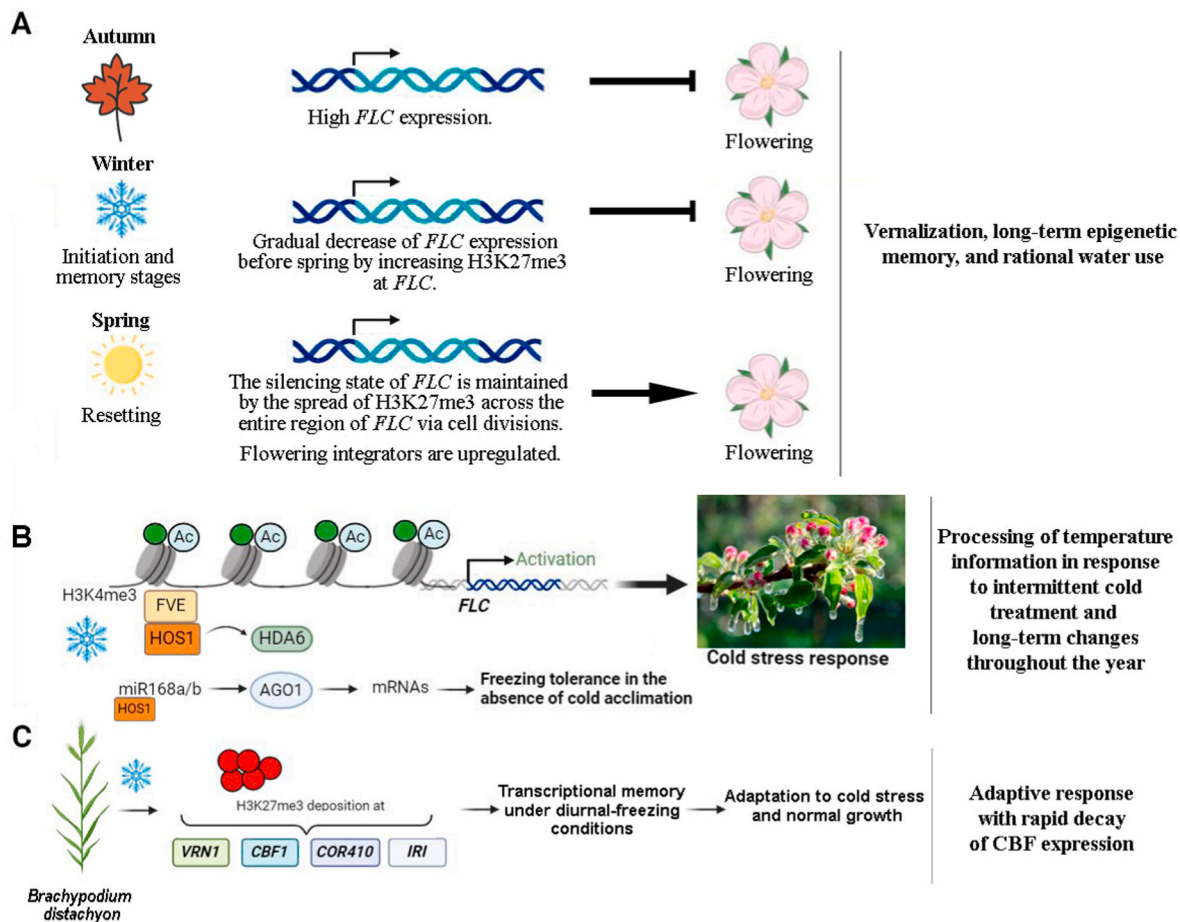


Fig. 3. General presentation of epigenetic factors involved in plant cold responses. Perception of low temperature by plants includes two sequential processes, such as sensing the chilling to induce cold acclimation, and counting the dosage of vernalization (induction of flowering process by exposure to the prolonged cold) for future developmental transitions. **A.** Vernalization is divided into three stages: vernalization initiation by cold exposure, vernalization memory, and vernalization resetting. In *Arabidopsis*, *FLC* is tightly controlled by chromatin modifications occurred via histone modifications. During initiation, the *cis*-acting cold memory region at *FLC* operates with the bivalent active histone marks H3K4me3 and repressive marks H3K27me3. This process is controlled by the PRC2 complex. The memory stage is controlled by H3K27me3 deposition at *FLC* locus (by PRC2) and H3K9me3 (by VRN1). At these stages, *FLC* is suppressed gradually. The resulting low *FLC* transcript level allows plants to flower in spring. A detailed description of these processes is presented by Xu and Chong (2018) and Ding et al. (2020). In addition, *FLC* silencing reduces plant water use due to the control of flowering time (Ferguson et al., 2019). **B.** A model for the involvement of HOS1 in the response to cold stress through epigenetic mechanisms. FVE is an integral component of multiple chromatin-modifying complexes. FVE acts as a platform for the binding of HDA6 and HOS1 to *FLC* chromatin. Cold-activated HOS1 prevents HDA6 from binding to *FLC* chromatin to activate *FLC* expression, resulting in floral repression under cold conditions. Unlike the regulation of ICE1, the role of HOS1 at *FLC* is not an acute temperature response. HOS1 plays a role in processing temperature information in response to both intermittent single-day cold treatment and longer-term changes throughout the year (MacGregor and Penfield, 2015). HOS1 may be involved in epigenetic mechanisms not only by chromatin modifications, but also via microRNAs (miRNAs). HOS1 is enriched at the chromatin of the miR168a/b promoter. By regulating miR168a/b and a component of the miRNA processing machinery (AGO1) HOS1 may influence freezing tolerance in the absence of cold acclimation (Wang et al., 2015). The miRNA strand is incorporated into the AGO protein to form the RNA induced silencing complex, which binds to target mRNAs and represses gene expression via mRNA cleavage. **C.** *Brachypodium distachyon* as an example of cold adaptation via transcriptional memory mediated through histone modifications (H3K27me3 deposition). Adaptation to cold stress occurs in response to repeated chilling with initial activation of *CBF* genes and subsequent attenuation of *CBF* expression and replacement of cold-responsive genes with growth-related genes. Transcriptional memory is transient and reversible for cold stress genes, while permanent for *VRN1*. Abbreviations: VRN1, B3 domain-containing transcription factor; FVE, WD-40 repeat-containing protein MS14; IRI, Ice recrystallization inhibition protein; HDA6, histone deacetylase 6; AGO1, Protein argonaute 1; CBF1, Dehydration-responsive element-binding protein 1 B; COR410, Dehydrin COR410; PRC2; Polycomb repressive complex 2.

influence of abiotic stress have already been quite well studied (Han and Wagner, 2014; Avramova, 2015; Lämke and Bäurle, 2017; Bäurle and Trindade, 2020; Liu et al., 2022). An important advantage of cold memory is the lower metabolic cost of repeated stressful events, which allows the plant to grow under unfavorable conditions (Vyse et al., 2019). Mechanisms of chromatin modification include DNA methylation, histone-modifying enzymes and histone variants, they include also non-coding RNAs and chromatin remodeling complexes (Han and Wagner, 2014; Weber and Henikoff, 2014; Kim, 2021; Nie, 2021). Epigenetic regulation of cold stress and mechanisms of cold priming were recently summarized (Satyakam et al., 2022; Baier et al., 2019). In this work, we focus on those mechanisms that may be involved in flavonoid biosynthesis (Fig. 3).

The most studied process of plant response to cold is vernalization (induction of flowering process by exposure to the prolonged cold). Xu and Chong (2018) placed FLC and vernalization proteins such as VRN1 (the B3 domain-containing transcription factor VRN1) at the center of regulatory networks that control the vernalization process in *Arabidopsis* and wheat, respectively. Chromatin marks associated with cold priming are mainly histone H3 lysine 4 trimethylation (H3K4me3), which marks active chromatin, and trimethylation of lysine 27 of histone H3 (H3K27me3), which defines transcriptionally silent chromatin (Xu and Chong, 2018). The Polycomb repressive complex 2 (PRC2) and Trithorax-group complex are responsible for the maintenance of H3K27me3 or H3K4me3 levels at VRN1 (Xu and Chong, 2018). The flowering repressor FLC is a well-known player in chromatin modification processes and is involved in long-term epigenetic memory (Qüesta et al., 2020). FLC is suppressed by vernalization to initiate the floral transition in spring. Gao et al. (2023) demonstrated how the active chromatin state at FLC switches to a Polycomb-repressed state. They identified a *cis*-acting cold memory region at FLC with bivalent active histone marks H3K4me3 and repressive marks H3K27me3 and showed that cold memory is formed in response to cold through changes in chromatin state. Most likely, FLC plays a role in generating seasonal temperature memory throughout the year, not just during “winter memory” (Buzas et al., 2021). Li et al. (2024) suggested that temperature changes that affect the chromatin state at the FLC locus may be related to the regulation of secondary metabolism. However, there is no experimental confirmation of this assumption yet.

HOS1 has long been known to be a protein involved in chromatin modification during cold stress through interaction with histone deacetylase 6 (HDA6) and HDA15 (Jung et al., 2013). HOS1 binds to FLC chromatin and activates FLC transcription (Jung et al., 2013). H3 acetylation (H3Ac) and H3K4 trimethylation, which are markers of active gene expression, were found to be reduced in the *hos1-3* mutant line. In contrast, H3K27Me3, which is a repressive chromatin mark, was increased in the mutant line, consistent with the low level of FLC expression. The role of HOS1 in chromatin modification is temperature dependent, as cold stress increases HOS1 binding at the FLC promoter and decreases HDA6 binding (Jung et al., 2013; MacGregor and Penfield, 2015).

Zuther et al. (2019) showed that plants are able to remember a cold priming event, thereby improving their freezing tolerance after subsequent cold stress. The response to cold priming in *Arabidopsis* was remembered for at least 7 days. The authors found different determinants for memory formation in different *Arabidopsis* accessions and suggested that a more frost-resistant variant with a northern origin is able to be more prepared for repeated stress and retains cold memory longer than a less frost-tolerant variant.

Leuendorf et al. (2020) studied the effects of intermittent or long-term cold stress (4 °C) on cold acclimation in *Arabidopsis*. Both regimes caused cold acclimation processes in dependence on duration of the treatment. In the priming experiments (a first cold treatment, recovery from chilling and second cold treatment), the freezing tolerance was maintained by cold memory, but this effect was no longer five days. The memory effect did not coincide with CBF or COR15 gene expression,

suggesting that CBF genes have no essential role in maintaining the priming-induced cold memory in *in vitro* grown seedlings of *Arabidopsis* (Col-0) after three days cold-priming at 4 °C (Leuendorf et al., 2020). This is probably due to genotype-dependent contribution of CBF transcription factors to long-term acclimation to cool temperature, which occurs even within the same plant family, such as *Arabidopsis* (Baker et al., 2022). The constitutive overexpression of CBFs usually provides high freezing tolerance but severely limits plant growth and delays development in many plant species.

In the grass *Brachypodium distachyon*, transcriptional memory provided plasticity to cold stress responses during cold acclimation, resulting in stress habituation, acquired stress responses, and growth continuation. Cold acclimation and the increase in freezing tolerance coincided with the establishment of transcriptional memory (Mayer and Charron, 2021). Transcriptional memory was transient and reversible for cold stress genes, while permanent for VRN1. Recovery from stress is a critical period during which cold memory can be formed. The authors concluded that not only stress-related genes, but also genes for growth and development are subject to regulation through transcriptional memory (Mayer and Charron, 2021).

Trees display the same basic principles of cold tolerance as herbaceous plants, but some features associated with longevity are noted (Bräutigam et al., 2013; Wisniewski et al., 2018; Canton et al., 2022). Norway spruce contains a high proportion of novel non-conserved microRNAs involved in temperature-dependent epigenetic memory. Memory effects in Norway spruce persisted for more than 20 years (Bräutigam et al., 2013). De-acclimation processes during sudden winter warming leading to frost damage are currently a focus of tree physiology. The importance of plastic epigenetic modifications and the study of stable epialleles as potential targets for selection are particularly emphasized in forest tree biology.

4. Epigenetic factors influencing the association of flavonoids with cold stress: is memory regulates cold-induced flavonoids?

Epigenetic mechanism such as DNA (de)methylation is involved in both gene regulation and chromatin landscape control (Zhang et al., 2018). Low temperatures altered anthocyanin accumulation in peach fruits through methylation of both biosynthetic and regulatory genes (Zhu et al., 2020). The expression of these genes and promoter methylation were negatively correlated. The authors suggested that DNA methylation status in peach fruits is maintained by two DNA methyltransferase genes and one DNA demethylase gene (Zhu et al., 2020). In orange fruits, DNA demethylase DML1 is responsible for demethylation of DFR and Ruby (encoding the MYB transcription factor) promoters, resulting in increased anthocyanin accumulation (Sicilia et al., 2020). The increase in anthocyanin content was specifically induced by low temperature (4 °C). Epigenetic modifications of anthocyanin biosynthesis caused by DNA methylation of MYB genes have also been identified in apple (El-Sharkawy et al., 2015; Jiang et al., 2020) and chrysanthemum (Tang et al., 2022), although these studies were conducted without cold exposure. Clonally propagated chrysanthemum plants retained somatic memory induced by methylation of MYB genes over 3 years of cultivation (Tang et al., 2022).

DNA demethylase ROS1 provides epigenetic control by preventing DNA hypermethylation. Cold stress induces demethylation of anthocyanin biosynthetic genes by ROS1 and increases anthocyanin content (Bharti et al., 2015). This observation is further supported by the fact that the cytosine methylation degree in anthocyanin-specific genes is significantly reduced during cold storage of orange fruits (Sicilia et al., 2020). AtROS1 also binds to the promoters of anthocyanin biosynthetic genes in apple fruits and leaves, which induces dynamic methylation-demethylation processes via the RRD-DME domain (Yu et al., 2022).

There is a question whether epigenetic mechanisms control flavonoid biosynthesis during vernalization. In wheat, VRN-B1 activates

flavonoid biosynthesis associated with the flowering period (Li et al., 2020), and at the same time, VRN1 is an important factor in the epigenetic memory of vernalization through PRC2-controlled histone modification (Xu and Chong, 2018). On the other hand, it is known that flavonoid biosynthetic genes *CHS*, *FLS*, and *DFR* are targets of the H3K27me3 repressive mark, which is mediated by PRC2 (Müller-Xing et al., 2014). Moreover, transcriptome analysis of various plant species revealed increased expression of genes involved in flavonoid biosynthesis during vernalization (Feng et al., 2017; Wang et al., 2021; Shu et al., 2023). These facts do not yet provide a complete picture of the relationship between flavonoids, cold and chromatin modifications during vernalization, although they leave room for discussion.

Histone variant deposition and histone methylation as chromatin-modifying factors play an important role in anthocyanin biosynthesis through the deposition of H2A.Z and H3K4me3 marks, respectively, at the loci of anthocyanin biosynthesis genes (Cai et al., 2019). Notably, H2A.Z deposition is regulated by the chromatin remodeling complex SWR1 (Cai et al., 2019). In flavonol biosynthesis, NF-Y complexes also play an essential role, regulating *CHS1* transcription by modulating H3K27me3 dynamics at the *CHS1* locus in tomato (Wang et al., 2021). Although it is clear that cold stress induces anthocyanin and flavonol biosynthesis, the role of H2A.Z and H3K4me3 marks, as well as chromatin remodeling complexes in cold responses remains to be elucidated.

Thus, the involvement of flavonoid biosynthesis in epigenetic regulation through chromatin modifications is well documented. A generalized view of these processes is presented in Fig. 4. Although we see a connection between the general mechanisms of chromatin-dependent regulation of cold adaptation processes and flavonoid biosynthesis, we do not know how the coordination of these processes occurs and whether it occurs at all. Does memory regulate cold-induced flavonoid biosynthesis? There is no data yet that could answer this question with sufficient certainty.

5. Conclusion and perspectives

As can be seen from the presented material, flavonoids are not always the first line of defense against cold; plants often rely on other protective mechanisms (for example, Brunáková et al., 2022; Wang et al., 2022). The reasons for such different evolutionary adaptability are not entirely clear. Genetic and epigenetic studies will shed light on these processes in the future. Both short-term and long-term plant adaptation to cold stress may involve various resistance mechanisms. The production of flavonoids is only one of these mechanisms, although an important one. There is virtually no doubt that flavonoid accumulation is controlled by epigenetic mechanisms such as DNA methylation or histone modifications. Although studies of epigenetic effects through chromatin modifications on flavonoid biosynthesis have advanced recently, there is still no information on the regulation of flavonoids by cold exposure through memory generation. Presently, we can consider two ways of chromatin-dependent modification of flavonoid biosynthesis: the actual modification of the expression of genes encoding MYB and bHLH transcription factors or functional genes for flavonoid biosynthesis, and the effect of proteins that simultaneously affect cold acclimation and flavonoid biosynthesis. If we learn to control the processes of epigenetic regulation of flavonoids, this will create a large layer of new research in the future to both breeders and bioengineers in the selection of initial forms of cold-resistant agricultural plants.

Outstanding questions

What molecular mechanisms (including chromatin modifications) regulate flavonoid biosynthesis through regulators such as VRN1 and HOS1?

Does FLC regulate flavonoid biosynthesis?

Did the processes of memory formation about the biosynthetic status of secondary metabolites participate in adaptation processes during the evolution of higher plants?

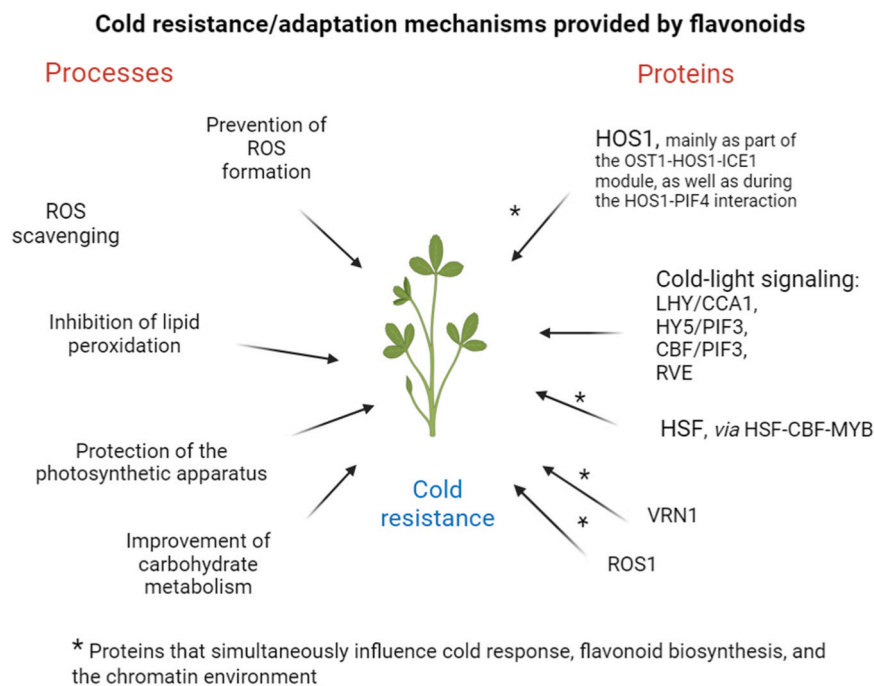


Fig. 4. Summary of processes by which flavonoids help plants adapt to cold stress. Proteins from various signaling systems that influence flavonoid biosynthesis under cold conditions are also presented. Asterisks indicate proteins that are involved in chromatin modification. Abbreviations: HOS1, E3 ubiquitin-protein ligase HOS1; LHY, protein late elongated hypocotyl; CCA1, circadian clock associated 1; HY5, transcription factor HY5; PIFs, phytochrome-interacting transcription factors; RVE, protein REVELLE; HSF, heat shock factor; VRN1, B3 domain-containing transcription factor; ROS1, DNA glycosylase/AP lyase ROS1.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The authors reported there is no funding associated with the work featured in this article.

Author contributions

VPB contributed to conception, data analysis, and manuscript writing. YAY and AVF performed analysis, interpretation and presentation of data, and final approval. All authors contributed to the article and approved the submitted version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

We would like to thank colleagues of our department for fruitful discussions on this topic. This research was conducted within the framework of state assignments of the Ministry of Science and Higher Education of the Russian Federation (theme No. 121031000144–5 and No. FFW-2024-0004 IACP FEB RAS).

References

- An, J.P., Zhang, X.W., Li, H.L., Wang, D.R., You, C.X., Han, Y., 2023. The E3 ubiquitin ligase SINA1 and SINA2 integrate with the protein kinase CIPK20 to regulate the stability of RGL2a, a positive regulator of anthocyanin biosynthesis. *New Phytol.* 239, 1332–1352. <https://doi.org/10.1111/nph.18997>.
- An, J.P., Li, R., Qu, F.J., You, C.X., Wang, X.F., Hao, Y.J., 2018. R2R3-MYB transcription factor MdMYB23 is involved in the cold tolerance and proanthocyanidin accumulation in apple. *Plant J.* 96, 562–577. <https://doi.org/10.1111/tj.14050>.
- Andrási, N., Pettkó-Szandtner, A., Szabados, L., 2021. Diversity of plant heat shock factors: regulation, interactions, and functions. *J. Exp. Bot.* 72, 1558–1575. <https://doi.org/10.1093/jxb/eraa576>.
- Avramova, Z., 2015. Transcriptional ‘memory’ of a stress: transient chromatin and memory (epigenetic) marks at stress-response genes. *Plant J.* 83, 149–159. <https://doi.org/10.1111/tj.12832>.
- Baker, C.R., Stewart, J.J., Amstutz, C.L., Ching, L.G., Johnson, J.D., Niyogi, K.K., Adams 3rd, W.W., Demmig-Adams, B., 2022. Genotype-dependent contribution of CBF transcription factors to long-term acclimation to high light and cool temperature. *Plant Cell Environ.* 45, 392–411. <https://doi.org/10.1111/pce.14231>.
- Baier, M., Bittner, A., Prescher, A., van Buer, J., 2019. Preparing plants for improved cold tolerance by priming. *Plant Cell Environ.* 42, 782–800. <https://doi.org/10.1111/pce.13394>.
- Bäurle, I., Trindade, I., 2020. Chromatin regulation of somatic abiotic stress memory. *J. Exp. Bot.* 71, 5269–5279. <https://doi.org/10.1093/jxb/eraa098>.
- Bharti, P., Mahajan, M., Vishwakarma, A.K., et al., 2015. ATROS1 overexpression provides evidence for epigenetic regulation of genes encoding enzymes of flavonoid biosynthesis and antioxidant pathways during salt stress in transgenic tobacco. *J. Exp. Bot.* 66, 5959–5969. <https://doi.org/10.1093/jxb/erv304>.
- Bhatia, C., Gaddam, S.R., Pandey, A., Trivedi, P.K., 2021. COP1 mediates light-dependent regulation of flavonol biosynthesis through HY5 in *Arabidopsis*. *Plant Sci.* 303, 110760. <https://doi.org/10.1016/j.plantsci.2020.110760>.
- Bozzo, G.G., Unterlander, N., 2021. In through the out door: biochemical mechanisms affecting flavonoid glycoside catabolism in plants. *Plant Sci.* 308, 110904. <https://doi.org/10.1016/j.plantsci.2021.110904>.
- Bräutigam, K., Vining, K.J., Lafon-Placette, C., Fossdal, C.G., Mirouze, M., Marcos, J.G., Fluch, S., Fraga, M.F., Guevara, M.A., Abarca, D., Johnsen, O., Maury, S., Strauss, S.H., Campbell, M.M., Rohde, A., Díaz-Salá, C., Cervera, M.T., 2013. Epigenetic regulation of adaptive responses of forest tree species to the environment. *Ecol. Evol.* 3, 399–415. <https://doi.org/10.1002/ece3.461>.
- Bruňáková, K., Bálintová, M., Petjiová, L., Čellárová, E., 2022. Does phenotyping of *Hypericum* secondary metabolism reveal a tolerance to biotic/abiotic stressors? *Front. Plant Sci.* 13, 1042375. <https://doi.org/10.3389/fpls.2022.1042375>.
- Brunetti, C., Fini, A., Sebastiani, F., Gori, A., Tattini, M., 2018. Modulation of phytohormone signaling: a primary function of flavonoids in plant-environment interactions. *Front. Plant Sci.* 9, 1042. <https://doi.org/10.3389/fpls.2018.01042>.
- Brunetti, C., Sebastiani, F., Tattini, M., 2019. Review: ABA, flavonols, and the evolvability of land plants. *Plant Sci.* 280, 448–454. <https://doi.org/10.1016/j.plantsci.2018.12.010>.
- Bulgakov, V.P., 2024. Chromatin modifications and memory in regulation of stress-related polyphenols: finding new ways to control flavonoid biosynthesis. *Crit. Rev. Biotechnol.* 2, 1–17. <https://doi.org/10.1080/07388551.2024.2336529>.
- Bulgakov, V.P., Avramenko, T.V., Tsitsiashvili, G.S., 2017. Critical analysis of protein signaling networks involved in the regulation of plant secondary metabolism: focus on anthocyanins. *Crit. Rev. Biotechnol.* 37, 685–700. <https://doi.org/10.3109/07388551.2016.1141391>.
- Bulgakov, V.P., Koren, O.G., 2022. Basic protein modules combining abscisic acid and light signaling in *Arabidopsis*. *Front. Plant Sci.* 12, 808960. <https://doi.org/10.3389/fpls.2021.808960>.
- Buzas, D.M., Nishio, H., Kudoh, H., 2021. The flowering season-meter at FLOWERING LOCUS C across life histories in crucifers. *Front. Plant Sci.* 12, 640442. <https://doi.org/10.3389/fpls.2021.640442>.
- Cai, H., Zhang, M., Chai, M., He, Q., Huang, X., Zhao, L., Qin, Y., 2019. Epigenetic regulation of anthocyanin biosynthesis by an antagonistic interaction between H2A.Z and H3K4me3. *New Phytol.* 221, 295–308. <https://doi.org/10.1111/nph.15306>.
- Canton, M., Forestan, C., Marconi, G., Carrera, E., Bonghi, C., Varotto, S., 2022. Evidence of chromatin and transcriptional dynamics for cold development in peach flower bud. *New Phytol.* 236, 974–988. <https://doi.org/10.1111/nph.18393>.
- Catalá, R., Medina, J., Salinas, J., 2011. Integration of low temperature and light signaling during cold acclimation response in *Arabidopsis*. *Proc. Natl. Acad. Sci. U.S.A.* 108, 16475–16480. <https://doi.org/10.1073/pnas.1107161108>.
- Chang, Y.Y., Mitra, S., Yu, S.J., 2023. Maintenance of abiotic stress memory in plants: lessons learned from heat acclimation. *Plant Cell* 35, 187–200. <https://doi.org/10.1093/plcell/koac313>.
- Chen, D., Xu, G., Tang, W., Jing, Y., Ji, Q., Fei, Z., Lin, R., 2013. Antagonistic basic helix-loop-helix/bZIP transcription factors form transcriptional modules that integrate light and reactive oxygen species signaling in *Arabidopsis*. *Plant Cell* 25, 1657–1673. <https://doi.org/10.1105/tpc.112.104869>.
- Chen, X., Wu, Y., Yu, Z., Gao, Z., Ding, Q., Shah, S.H.A., Lin, W., Li, Y., 2023. BcMYB111 responds to BcCBF2 and induces flavonol biosynthesis to enhance tolerance under cold stress in non-heading Chinese cabbage. *Int. J. Mol. Sci.* 24, 8670. <https://doi.org/10.3390/ijms24108670>. Hou X.
- Choudhury, F.K., Rivero, R.M., Blumwald, E., Mittler, R., 2017. Reactive oxygen species, abiotic stress and stress combination. *Plant J.* 90, 856–867. <https://doi.org/10.1111/tj.13299>.
- Crifo, T., Petrone, G., Lo Cicero, L., Lo Piero, A.R., 2012. Short cold storage enhances the anthocyanin contents and level of transcripts related to their biosynthesis in blood oranges. *J. Agric. Food Chem.* 60, 476–481. <https://doi.org/10.1021/jf203891e>.
- Daryanavard, H., Postiglione, A.E., Mühlemann, J.K., Muday, G.K., 2023. Flavonols modulate plant development, signaling, and stress responses. *Curr. Opin. Plant Biol.* 72, 102350. <https://doi.org/10.1016/j.cpb.2023.102350>.
- Davletova, S., Rizhsky, L., Liang, H., Shengqiang, Z., Oliver, D.J., Coutu, J., Shulaev, V., Schlauch, K., Mittler, R., 2005. Cytosolic ascorbate peroxidase 1 is a central component of the reactive oxygen gene network of *Arabidopsis*. *Plant Cell* 17, 268–281. <https://doi.org/10.1105/tpc.104.026971>.
- Ding, Y., Li, H., Zhang, X., Xie, Q., Gong, Z., Yang, S., 2015. OST1 kinase modulates freezing tolerance by enhancing ICE1 stability in *Arabidopsis*. *Dev. Cell* 32, 278–289. <https://doi.org/10.1016/j.devcel.2014.12.023>.
- Ding, Y., Shi, Y., Yang, S., 2020. Molecular regulation of plant responses to environmental temperatures. *Mol. Plant* 13, 544–564. <https://doi.org/10.1016/j.molp.2020.02.004>.
- Dong, C.H., Agarwal, M., Zhang, Y.Y., Xie, Q., Zhu, J.K., 2006. The negative regulator of plant cold responses, HOS1, is a RING E3 ligase that mediates the ubiquitination and degradation of ICE1. *Proc. Natl. Acad. Sci. U.S.A.* 103, 8281–8286. <https://doi.org/10.1073/pnas.0602874103>.
- El-Sharkawy, I., Liang, D., Xu, K., 2015. Transcriptome analysis of an apple (*Malus domestica*) yellow fruit somatic mutation identifies a gene network module highly associated with anthocyanin and epigenetic regulation. *J. Exp. Bot.* 66, 7359–7376. <https://doi.org/10.1093/jxb/erv433>.
- Feng, G., Huang, L., Li, J., Wang, J., Xu, L., Pan, L., Zhao, X., Wang, X., Huang, T., Zhang, X., 2017. Comprehensive transcriptome analysis reveals distinct regulatory programs during vernalization and floral bud development of orchardgrass (*Dactylis glomerata* L.). *BMC Plant Biol.* 17, 216. <https://doi.org/10.1186/s12870-017-1170-8>.
- Ferguson, J.N., Meyer, R.C., Edwards, K.D., Humphry, M., Brendel, O., Bechtold, U., 2019. Accelerated flowering time reduces lifetime water use without penalizing reproductive performance in *Arabidopsis*. *Plant Cell Environ.* 42, 1847–1867. <https://doi.org/10.1111/pce.13527>.
- Franklin, K.A., Whitelam, G.C., 2007. Light-quality regulation of freezing tolerance in *Arabidopsis thaliana*. *Nat. Genet.* 39, 1410–1413. <https://doi.org/10.1038/ng.2007.3>.
- Friedrich, T., Oberkofler, V., Trindade, I., et al., 2021. Heteromeric HSF2A/HSF3A complexes drive transcriptional memory after heat stress in *Arabidopsis*. *Nat. Commun.* 3426. <https://doi.org/10.1038/s41467-021-23786-6>.

- Fürtauer, L., Weiszmann, J., Weckwerth, W., Nägele, T., 2019. Dynamics of plant metabolism during cold acclimation. *Int. J. Mol. Sci.* 20, 5411. <https://doi.org/10.3390/ijms20215411>.
- Gallusci, P., Agius, D.R., Moschou, P.N., Dobránszki, J., Kaiserli, E., Martinelli, F., 2023. Deep inside the epigenetic memories of stressed plants. *Trends Plant Sci.* 28, 142–153. <https://doi.org/10.1016/j.tplants.2022.09.004>.
- Gangappa, S.N., Botto, J.F., 2016. The multifaceted roles of HY5 in plant growth and development. *Mol. Plant* 9, 1353–1365. <https://doi.org/10.1016/j.molp.2016.07.002>.
- Gao, Z., Li, Y., Ou, Y., Yin, M., Chen, T., Zeng, X., Li, R., He, Y., 2023. A pair of readers of bivalent chromatin mediate formation of POLYCOMB-based "memory of cold" in plants. *Mol. Cell* 83, 1109–1124.e4. <https://doi.org/10.1016/j.molcel.2023.02.014>.
- Genzel, F., Dicke, M.D., Junker-Frohn, L.V., Neuwohner, A., Thiele, B., Putz, A., Usadel, B., Wormit, A., Wiese-Klinkenberg, A., 2021. Impact of moderate cold and salt stress on the accumulation of antioxidant flavonoids in the leaves of two *Capsicum* cultivars. *J. Agric. Food Chem.* 69, 6431–6443. <https://doi.org/10.1021/acs.jafc.1c00908>.
- Gorpenchenko, T.Y., Veremeichik, G.N., Shkryl, Y.N., Yugay, Y.A., Grigorochuk, V.P., Bulgakov, D.V., Rusapetova, T.V., Vereshchagina, Y.V., Mironova, A.A., Subbotin, E. P., Kulchin, Y.N., Bulgakov, V.P., 2023. Suppression of the *HOS1* gene affects the level of ROS depending on light and cold. *Life* 13, 524. <https://doi.org/10.3390/life13020524>.
- Guo, X., Liu, D., Chong, K., 2018. Cold signaling in plants: insights into mechanisms and regulation. *J. Integr. Plant Biol.* 60, 745–756. <https://doi.org/10.1111/jipb.12706>.
- Han, S.K., Wagner, D., 2014. Role of chromatin in water stress responses in plants. *J. Exp. Bot.* 65, 2785–2799. <https://doi.org/10.1093/jxb/ert403>.
- He, J., Yao, L., Pecoraro, L., Liu, C., Wang, J., Huang, L., Gao, W., 2023. Cold stress regulates accumulation of flavonoids and terpenoids in plants by phytohormone, transcription process, functional enzyme, and epigenetics. *Crit. Rev. Biotechnol.* 43, 680–697. <https://doi.org/10.1080/07388551.2022.2053056>, 10.1080/07388551.2022.2053056.
- Hildreth, S.B., Littleton, E.S., Clark, L.C., Puller, G.C., Kojima, S., Winkel, B.S.J., 2022. Mutations that alter *Arabidopsis* flavonoid metabolism affect the circadian clock. *Plant J.* 110, 932–945. <https://doi.org/10.1111/tj.15718>.
- Hoermiller, I.L., Naegle, T., Augustin, H., Stutz, S., Weckwerth, W., Heyer, A.G., 2017. Subcellular reprogramming of metabolism during cold acclimation in *Arabidopsis thaliana*. *Plant Cell Environ.* 40, 602–610. <https://doi.org/10.1111/pce.12836>.
- Hu, Y., Han, X., Yang, M., Zhang, M., Pan, J., Yu, D., 2019. The transcription factor INDUCER OF CBF EXPRESSION1 interacts with ABSICISIC ACID INSENSITIVE5 and DELLA proteins to fine-tune abscisic acid signaling during seed germination in *Arabidopsis*. *Plant Cell* 31, 1520–1538. <https://doi.org/10.1105/tpc.18.00825>.
- Huang, Y.C., Niu, C.Y., Yang, C.R., Jinn, T.L., 2016. The heat stress factor HSPA6b connects ABA signaling and ABA-mediated heat responses. *Plant Physiol.* 172, 1182–1199. <https://doi.org/10.1105/tpc.18.00825>.
- Jiang, B., Shi, Y., Peng, Y., Jia, Y., Yan, Y., Dong, X., Li, H., Dong, J., Li, J., Gong, Z., Thomashow, M.F., Yang, S., 2020a. Cold-induced CBF-PIF3 interaction enhances freezing tolerance by stabilizing the phyB thermosensor in *Arabidopsis*. *Mol. Plant* 13, 894–906. <https://doi.org/10.1016/j.molp.2020.04.006>.
- Jiang, B., Shi, Y., Zhang, X., Xin, X., Qi, L., Guo, H., Li, J., Yang, S., 2017. PIF3 is a negative regulator of the CBF pathway and freezing tolerance in *Arabidopsis*. *Proc. Natl. Acad. Sci. U.S.A.* 114, E6695–E6702. <https://doi.org/10.1073/pnas.1706226114>.
- Jiang, H., Zhou, L.J., Gao, H.N., Wang, X.F., Li, Z.W., Li, Y.Y., 2022. The transcription factor MdMYB2 influences cold tolerance and anthocyanin accumulation by activating SUMO E3 ligase MdSIZ1 in apple. *Plant Physiol.* 189, 2044–2060. <https://doi.org/10.1093/plphys/kiac211>.
- Jiang, S., Wang, N., Chen, M., Zhang, R., Sun, Q., Xu, H., Zhang, Z., Wang, Y., Sui, X., Wang, S., Fang, H., Zuo, W., Su, M., Zhang, J., Fei, Z., Chen, X., 2020. Methylation of MdMYB1 locus mediated by RdDM pathway regulates anthocyanin biosynthesis in apple. *Plant Biotechnol. J.* 18, 1736–1748. <https://doi.org/10.1111/pbi.13337>.
- Jin, H.X., Jiang, M., Yang, J.F., Wu, Z.H., Ma, L.L., Wang, C.C., Liang, C., Ning, X.Y., Ge, L.F., Chen, S., 2022. A survey of enhanced cold tolerance and low-temperature-induced anthocyanin accumulation in a novel *Zoysia japonica* biotype. *Plants* 11, 429. <https://doi.org/10.3390/plants11030429>.
- Jung, J.H., Park, J.H., Lee, S., To, T.K., Kim, J.M., Seki, M., Park, C.M., 2013. The cold signaling attenuator HIGH EXPRESSION OF OSMOTICALLY RESPONSIVE GENE1 activates FLOWERING LOCUS C transcription via chromatin remodeling under short-term cold stress in *Arabidopsis*. *Plant Cell* 25, 4378–4390. <https://doi.org/10.1105/tpc.113.118364>.
- Kidokoro, S., Hayashi, K., Haraguchi, H., Ishikawa, T., Soma, F., Konoura, I., Toda, S., Mizoi, J., Suzuki, T., Shinozaki, K., Yamaguchi-Shinozaki, K., 2021. Posttranslational regulation of multiple clock-related transcription factors triggers cold-inducible gene expression in *Arabidopsis*. *Proc. Natl. Acad. Sci. U.S.A.* 118, e2021048118. <https://doi.org/10.1073/pnas.2021048118>.
- Kidokoro, S., Konoura, I., Soma, F., Suzuki, T., Miyakawa, T., Tanokura, M., Shinozaki, K., Yamaguchi-Shinozaki, K., 2023. Clock-regulated coactivators selectively control gene expression in response to different temperature stress conditions in *Arabidopsis*. *Proc. Natl. Acad. Sci. U.S.A.* 120, e2216183120. <https://doi.org/10.1073/pnas.2216183120>.
- Kidokoro, S., Shinozaki, K., Yamaguchi-Shinozaki, K., 2022. Transcriptional regulatory network of plant cold-stress responses. *Trends Plant Sci.* 27, 922–935. <https://doi.org/10.1016/j.tplants.2022.01.008>.
- Kim, J.H., 2021. Multifaceted chromatin structure and transcription changes in plant stress response. *Int. J. Mol. Sci.* 22, 2013. <https://doi.org/10.3390/ijms22042013>.
- Kim, J.H., Lee, H.J., Jung, J.H., Lee, S., Park, C.M., 2017. HOS1 facilitates the phytochrome B-mediated inhibition of PIF4 function during hypocotyl growth in *Arabidopsis*. *Mol. Plant* 10, 274–284. <https://doi.org/10.1016/j.molp.2016.11.009>.
- Kim, Y.S., Lee, M., Lee, J.H., Lee, H.J., Park, C.M., 2015. The unified ICE-CBF pathway provides a transcriptional feedback control of freezing tolerance during cold acclimation in *Arabidopsis*. *Plant Mol. Biol.* 89, 187–201. <https://doi.org/10.1007/s11103-015-0365-3>.
- Lämke, J., Bäurle, I., 2017. Epigenetic and chromatin-based mechanisms in environmental stress adaptation and stress memory in plants. *Genome Biol.* 18, 124. <https://doi.org/10.1186/s13059-017-1263-6>.
- Lazaro, A., Valverde, F., Piñeiro, M., Jarillo, J.A., 2012. The *Arabidopsis* E3 ubiquitin ligase HOS1 negatively regulates CONSTANS abundance in the photoperiodic control of flowering. *Plant Cell* 24, 982–999. <https://doi.org/10.1105/tpc.110.081885>.
- Leuendorf, J.E., Frank, M., Schmölling, T., 2020. Acclimation, priming and memory in the response of *Arabidopsis thaliana* seedlings to cold stress. *Sci. Rep.* 10, 689. <https://doi.org/10.1038/s41598-019-56797-x>.
- Li, H.L., Liu, Z.Y., Wang, X.N., Han, Y., You, C.X., An, J.P., 2023. E3 ubiquitin ligases SINA4 and SINA11 regulate anthocyanin biosynthesis by targeting the IAA29-ARF5-1-ERF3 module in apple. *Plant Cell Environ.* 46, 3902–3918. <https://doi.org/10.1111/pce.14709>.
- Li, Q., Duncan, S., Li, Y., Huang, S., Luo, M., 2024. Decoding plant specialized metabolism: new mechanistic insights. *Trends Plant Sci.* 29, 535–545. <https://doi.org/10.1016/j.tplants.2023.11.015>.
- Li, Y., Xiong, H., Guo, H., Zhou, C., Xie, Y., Zhao, L., Gu, J., Zhao, S., Ding, Y., Liu, L., 2020. Identification of the vernalization gene VRN-B1 responsible for heading date variation by QTL mapping using a RIL population in wheat. *BMC Plant Biol.* 20, 331. <https://doi.org/10.1186/s12870-020-02539-5>.
- Liu, B., Wang, X.Y., Cao, Y., Arora, R., Zhou, H., Xia, Y.P., 2020. Factors affecting freezing tolerance: a comparative transcriptomics study between field and artificial cold acclimations in overwintering evergreens. *Plant J.* 103, 2279–2300. <https://doi.org/10.1111/tj.14899>.
- Liu, H., Able, A.J., Able, J.A., 2022. Priming crops for the future: rewiring stress memory. *Trends Plant Sci.* 27, 699–716. <https://doi.org/10.1016/j.tplants.2021.11.015>.
- Liu, Z., Wang, Y., Fan, K., Li, Z., Jia, Q., Lin, W., Zhang, Y., 2021. Phytochrome-interacting factor 4 (PIF4) negatively regulates anthocyanin accumulation by inhibiting PAPI1 transcription in *Arabidopsis* seedlings. *Plant Sci.* 303, 110788. <https://doi.org/10.1016/j.plantsci.2020.110788>.
- Lloyd, J.P.B., Lister, R., 2022. Epigenome plasticity in plants. *Nat. Rev. Genet.* 23, 55–68. <https://doi.org/10.1038/s41576-021-00407-y>.
- Lo Piero, A.R., Puglisi, I., Rapisarda, P., Petrone, G., 2005. Anthocyanins accumulation and related gene expression in red orange fruit induced by low temperature storage. *J. Agric. Food Chem.* 53, 9083–9088. <https://doi.org/10.1021/jf051609s>.
- Lo Piero, A.R., 2015. The State of the art in biosynthesis of anthocyanins and its regulation in pigmented sweet oranges [*Citrus sinensis* L. Osbeck]. *J. Agric. Food Chem.* 63, 4031–4041. <https://doi.org/10.1021/acs.jafc.5b01123>.
- MacGregor, D.R., Penfield, S., 2015. Exploring the pleiotropy of *hos1*. *J. Exp. Bot.* 66, 1661–1671. <https://doi.org/10.1093/jxb/erv022>.
- Maier, A., Schrader, A., Kockelink, L., Falke, C., Welter, B., Iniesto, E., Rubio, V., Uhrig, J.F., Hülskamp, M., Hoecker, U., 2013. Light and the E3 ubiquitin ligase COP1/SPA control the protein stability of the MYB transcription factors PAPI1 and PAPI2 involved in anthocyanin accumulation in *Arabidopsis*. *Plant J.* 74, 638–651. <https://doi.org/10.1111/tj.12153>.
- Mayer, B.F., Charron, J.B., 2021. Transcriptional memories mediate the plasticity of cold stress responses to enable morphological acclimation in *Brachypodium distachyon*. *New Phytol.* 229, 1615–1634. <https://doi.org/10.1111/nph.16945>.
- Müller-Xing, R., Xing, Q., Goodrich, J., 2014. Footprints of the sun: memory of UV and light stress in plants. *Front. Plant Sci.* 5, 474. <https://doi.org/10.3389/fpls.2014.00474>.
- Naik, J., Rajput, R., Stracke, R., Pandey, A., 2023. The HSF-DREB-MYB transcriptional regulatory module regulates flavonol biosynthesis and flavonoid B-ring hydroxylation in banana (*Musa acuminata*). *bioRxiv* 2023 (08.23), 554507. <https://doi.org/10.1101/2023.08.23.554507>.
- Nakabayashi, R., Yonekura-Sakakibara, K., Urano, K., Suzuki, M., Yamada, Y., Nishizawa, T., Matsuda, F., Kojima, M., Sakakibara, H., Shinozaki, K., Michael, A.J., Tohge, T., Yamazaki, M., Saito, K., 2014. Enhancement of oxidative and drought tolerance in *Arabidopsis* by overaccumulation of antioxidant flavonoids. *Plant J.* 77, 367–379. <https://doi.org/10.1111/tj.12388>.
- Naróg, D., Sobkowiak, A., 2023. Electrochemistry of flavonoids. *Molecules* 28, 7618. <https://doi.org/10.3390/molecules28227618>.
- Nie, W.F., 2021. DNA methylation: from model plants to vegetable crops. *Biochem. Soc. Trans.* 49, 1479–1487. <https://doi.org/10.1042/BST20210353>.
- Olate, E., Jiménez-Gómez, J.M., Holuigue, L., Salinas, J., 2018. NPR1 mediates a novel regulatory pathway in cold acclimation by interacting with HSPA1 factors. *Nat. Plants* 4, 811–823. <https://doi.org/10.1038/s41477-018-0254-2>.
- Pan, C., Yang, D., Zhao, X., Liu, Y., Li, M., Ye, L., Ali, M., Yu, F., Lamin-Samu, A.T., Fei, Z., Lu, G., 2021. PIF4 negatively modulates cold tolerance in tomato anthers via temperature-dependent regulation of tapetal cell death. *Plant Cell* 33, 2320–2339. <https://doi.org/10.1093/plcell/koab120>.
- Pérez-García, P., Ma, Y., Yanovsky, M.J., Mas, P., 2015. Time-dependent sequestration of RVE8 by LNK proteins shapes the diurnal oscillation of anthocyanin biosynthesis. *Proc. Natl. Acad. Sci. U.S.A.* 112, 5249–5253. <https://doi.org/10.1073/pnas.1420792112>.
- Petrussa, E., Braidot, E., Zancani, M., Peresson, C., Bertolini, A., Patui, S., Vianello, A., 2013. Plant flavonoids - biosynthesis, transport and involvement in stress responses. *Int. J. Mol. Sci.* 14, 14950–14973. <https://doi.org/10.3390/ijms140714950>.

- Qüesta, J.I., Antoniou-Kourounioti, R.L., Rosa, S., Li, P., Duncan, S., Whittaker, C., Howard, M., Dean, C., 2020. Noncoding SNPs influence a distinct phase of POLYCOMB silencing to destabilize long-term epigenetic memory at *Arabidopsis FLC*. *Genes Dev.* 34, 446–461. <https://doi.org/10.1101/gad.333245.119>.
- Roeber, V.M., Bajaj, I., Rohde, M., Schmillig, T., Cortleven, A., 2021. Light acts as a stressor and influences abiotic and biotic stress responses in plants. *Plant Cell Environ.* 44, 645–664. <https://doi.org/10.1111/pce.13948>.
- Satyakam, Zinta G., Singh, R.K., Kumar, R., 2022. Cold adaptation strategies in plants - an emerging role of epigenetics and antifreeze proteins to engineer cold resilient plants. *Front. Genet.* 13, 909007 <https://doi.org/10.3389/fgene.2022.909007>.
- Schulz, E., Tohge, T., Zuther, E., Fernie, A.R., Hinch, D.K., 2016. Flavonoids are determinants of freezing tolerance and cold acclimation in *Arabidopsis thaliana*. *Sci. Rep.* 6, 34027 <https://doi.org/10.1038/srep34027>, 10.1038/srep.34027.
- Shkryl, Y., Yugay, Y., Avramenko, T., Grigorchuk, V., Gorpenchenko, T., Grischenko, O., Bulgakov, V., 2021. CRISPR/Cas9-mediated knockout of HOS1 reveals its role in the regulation of secondary metabolism in *Arabidopsis thaliana*. *Plants* 10, 104. <https://doi.org/10.3390/plants10010104>.
- Shu, W., Shi, M., Zhang, Q., Xie, W., Chu, L., Qiu, M., Li, L., Zeng, Z., Han, L., Sun, Z., 2023. Transcriptomic and metabolomic analyses reveal differences in flavonoid pathway gene expression profiles between two *Dendrobium* varieties during vernalization. *Int. J. Mol. Sci.* 24, 11039 <https://doi.org/10.3390/ijms241311039>.
- Sicilia, A., Scialò, E., Puglisi, I., Lo Piero, A.R., 2020. Anthocyanin biosynthesis and DNA methylation dynamics in sweet orange fruit [*Citrus sinensis* L. (Osbeck)] under cold stress. *J. Agric. Food Chem.* 68, 7024–7031. <https://doi.org/10.1021/acs.jafc.0c02360>.
- Sudheeran, P.K., Feygenberg, O., Maurer, D., Alkan, N., 2018. Improved cold tolerance of mango fruit with enhanced anthocyanin and flavonoid contents. *Molecules* 23, 1832. <https://doi.org/10.3390/molecules23071832>.
- Swindell, W.R., Huebner, M., Weber, A.P., 2007. Transcriptional profiling of *Arabidopsis* heat shock proteins and transcription factors reveals extensive overlap between heat and non-heat stress response pathways. *BMC Genom.* 8, 125. <https://doi.org/10.1186/1471-2164-8-125>.
- Tang, M., Xue, W., Li, X., Wang, L., Wang, M., Wang, W., Yin, X., Chen, B., Qu, X., Li, J., Wu, Y., Gao, X., Wei, X., Bu, F., Zhang, L., Sui, Z., Ding, B., Wang, Y., Zhang, Q., Li, Y., Zhang, Y., 2022. Mitotically heritable epigenetic modifications of CmMYB6 control anthocyanin biosynthesis in chrysanthemum. *New Phytol.* 236, 1075–1088. <https://doi.org/10.1111/nph.18389>.
- Thakur, P., Kumar, S., Malik, J.A., Berger, J.D., Nayyar, H., 2010. Cold stress effects on reproductive development in grain crops: an overview. *Environ. Exp. Bot.* 67, 429–443. <https://doi.org/10.1016/j.envexpbot.2009.09.004>.
- Toledo-Ortiz, G., Johansson, H., Lee, K.P., Bou-Torrent, J., Stewart, K., Steel, G., Rodríguez-Concepción, M., Halliday, K.J., 2014. The HY5-PIF regulatory module coordinates light and temperature control of photosynthetic gene transcription. *PLoS Genet.* 10, e1004416 <https://doi.org/10.1371/journal.pgen.1004416>.
- Vyse, K., Pagter, M., Zuther, E., Hinch, D.K., 2019. Deacclimation after cold acclimation—a crucial, but widely neglected part of plant winter survival. *J. Exp. Bot.* 70, 4595–4604. <https://doi.org/10.1093/jxb/erz229>.
- Wang, B., Duan, C.G., Wang, X., Hou, Y.J., Yan, J., Gao, C., Kim, J.H., Zhang, H., Zhu, J. K., 2015. HOS1 regulates Argonaute 1 by promoting transcription of the microRNA gene MIR168b in *Arabidopsis*. *Plant J.* 81, 861–870. <https://doi.org/10.1111/tpj.12772>.
- Wang, F., Wu, N., Zhang, L., Ahammed, G.J., Chen, X., Xiang, X., Zhou, J., Xia, X., Shi, K., Yu, J., Foyer, C.H., Zhou, Y., 2018. Light signaling-dependent regulation of photoinhibition and photoprotection in tomato. *Plant Physiol.* 176, 1311–1326. <https://doi.org/10.1104/pp.17.01143>.
- Wang, H., Guo, L., Zha, R., Gao, Z., Yu, F., Wei, Q., 2022. Histological, metabolomic and transcriptomic analyses reveal mechanisms of cold acclimation of the Moso bamboo (*Phyllostachys edulis*) leaf. *Tree Physiol.* 42, 2336–2352. <https://doi.org/10.1093/treephys/tpac064>.
- Wang, N., Liu, W., Yu, L., Guo, Z., Chen, Z., Jiang, S., Xu, H., Fang, H., Wang, Y., Zhang, Z., Chen, X., 2020b. HEAT SHOCK FACTOR A8a modulates flavonoid synthesis and drought tolerance. *Plant Physiol.* 184, 1273–1290. <https://doi.org/10.1104/pp.20.01106>.
- Wang, P., Liu, D., Yang, F.H., Ge, H., Zhao, X., Chen, H.G., Du, T., 2021. Identification of key gene networks controlling vernalization development characteristics of *Isatis indigotica* by full-length transcriptomes and gene expression profiles. *Physiol. Mol. Biol. Plants* 27, 2679–2693. <https://doi.org/10.1007/s12298-021-01110-2>.
- Wang, P., Liu, W.C., Han, C., Wang, S., Bai, M.Y., Song, C.P., 2024. Reactive oxygen species: multidimensional regulators of plant adaptation to abiotic stress and development. *J. Integr. Plant Biol.* 66, 330–367. <https://doi.org/10.1111/jipb.13601>.
- Wang, W., Wang, X., Zhang, J., Huang, M., Cai, J., Zhou, Q., Dai, T., Jiang, D., 2020a. Salicylic acid and cold priming induce late-spring freezing tolerance by maintaining cellular redox homeostasis and protecting photosynthetic apparatus in wheat. *Plant Growth Regul.* 90, 109–121.
- Weber, C.M., Henikoff, S., 2014. Histone variants: dynamic punctuation in transcription. *Genes Dev.* 28, 672–682. <https://doi.org/10.1101/gad.238873.114>.
- Wisniewski, M., Nassuth, A., Arora, R., 2018. Cold hardness in trees: a mini-review. *Front. Plant Sci.* 9, 1394. <https://doi.org/10.3389/fpls.2018.01394>.
- Xiang, M., Ding, W., Wu, C., Wang, W., Ye, S., Cai, C., Hu, X., Wang, N., Bai, W., Tang, X., Zhu, C., Yu, X., Xu, Q., Zheng, Y., Ding, Z., Lin, C., Zhu, Q., 2021. Production of purple Ma bamboo (*Dendrocalamus latiflorus* Munro) with enhanced drought and cold stress tolerance by engineering anthocyanin biosynthesis. *Planta* 254, 50. <https://doi.org/10.1007/s00425-021-03696-z>.
- Xiao, Y., Chu, L., Zhang, Y., Bian, Y., Xiao, J., Xu, D., 2022. HY5: a pivotal regulator of light-dependent development in higher plants. *Front. Plant Sci.* 12, 800989 <https://doi.org/10.3389/fpls.2021.800989>.
- Xie, Y., Chen, P., Yan, Y., Bao, C., Li, X., Wang, L., Shen, X., Li, H., Liu, X., Niu, C., Zhu, C., Fang, N., Shao, Y., Zhao, T., Yu, J., Zhu, J., Xu, L., van Nocker, S., Ma, F., Guan, Q., 2018. An atypical R2R3 MYB transcription factor increases cold hardness by CBF-dependent and CBF-independent pathways in apple. *New Phytol.* 218, 201–218. <https://doi.org/10.1111/nph.14952>.
- Xu, S., Chong, K., 2018. Remembering winter through vernalisation. *Nat. Plants* 4, 997–1009. <https://doi.org/10.1038/s41477-018-0301-z>.
- Ye, K., Li, H., Ding, Y., Shi, Y., Song, C., Gong, Z., Yang, S., 2019. BRASSINOSTEROID-INSENSITIVE2 negatively regulates the stability of transcription factor ICE1 in response to cold stress in *Arabidopsis*. *Plant Cell* 31, 2682–2696. <https://doi.org/10.1105/tpc.19.00058>.
- Yong, Y., Zhang, Y., Lyu, Y., 2019. A MYB-related transcription factor from *Lilium lancifolium* L. (LMYB3) is involved in anthocyanin biosynthesis pathway and enhances multiple abiotic stress tolerance in *Arabidopsis thaliana*. *Int. J. Mol. Sci.* 20, 3195. <https://doi.org/10.3390/ijms20133195>.
- Yu, L., Sun, Y., Zhang, X., Chen, M., Wu, T., Zhang, J., Xing, Y., Tian, J., Yao, Y., 2022. ROS1 promotes low temperature-induced anthocyanin accumulation in apple by demethylating the promoter of anthocyanin-associated genes. *Hortic. Res.* 9, uhae007 <https://doi.org/10.1093/hr/uhae007>.
- Zhang, H., Lang, Z., Zhu, J.K., 2018. Dynamics and function of DNA methylation in plants. *Nat. Rev. Mol. Cell Biol.* 19, 489–506. <https://doi.org/10.1038/s41580-018-0016-z>.
- Zhang, Y., Yang, L., Hu, H., Yang, J., Cui, J., Wei, G., Xu, J., 2022. Transcriptome and metabolome changes in Chinese cedar during cold acclimation reveal the roles of flavonoids in needle discoloration and cold resistance. *Tree Physiol.* 42, 1858–1875. <https://doi.org/10.1093/treephys/tpac046>.
- Zhao, H., Xu, D., Tian, T., Kong, F., Lin, K., Gan, S., et al., 2021. Molecular and functional dissection of EARLY-FLOWERING 3 (ELF3) and ELF4 in *Arabidopsis*. *Plant Sci.* 303, 110786 <https://doi.org/10.1016/j.plantsci.2020.110786>.
- Zhao, J., 2015. Flavonoid transport mechanisms: how to go, and with whom. *Trends Plant Sci.* 20, 576–585. <https://doi.org/10.1016/j.tplants.2015.06.007>.
- Zhou, J., Wang, J., Shi, K., Xia, X.J., Zhou, Y.H., Yu, J.Q., 2012. Hydrogen peroxide is involved in the cold acclimation-induced chilling tolerance of tomato plants. *Plant Physiol. Biochem.* 60, 141–149. <https://doi.org/10.1016/j.plaphy.2012.07.010>.
- Zhou, L.J., Li, Y.Y., Zhang, R.F., Zhang, C.L., Xie, X.B., Zhao, C., Hao, Y.J., 2017. The small ubiquitin-like modifier E3 ligase MdsI21 promotes anthocyanin accumulation by sumoylating MdMYB1 under low-temperature conditions in apple. *Plant Cell Environ.* 40, 2068–2080. <https://doi.org/10.1111/pce.12978>.
- Zhou, H., He, J., Zhang, Y., Zhao, H., Sun, X., Chen, X., Liu, X., Zheng, Y., Lin, H., 2024. RHA2b-mediated MYB30 degradation facilitates MYB75-regulated, sucrose-induced anthocyanin biosynthesis in *Arabidopsis* seedlings. *Plant Commun.* 5, 100744. <https://doi.org/10.1016/j.xplc.2023.100744>.
- Zhu, Y.C., Zhang, B., Allan, A.C., Lin-Wang, K., Zhao, Y., Wang, K., Chen, K.S., Xu, C.J., 2020. DNA demethylation is involved in the regulation of temperature-dependent anthocyanin accumulation in peach. *Plant J.* 102, 965–976. <https://doi.org/10.1111/tpj.14680>.
- Zuther, E., Schaarschmidt, S., Fischer, A., Erban, A., Pagter, M., Mubeen, U., Giavalisco, P., Kopka, J., Sprenger, H., Hinch, D.K., 2019. Molecular signatures associated with increased freezing tolerance due to low temperature memory in *Arabidopsis*. *Plant Cell Environ.* 42, 854–873. <https://doi.org/10.1111/pce.13502>.