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Review

HY5, an integrator of light and temperature signals in the regulation of anthocyanins biosynthesis in Arabidopsis

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Abstract: Anthocyanins are well-known plant specialized metabolites and this group can be classified into the phenolic compound class based on their chemical structure characterizing by a C6-C3-C6 carbon framework. Anthocyanins have been identified to play various functions in plants, for example, pigmentation of floral organs, UV protection, and defense system. In addition to their functions in plant growth and development, anthocyanins are also considered as a good natural antioxidant which can be used for human. Because of important functions, the biosynthesis of anthocyanins is precisely regulated by a number of endogenous and exogenous factors. In the plant, light and temperature are critical environmental factors contributing to various developmental processes. From the first identification, ELONGATED HYPOCOTYL 5 (HY5) has been documented to play as an important transcription factor that is involved in a number of signal transduction ways including light and temperature pathways. The purpose of this review is to provide a precise overview of current research progress on the regulation of anthocyanins biosynthesis under the control of HY5 transcription factor.

Keywords: anthocyanins biosynthesis; HY5; light; MYB; temperature; transcription

1. Introduction

Based on the biosynthetic pathway, the plant specialized metabolites can be clustered into three categories including the terpenes, phenylpropanoids, and nitrogen-containing compounds [1]. In phenolics compound group, flavonoid is a well-known subgroup characterizing by a C6-C3-C6

carbon framework in chemical structure. More than 6000 flavonoid compounds were isolated and the number actually continues increasing [2]. A number of *in vivo* and *in vitro* studies have evidenced the biological functions of plant flavonoids in humans and other animals. These natural compounds have positive effects with respect to anti-oxidation, anti-cell proliferation, apoptosis stimulation, anti-inflammation, anti-angiogenesis, anti-invasiveness, and the induction of cell differentiation [3,4]. In addition, *in vivo* studies have demonstrated the positive roles of flavonoids in the prevention of several kinds of cancer in the colon, skin, and lungs [3,5]. In plants, anthocyanins were found to function in UV protection, plant defense system, and pollinator attraction [6]. Besides, anthocyanins are a well-known natural antioxidant in cells and this implies that anthocyanins positively functions in plant response to abiotic stress conditions [7–12]. Moreover, anthocyanins are naturally presences in and responsible for the characteristic color of various fruits such as blueberry, cranberry, and strawberry. Therefore, the anthocyanins accumulation can determine the quality as well as the commercial value of these fruits.

Basically, anthocyanins are synthesized through the phenylpropanoid pathway via a number of steps catalyzed by various cytosolic enzymes. These enzymes were found to weakly associate with the cytoplasmic face of the endoplasmic reticulum (ER) and membranes [13,14]. Moreover, some of these are also present in various organelles such as vacuoles, plastids, and nuclei [15–18]. For example, chalcone synthase (CHS) is a key enzyme of the flavonoids pathway and it is found in the plastids and nuclei [16,17]. Many lines of evidence suggest that anthocyanins biosynthesis is stimulated by different environmental factors such as light, temperature, and biotic and abiotic stress conditions [19–23].

2. Anthocyanins biosynthetic pathway

Anthocyanins can be considered as a product of the general phenylpropanoid pathway [24]. The general phenylpropanoid pathway starts from an essential amino acid (i.e., L-Phenylalanine), which contains a single benzene ring. The L-Phenylalanine is transformed into p-coumaroyl-CoA via three steps catalyzed by phenylalanine ammonia lyase (PAL), cinnamate 4-hydroxylase (C4H), and 4-coumarate CoA ligase (4CL). Besides, another amino acid (i.e., L-tyrosine) can also be converted into p-coumaric acid, a precursor of p-coumaroyl-CoA, by a reaction catalyzed by tyrosine ammonia lyase (TAL). A condensation reaction between one molecule of p-coumaroyl-CoA and three molecules of malonyl-CoA is catalyzed by chalcone synthase (CHS/TT4) to produce chalcone [25,26]. Next, chalcone isomerase (CHI/TT5) catalyzes the production of a colorless flavanone (i.e., naringenin) from chalcone. Next, flavanone 3-hydroxylase (F3H/TT6) uses the substrate (naringenin) to produce dihydrokaempferol. This dihydrokaempferol can also be hydroxylated on the 3’ position of the benzene ring to generate dihydroquercetin by a reaction catalyzed by F3’H/TT7. From these two dihydroflavonols (dihydrokaempferol and dihydroquercetin), the colored anthocyanidins (unstable pigments) can be synthesized by two reactions catalyzed by dihydroflavonol reductase (DFR/TT3) and leucoanthocyanidin oxidase (LDOX). In detail, DFR converts each dihydroflavonol to the colorless compound (leucocyanidin). Afterwards, LDOX catalyzes the oxidation reactions producing the colored anthocyanidins. Depending on the pH and other factors, the colored anthocyanidins can reflect light wavelengths corresponding to red, orange, or purple colors. These unstable colored anthocyanidins can then be converted to stable compounds by glycosylation

catalyzed by UDP-glucose: flavonoid 3-*O*-glucosyl transferase (UF3GT). In the final step, cyanidin-3-glucoside can be methylated by methyltransferases (MTs) [25,26].

3. Transcriptional regulation of anthocyanins biosynthesis in the Arabidopsis vegetative tissues

MYB is a large eukaryotic gene family that contributes diverse functions to these organisms. Based on the number of imperfect repeat motifs in the MYB domain, the MYB gene family is classified into five groups: R1R2R3R4 MYB, R1R2R3 MYB, R2R3 MYB, single repeat MYB, and MYB-like type [27–29]. Every MYB protein contains a DNA MYB-binding domain [30] and a highly diverse C-terminal region. The C-terminal domain mediates interactions of MYB transcription factors with other regulatory proteins [31–33]. Several MYB proteins are known to control many aspects of plant specialized metabolism, including anthocyanins biosynthesis [34]. Genetic and molecular research in Arabidopsis and other plant species have revealed that many MYB transcription factors are master regulators and directly regulate the expression of most of the structural genes encoding enzymes involved in the anthocyanins biosynthetic pathway. As we mentioned in the previous part, the anthocyanins biosynthesis starts from the step condensing p-coumaroyl-CoA and three molecules of malonyl-CoA in a reaction catalyzed by a key enzyme, CHS. Based on the reduction of pigments (because of lack of proanthocyanidins) in the seed coat (the seeds have yellow instead of dark brown color), the Arabidopsis mutants of different genes involved in the anthocyanins biosynthesis were firstly isolated around three decades ago [35,36]. Since the mutants were selected based on the seed coat (transparent testa) phenotype, they were named "*tt*" [35,37]. In Arabidopsis, several anthocyanins biosynthesis enzymes such as CHS, CHI, F3H, and DFR are only encoded by a single gene for each. Therefore, the changes in these genes expression can directly alter the anthocyanins accumulation in plants [21,38]. Various environmental factors including light, temperature, and stress conditions can tightly regulate the expression of these genes and subsequently influence the anthocyanins accumulation in Arabidopsis [19–23]. These environmental factors can be received by various plant receptors and the signals are transferred to downstream transcription factors which can directly or indirectly regulate the expression of anthocyanins biosynthesis genes. For instance, different light conditions (blue, UV-A, and UV-B) and temperature were found to control the *CHS* expression via several photoreceptors and transcription factors [21,23,39,40].

In brief, the anthocyanins biosynthesis includes two main steps (early and late steps) (Figure 1). The early step is involved in the flavonoids biosynthesis (both anthocyanins and flavonols) while the late step is more specific to anthocyanins biosynthesis (Figure 1). Several R2R3-MYB transcription factors, including MYB11, MYB12, and MYB111, have been evidenced as activators of early genes such as *CHS*, *CHI*, and *F3H* which are responsible for both anthocyanins and flavonols biosynthesis [34,41]. These MYB transcription factors belong to subgroup 7 of Arabidopsis R2R3-MYB gene family and seem to work redundantly in the regulation of early gene expression [34]. While MYB11, MYB12, and MYB111 can work in regulating *CHS*, *CHI*, and *F3H* transcription independently from the basic helix-loop-helix (bHLH) partner [34,41], expression levels of late stage genes, *DFR* and *LDOX*, are regulated by the MBW (MYB/bHLH/WD40) complex, which is comprised of three transcription factors, PRODUCTION OF ANTHOCYANIN PIGMENT 1 (PAP1), TRANSPARENT TESTA 8 (TT8), and TRANSPARENT TESTA GLABRA 1 (TTG1) (Figure 1). PAP1 or AtMYB75 is an R2R3-MYB transcription factor and the ectopic expression of this *PAP1*

gene can lead to over-production of anthocyanins in Arabidopsis plants [42]. TTG1 is a WD40 repeat transcription factor functioning in anthocyanins accumulation and post-embryonic development in Arabidopsis [35,43,44]. The basic/helix-loop-helix (bHLH) protein, TT8, is known to form a ternary protein complex (MBW) with PAP1 and TTG1 to activate the expression of late stage genes [45,46]. The TT8 and PAP1 can work as DNA-binding proteins and somehow they can reciprocally regulate the binding and transcriptional activities [46]. The TTG1 was found to be important for the MBW complex activity and it is hypothesized to function in the prevention of other negative regulators [46]. However, the underlying molecular mechanism of these complex components has not been fully understood. In fact, in the Arabidopsis activation-tagging line *pap1-D*, the overexpression of *PAP1* leads to upregulate of *DFR* and *LDOX* transcription, whereas the overexpression of *TTG1* in *TTG1-overexpression* transgenic plants does not [42,43]. In addition to positive regulators, several repressors have been reported, for example MYB-like 2 (MYBL2) and SQUAMOSAL PROMOTER BINDING PROTEIN-LIKE 9 (SPL9), which can interfere with the formation of the MBW complex under various conditions [47–49]. Nguyen et al. (2015) found that the overexpression of *MYB-like Domain* (*MYBD*) gene can increase the anthocyanins accumulation in Arabidopsis [21]. This study showed that HY5 can activate the expression of *MYBD* and this MYBD transcription factor directly binds to the promoter of *MYBL2* and suppresses the transcription of this gene resulting in the upregulation of late stage genes such as *DFR* and *LDOX* [21]. Besides, HY5 and PHYTOCHROME INTERACTING FACTOR 3 (PIF3) transcription factors were investigated to act as direct regulators of genes involved in this biosynthetic pathway (i.e., *CHS*, *CHI*, and *PAP1*) [50–52].

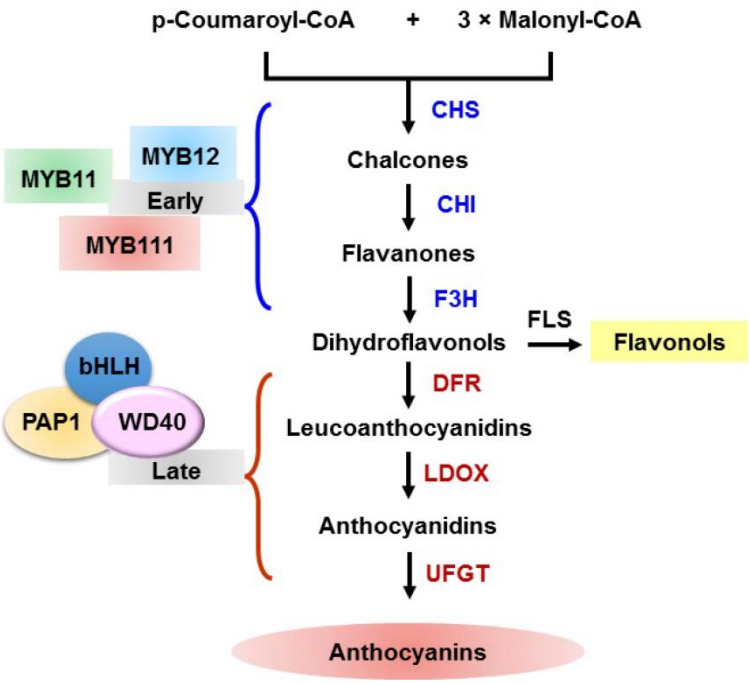

Figure 1. Transcriptional regulation of early and late anthocyanins biosynthesis genes (The MYB11, MYB12, and MYB111 activate the early genes including *CHS*, *CHI*, and *F3H*. The transcription of late stage genes (*DFR*, *LDOX*, and *UF3GT*) is regulated by the MBW (MYB/bHLH/WD40) complex, which is comprised of three transcription factors, PAP1, TT8, and TTG1).

4. Light and temperature govern anthocyanins biosynthesis

For the past several decades, the biological functions of anthocyanins have been widely studied and found to play many important roles in plants. Because anthocyanins can adsorb in the UV spectra, they may function as sunscreens, impart various colors to plant organs (i.e., flowers, fruits, and other vegetative tissues), and display high antioxidant activities in stressed plant cells [53,54]. Therefore, anthocyanins biosynthesis is precisely regulated by various environmental effects including light and temperature.

The *Arabidopsis* seedlings grown under reduced light cannot produce as much anthocyanins as normal seedlings exposed to more intense light [55]. In fact, photosynthesis has been shown to play a role in regulating anthocyanins biosynthesis. In the photosynthetic electron transfer (PET) chain, the redox conditions of the plastoquinone (PQ) pool control anthocyanins biosynthesis genes in cooperation with ethylene and carbohydrates [56]. Moreover, anthocyanins biosynthesis was found to be regulated by light in terms of duration, quality, and quantity [57]. High intensity light was shown to increase anthocyanins accumulation in comparison to plants exposed to lower light intensities [47]. Different light wavelengths have different effects on anthocyanins biosynthesis [58–62]. The quantity of anthocyanins accumulation in many kinds of fruits, such as blueberry, cranberry, and strawberry can determine their quality and commercial value. Many studies have been conducted on the important functions of light during this process [58–62]. Among the different colors of light, blue light has been shown to be the most effective in increasing anthocyanins accumulation [59,61]. Around 20 years ago, Saure performed experiments on apples and showed that anthocyanins levels were strongly impacted by both the quantity and quality of light [58]. In this experiment, Saure found that blue-violet and UV light resulted in stronger effects than far red on anthocyanins production in apples [58]. In addition, a study on strawberry also reported that that blue light played a higher inductive role in anthocyanins accumulation in comparison to green and red light during fruit development and in postharvest fruits [60,62]. These studies provided important and interesting observations that can be applied to increase the quality of agricultural products.

Ambient temperature also plays a role in the regulation of anthocyanins biosynthesis. In *Arabidopsis*, anthocyanins accumulation significantly increased after treatment under cold conditions (4°C) while the high temperature was shown to repress the anthocyanins biosynthesis [23,63]. The same effect of temperature was also observed in grape berry skins [64,65]. In experiments conducted by Mori et al. (2005), the temperature was reduced at night time (15°C) resulting in an increase of anthocyanins accumulation in the skin of berries in comparison to a high temperature (30°C) treatment at night time [64]. Increases in anthocyanins levels in response to low temperatures were caused by induction of structural gene expression and activation of enzymes involved in anthocyanins biosynthesis [64].

5. Light and temperature signaling pathways integrate at HY5 to control anthocyanins biosynthesis

The *hy5* mutant was first identified a few decades ago it is now well-known that HY5 basic leucine zipper (bZIP) transcription factor which plays a diverse function in plant growth and development [66,67]. HY5 has been characterized to function in the regulation of different developmental processes (including photomorphogenesis, anthocyanins biosynthesis, cell elongation,

and chloroplast development) and this transcription factor is considered as a central regulator which integrates various signaling pathways in the plant cells [66–68]. This transcription factor has been documented as a downstream worker of different light photoreceptors such as phytochromes, cryptochromes, and UV-B photoreceptors [66–69]. It is well-known that CONSTITUTIVE PHOTOMORPHOGENIC1 (COP1) and SUPPRESSOR OF PHYA-105 (SPA) proteins can comprise an E3 ubiquitin ligase complex which is a major repressor of photomorphogenesis in Arabidopsis [70–72]. In downstream of the light signaling pathway, the E3 ubiquitin ligase complex (COP1/SPA) was found to be able to interact directly with and regulate HY5 protein stability in the nucleus [69,73,74]. Generally, the COP1/SPA complex is negatively regulated by the light signal. The activities of the COP1/SPA complex can be repressed by the direct interaction with the light-activated photoreceptors which can trigger the nuclear exclusion of COP1, disrupt the COP1-SPA interaction, and even promote SPA protein degradation [72]. In the absence of light, COP1/SPA is localized in the nucleus and can directly interact with HY5 to induce its ubiquitin-mediated degradation whereas the light can translocate the COP1 to the cytosol leading to the high accumulation of HY5 protein in the nucleus [72,74]. On the other hand, high temperature is known to positively regulate the COP1 protein [75]. The high temperature was found to trigger the nuclear import of COP1 [76]. However, the underlying mechanism is still unknown [75,76]. These indicate that light and high temperature signals differently regulate the HY5 protein stability via their different effects on the COP1 function (Figure 2).

HY5 has been evidenced to function as a transcriptional activator or repressor [21,22,50,52,67,69,77–79]. However, a previous study showed that HY5 protein does not contain an activation or repression domain [69]. Therefore, it was hypothesized that HY5 regulates the transcription of its targets relied on its DNA-binding activity and other interacting partners [80]. Recently, based on the functional characterizations of activator-domain and repressor-domain fused HY5 proteins (HY5-VP6 and HY5-SRDX, respectively), Burko et al. (2020) found that the primary activity of HY5 is a transcriptional activator and this function depends on other partners [79]. Previous studies found that HY5 can directly bind to and activate both early and late biosynthesis genes including *CHS*, *DFR*, *LDOX*, and *UF3GT* [50,78]. Besides, HY5 was also found to be a direct transcriptional regulator of several regulatory genes such as *MYB12*, *MYB111*, *PAP1*, *MYBD*, and *MYBL2* [21,22,52,77]. HY5 may act as a light-cytokinin integrator to activate the expression of *MYBD* which subsequently regulate the anthocyanins accumulation in Arabidopsis plant [21]. On the other hand, Wang et al. (2016) found that HY5 functions as a repressor of *MYBL2* transcription under light-growth conditions [22]. Moreover, HY5 was also characterized as a positive regulator of a micro RNA, *microRNA858a* (*miR858a*), which can increase the anthocyanins accumulation via direct inhibition of *MYBL2* translation [22]. Recently, a study has shown that high ambient temperature can attenuate the anthocyanins biosynthesis via a mechanism involved in HY5 and COP1 [23]. This study found that the high temperature conditions promote the COP1-mediated degradation of the HY5 proteins and this result in the reduction of transcript levels of both early and late anthocyanins biosynthesis genes [23]. Overall, the HY5 transcription factor could be considered as a central integrator of light and temperature signaling pathways in the regulation of anthocyanins biosynthesis (Figure 2).

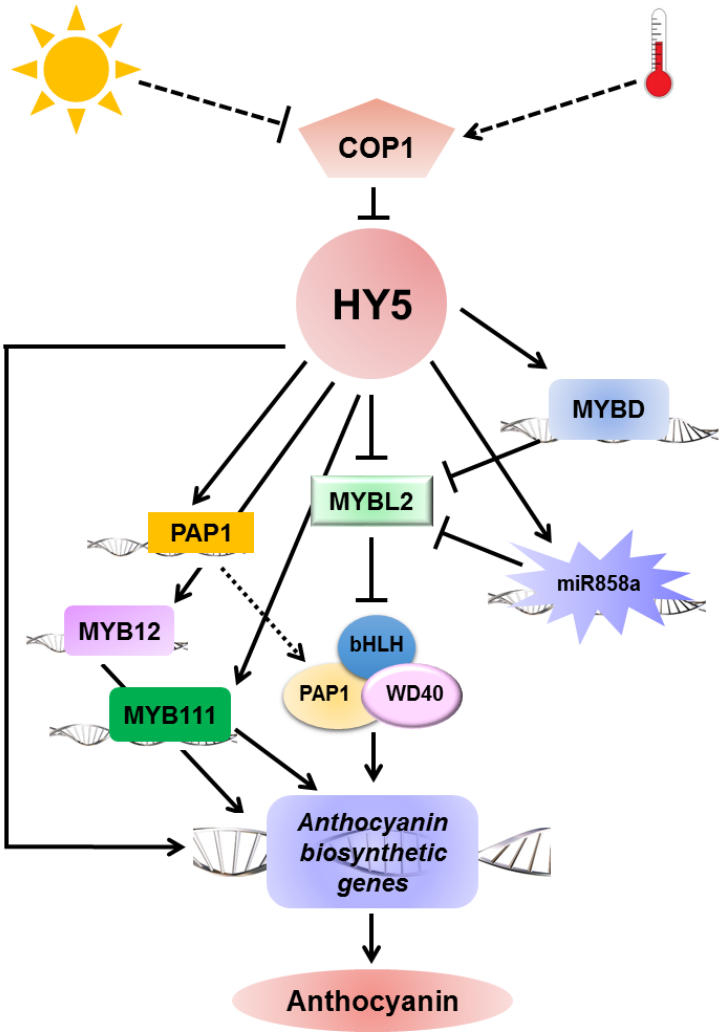

Figure 2. HY5 centralizes the light and temperature signals to headquarter the anthocyanins biosynthesis (In response to light and/or temperature signals, the stability of HY5 proteins can be controlled by COP1. The HY5 transcription factor can directly activate anthocyanins biosynthesis via the regulation of both early and late biosynthesis genes including *CHS*, *DFR*, *LDOX*, and *UF3GT*. Besides, HY5 is able to indirectly control the anthocyanins biosynthesis via its transcriptional regulation of several regulatory genes such as *MYB12*, *MYB111*, *PAP1*, *MYBD*, and *MYBL2*).

6. Conclusions

A number of studies on anthocyanins have clarified its biosynthetic pathway, its biochemical characteristics, and its biological functions in plants as well as its contribution to human health. Since its important functions, the biosynthesis of anthocyanins is influenced by many environmental factors including light and temperature. It is interesting that HY5 can directly or indirectly regulate the anthocyanins biosynthesis in response to light and temperature conditions. This indicates that HY5 is an important transcription factor functioning in the regulation of anthocyanins biosynthesis which could provide great potential for future applications in agriculture production.

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Conflict of interest

The author declares there is no conflict of interest.

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