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Mini-review

Histone variant H2A.Z and transcriptional activators may antagonistically regulate flavonoid biosynthesis

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Abstract: Flavonoid is an important group of plant secondary metabolites. The biosynthesis of this flavonoid group can be precisely regulated by many environmental factors. Currently, histone variants have been documented as important factors in the regulation of eukaryotic gene expression. H2A.Z histone variant has been found to function in numerous plant physiological programs including flavonoid biosynthesis. Moreover, the environmental changes have been shown to significantly influence the replacement between histone proteins and their variants leading to alterations in gene expression. Based on the recent studies, this mini-review is to provide an updated view on the functions of histone variant H2A.Z in the regulation of flavonoid biosynthetic gene expression. In addition, this also suggests a model in which the H2A.Z-containing nucleosomes can be evicted upon environmental stress conditions to facilitate the targeting of transcriptional activators to these flavonoid biosynthetic genes resulting in gene activation and flavonoid accumulation in Arabidopsis plants.

Keywords: environmental stress; flavonoids biosynthesis; H2A.Z; MYB; transcription

In various agricultural products such as fruits (such as blueberry, cranberry, and strawberry) and grains (i.e., red bean, red rice, and red corn), the flavonoid accumulation is very important since this can determine the quality as well as the commercial value of these products. As one of the plant flavonoids, anthocyanin is known as an antioxidant and people have widely used the extracted anthocyanin as a dietary supplement and a natural dye for food and cotton fabric. Because of its scavenging ability, flavonoid can positively function in plant response to abiotic stress conditions [1,2]. Besides, since anthocyanin colors different plant organs such as leaf and flower, it

can also function in UV protection, plant defense system, and pollinator attraction [3].

Many lines of evidence suggest that flavonoid biosynthesis is stimulated by different environmental factors such as light, temperature, biotic and abiotic stress conditions [4–7]. In Arabidopsis, several transcription factors have been identified to function in the regulation of flavonoid biosynthesis. The transcription factors were found to directly associate and activate the expression of flavonoid biosynthetic genes. For instance, different R2R3-MYB transcription factors (MYB11, MYB12, and MYB111) have been documented as activators of some flavonoid biosynthetic genes such as *chalcone synthase* (*CHS*), *chalcone isomerase* (*CHI*), and *flavanone 3-hydroxylase* (*F3H*) [8,9]. On the other hand, a transcription factor complex named MBW (MYB/bHLH/WD40) which is comprised of three types of transcription factor, (1) R2R3-MYB (i.e., MYB75), (2) bHLH (i.e., transparent testa 8, TT8), and (3) WD-repeat (i.e., transparent testa glabra 1, TTG1) is well-known to regulate the expression of other flavonoid biosynthetic genes such as *dihydroflavonol 4-reductase* (*DFR*), *leucoanthocyanidin dioxygenase* (*LDOX*), and *udp-glucose: flavonoid-3-o-glucosyltransferase* (*UF3GT*) [5].

In the plant nucleus, genomic DNA is arranged in a higher structure known as chromatin which is consisted by nucleosomes. Each nucleosome is comprised by a region of DNA wrapped around a histone core (consisting of eight histone proteins including a pair of each H2A, H2B, H3, and H4) [10]. Basically, the chromatin structure can be modified via post-translational modifications of histone proteins which can subsequently alter the interactions between DNA and histone core leading to gene activation or silencing (reviewed by Kim et al. 2015 [11]). In addition to histone modifications, the replacement of a histone protein by its variant can also result in the alteration of stability and accessibility in a given genome region and thereby induce or suppress gene expression [12]. For instance, the reduction of H2A.Z levels can either increase or decrease the expression of different genes upon different environmental conditions such as phosphate starvation, heat shock, drought and salt stresses [7,13–16]. A previous study proposed that the H2A.Z-containing nucleosomes can influence the gene transcription via two aspects: (1) these HA2.Z nucleosomes may interrupt the occupation of RNA polymerase and (2) these can also disturb the association of transcription activators or repressors to their targets and by that activate or suppress the expression of these targeted genes [13].

In mammalian embryonic stem cells (ESCs), the chromatin immunoprecipitation-sequencing (ChIP-seq) revealed that H2A.Z-enriched promoters and enhancers are highly accessible, and these regions are likely to be co-enriched with H3K4 trimethylation (H3K4me3) [17]. It is known that the histone H3K4 and H3K27 are tri-methylated by the MLL (histone H3K4 methyltransferases) and PRC2 (polycomb group) complexes, respectively [18]. Hu et al. (2013) also showed that H2A.Z may act as a general facilitator for the H3K4me3 and H3K27me3 enrichment via facilitating the recruitment of these MLL and PRC2 complexes to the gene promoters and enhancers [17]. In Arabidopsis, a recent study clearly demonstrated that H2A.Z can facilitate the deposition of H3K4me3 leading to increased transcription of *MIR156A* and *MIR156C* genes and the H3K4me3 enrichment is accounted by the H3K4 methyltransferase-arabidopsis trithorax7 (ATXR7) [19]. Arabidopsis genome-wide analysis showed that H2A.Z prefers to associate with H3K27me3 at enhancers to suppress enhancer activity presumably by repressing the enhancement of H3K4me3 [20]. Interestingly, Cai et al. (2019) have found that the reduction of H2A.Z at different Arabidopsis genes involved in flavonoid biosynthesis (such as *CHS*, *CHI*, *F3H*, *F3'H*, and *DFR*) is associated with the increased H3K4me3 enrichment at these gene loci [7]. Overall, these studies

point out that H2A.Z-containing nucleosomes do not only work as facilitators for the H3K4me3 enrichment, but they can also interfere the targeting or functions of H3K4 tri-methyltransferase complexes leading to reduced H3K4me3 deposition as well. On the other hand, the increased enrichment of H3K4me3 at the flavonoid biosynthetic genes was found to impair the H2A.Z levels at these gene loci [7]. As mentioned in a previous part, some studies have documented that H2A.Z-containing nucleosomes can either accelerate or decelerate the gene transcription in response to various environmental alterations [13–16]. Recently, Cai et al. (2019) have shown that drought stress can reduce the H2A.Z levels at flavonoid biosynthetic genes (*CHS*, *CHI*, *F3H*, *F3'H*, and *DFR*) leading to the induction of these genes [7]. In a previous study, Kumar et al. (2012) found that warm temperature induced the eviction of H2A.Z-nucleosomes at the proximal transcriptional start site (TSS) region of *flowering locus T* (*FT*) gene and this associated with the recruiting of PIF4 transcription factor to *FT* locus leading to induction of this gene transcription [21]. It is likely that the enrichment of H2A.Z at a certain locus can physically interfere the association of transcription activators to this locus, that subsequently regulates the given gene expression [13,16,21]. Many transcription factors have been identified to work as direct transcriptional activators of flavonoid biosynthetic genes such as MYB11, MYB12, MYB111, MYB75, HY5, and PIF3 [9,22,23]. These results imply that the environmental stress can induce the H2A.Z-nucleosomes eviction at the flavonoid biosynthetic genes; this can facilitate the targeting of different transcription activators to these loci and thereby activate the gene transcription leading to increase of flavonoid accumulation (Figure 1).

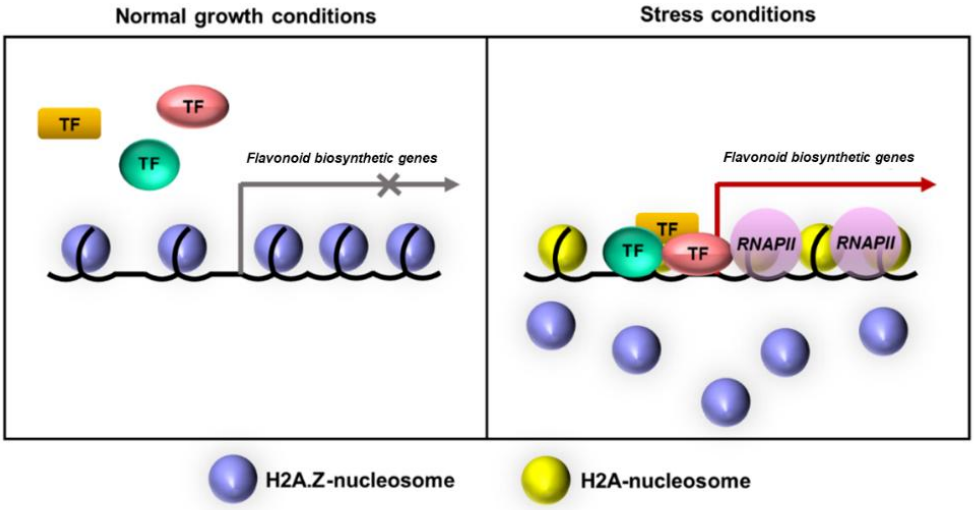

Figure 1. H2A.Z-nucleosomes determine the expression of flavonoid biosynthetic genes.

Under normal growth conditions, the occupation of H2A.Z-containing nucleosomes at flavonoid biosynthetic genes may disturb the association of different transcription activators leading to the low gene expression. Upon environmental stress conditions, H2A.Z-nucleosomes are evicted from the flavonoid biosynthetic gene loci and this can facilitate the binding of transcription activators to these genes resulting in gene activation.

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Conflict of interest

The authors declare no conflict of interest.

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