

Transcriptional control of flavonoid biosynthesis

Fine-tuning of the MYB-bHLH-WD40 (MBW) complex

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Keywords: flavonoids, MYBL2, SPL9, TT1, TCP3, MBW complexes, *Arabidopsis thaliana*

Flavonoids are plant secondary polyphenolic metabolites and fulfil many vital biological functions, offering a valuable metabolic and genetic model for studying transcriptional control of gene expression. *Arabidopsis thaliana* mainly accumulates 3 types of flavonoids, including flavonols, anthocyanins, and proanthocyanidins (PAs). Flavonoid biosynthesis involves a multitude of well-characterized enzymatic and regulatory proteins. Three R2R3-MYB proteins (MYB11, MYB12, and MYB111) control flavonol biosynthesis via activating the early biosynthetic steps, whereas the production of anthocyanins and PAs requires the MYB-bHLH-WD40 (MBW) complex to activate the late biosynthetic genes. Additional regulators of flavonoid biosynthesis have recently come to light, which interact with R2R3-MYBs or bHLHs to organize or disrupt the formation of the MBW complex, leading to enhanced or compromised flavonoid production. This mini-review gives an overview of how these novel players modulate flavonoid metabolism and thus plant developmental processes and further proposes a fine-tuning mechanism to complete the complex regulatory network controlling flavonoid biosynthesis.

Introduction

Flavonoids constitute a large family of plant secondary polyphenolic metabolites categorized into 6 major subgroups according to their molecular structures, including chalcones, flavones, flavonols, flavandiols, anthocyanins, and proanthocyanidins (PAs; also called condensed tannins). These natural endogenous compounds are widely distributed in higher plants and fulfill a variety of important biological functions. Besides genetically contributing to Mendel's elucidation of inheritance in peas (*Pisum sativum*), McClintock's discovery of transposable elements in maize (*Zea mays*), and genetic dissection of co-suppression phenomena in petunia (*Petunia hybrida*), flavonoids also provide plants with beautiful pigmentation to protect against UV radiation and attract pollinators and seed dispersers.¹ In addition, flavonoids exert potential beneficial effects

on human health and play vital roles in plant-microbe interactions and defense response as antimicrobial agents.¹

Arabidopsis (*Arabidopsis thaliana*) plants produce 3 major groups of flavonoids, including colorless to pale yellow flavonols in vegetative tissues and seeds, red to purple anthocyanins in vegetative organs, as well as colorless PAs in seeds, which turn brown upon oxidative reactions during seed desiccation.¹ Flavonoid biosynthesis is largely modulated at the transcriptional level and starts with the general phenylpropanoid metabolism involving phenylalanine ammonia-lyase (PAL), cinnamate 4-hydroxylase (C4H), and 4-coumarate:CoA ligase (4CL) (Fig. 1). Genetic and biochemical dissection of the flavonoid biosynthetic pathway reveals that *TRANSPARENT TESTA4* (*TT4*), *TT5*, *TT6*, and *TT7* encode chalcone synthase (CHS), chalcone isomerase (CHI), flavanone 3-hydroxylase (F3H), and flavanone 3'-hydroxylase (F3'H), respectively. Successive reactions catalyzed by these structural enzymes generate dihydroflavonols, the last common precursors for the biosynthesis of flavonols, anthocyanins, and PAs (Fig. 1).²⁻⁴ Dihydroflavonols are then oxidized by flavonol synthase (FLS) to produce flavonols, such as quercetins and kaempferols. These early biosynthetic steps are transcriptionally regulated by the 3 closely related R2R3-MYB proteins MYB11, MYB12, and MYB111, which activate the early flavonoid biosynthetic genes *CHS*, *CHI*, *F3H*, and *FLS1* (EBGs; Fig. 1).^{5,6} Intriguingly, the early flavonoid biosynthetic steps are even discovered in the bryophytes (*Physcomitrella patens* and *Marchantia polymorpha*), implying that flavonoids might have evolved to act first as chemical messengers and then UV sunscreens.⁷ Dihydroflavonol 4-reductase (DFR) encoded by the late flavonoid biosynthetic gene *DFR* (*TT3*) reduces dihydroflavonols to leucoanthocyanidins and further downstream catalytic enzymes, including leucoanthocyanidin dioxygenase (LDOX), anthocyanidin reductase (ANR, encoded by *BANYULS* or *BAN*) and *TT12*, eventually result in the production of anthocyanins and PAs (Fig. 1).²⁻⁴ Several of the late flavonoid biosynthetic genes (LBGs) are activated by the MYB-bHLH-WD40 (MBW) ternary transcriptional complex comprising 3 classes of regulatory proteins, including R2R3-MYBs, bHLHs, and *TRANSPARENT TESTA GLABROUS1* (*TTG1*; also termed *WD40*) (Fig. 1).²⁻⁴ Anthocyanin production is transcriptionally regulated by the MBW complex composed of *TTG1*, one R2R3-MYB protein from *PRODUCTION OF ANTHOCYANIN PIGMENTS* (*PAP1*), *PAP2*, *MYB113*, or *MYB114*, as well as one bHLH protein from *TT8*, *GLABROUS3* (*GL3*), or *ENHANCER OF GLABRA3* (*EGL3*) (Fig. 1).⁴ Seed-specific accumulation of PAs requires the activity of the MBW

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Submitted: 12/05/2013; Accepted: 12/13/2013; Published Online: 01/06/2014
Citation: Li S. Transcriptional control of flavonoid biosynthesis: Fine-tuning of the MYB-bHLH-WD40 (MBW) complex. *Plant Signaling & Behavior* 2014; 9:e27522; PMID: 24393776; <http://dx.doi.org/10.4161/psb.27522>

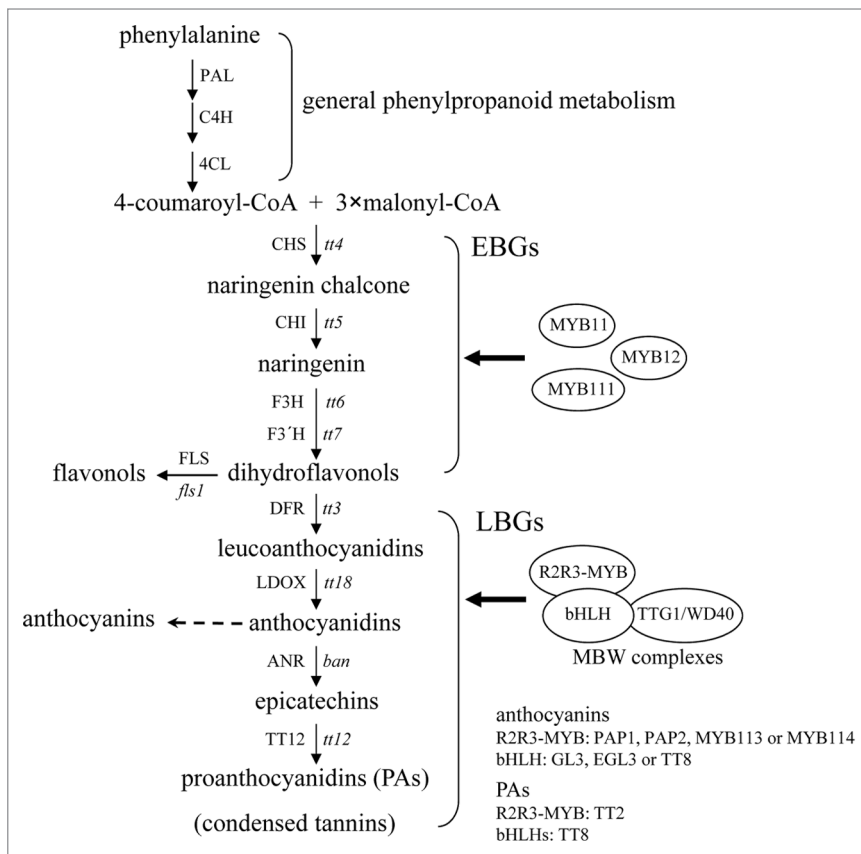


Figure 1. The biosynthetic pathway for flavonols, anthocyanins, and PAs in *Arabidopsis*. This pathway starts with the general phenylpropanoid metabolism and subsequent steps are catalyzed by a series of structural enzymes leading to the biosynthesis of 3 final end products, including flavonols, anthocyanins, and PAs. The early biosynthetic genes (EBGs) are activated by 3 functionally redundant R2R3-MYB proteins (MYB11, MYB12, and MYB111), whereas the expression of the late biosynthetic genes (LBGs) requires the transcriptional activation activity of the R2R3-MYB/bHLH/WD40 (MBW) complex. Enzymes are denoted in uppercase and corresponding genetic loci are indicated in italic lowercase letters. PAL, phenylalanine ammonia-lyase; C4H, cinnamate 4-hydroxylase; 4CL, 4-coumarate:CoA ligase; CHS, chalcone synthase; CHI, chalcone isomerase; F3H, flavanone 3-hydroxylase; F3'H, flavanone 3'-hydroxylase; DFR, dihydroflavonol 4-reductase; LDOX, leucoanthocyanidin dioxygenase; ANR, anthocyanidin reductase; *tt*, *transparent testa*; *ban*, *banyuls*.

complex consisting of TT2, TT8, and TTG1 (Fig. 1).^{2,8} Similar MBW complexes also control various aspects of epidermal cell patterning, such as the development of trichomes and root-hairless cells as well as the biosynthesis of seed mucilage.⁹ These epidermal cell-specific MBW complexes comprise TTG1, one R2R3-MYB protein from GL1 or WEREWOLF (WER) and one bHLH protein from GL3 or EGL3.⁹

As described above, the flavonoid biosynthetic pathway in *Arabidopsis* involves a plethora of functionally well-known catalytic or regulatory proteins. Additional regulators of flavonoid production have recently emerged, some of which participate in the flavonoid pathway via directly interacting with the component of the MBW complex.^{3,4,6,10-13} These modulators belong to different families of transcription factors, including the R3-MYB protein MYBL2, the miR156-targeted SQUAMOSA PROMOTER BINDING PROTEIN-LIKE9 (SPL9), the WIP-type zinc finger protein TT1, and the class II CIN-TCP protein TCP3.^{3,4,10-12}

Here, I summarize the current knowledge of how these novel players regulate flavonoid biosynthesis and thus plant developmental processes and further put forward a fine-adjusting mechanism to complete the complex regulatory network involved in flavonoid production.

MYBL2 Inhibits the Activity of the MBW Complex and Negatively Regulates Anthocyanin Biosynthesis

MYB proteins make up the largest transcription factor family in *Arabidopsis* and most of its members belong to plant-specific R2R3-MYBs.¹⁴ A group of R3-MYBs participates in the modulation of epidermal cell fates, acting as inhibitors of the MBW complex GL1-GL3/EGL3-TTG1.¹⁴⁻¹⁸ Five of these closely related R3-MYBs, namely CPC (CAPRICE), TRY (TRIPTYCHON), ETC1 (ENHANCER OF CAPRICE AND TRIPTYCHON1), ETC2, and ETC3, are capable of interacting with the bHLH proteins GL3, EGL3, and TT8 to counteract the transcriptional activity of the MBW complex by sequestering its bHLH component.^{16,17} Another related R3-MYB protein, TCL1 (TRICHOMELESS1), can be recruited to the *cis*-acting regulatory elements of *GL1* to inhibit its transcription and thus negatively regulates trichome formation.¹⁸

MYBL2 encodes a more distantly related small R3-MYB protein and its ectopic expression in *Arabidopsis* leaves prevents trichome initiation, implicating that MYBL2 exerts a similar regulatory function as other small R3-MYBs in the determination of epidermal cell fates.^{10,11,13} In contrast, the seed-specific expression of *MYBL2* or other small R3-MYB genes (*CPC*, *TRY*, *ETC1*, *ETC2*, and *ETC3*) under the control of the *TT8* promoter demonstrates that MYBL2 does not function redundantly with other small R3-MYBs and is the only small R3-MYB protein interfering with the flavonoid pathway.^{10,11} The loss of *MYBL2* activity in the *mybl2* null mutant does not affect the biosynthesis of flavonols and PAs in seeds or vegetative tissues, but results in anthocyanin hyperaccumulation and heightened expression of structural and regulatory anthocyanin genes, including *DFR*, *LDOX*, *GL3*, *TT8*, and *PAP1*.^{10,11} Transient expression analysis using the *DRF* promoter as a target activated by regulatory proteins (TT2, PAP1, TT8, and EGL3) provides evidence implying that MYBL2 directly inhibits the activity of the MBW complex.^{10,11} Consistently, MYBL2 fails to associate directly with the *DRF* promoter and interacts with the bHLH proteins GL3, EGL3, and TT8 in yeast cells.^{10,11} Besides, the expression of *MYBL2* is not only developmentally controlled but also regulated

by environmental stimuli, such as light intensity.^{10,11} These observations together indicate that MYBL2 interacts with the bHLHs by competing with R2R3-MYBs to prevent the formation of the MBW complex and thus negatively regulates anthocyanin production in response to developmental and environmental stimuli. Intriguingly, the R3-MYB protein PhMYBx from petunia operates as an inhibitor of anthocyanin biosynthesis via sequestering the bHLH protein PhAN1 into inactive complexes, indicative for a conserved regulatory mechanism among dicots.¹⁹

SPL9 Negatively Regulates Anthocyanin Accumulation via Destabilizing the MBW Complex

The *Arabidopsis* genome encodes 17 SQUAMOSA PROMOTER BINDING PROTEIN-LIKE (SPL) proteins that are classified into 2 groups.²⁰ The first group comprises only 5 members (SPL1, SPL7, SPL12, SPL14, and SPL16) and the remaining 12 SPL proteins fall into the second group. With the exception of SPL8, all members of the second group are targeted by miR156/157 for posttranscriptional regulation.^{20,21} These plant-specific SPB-box proteins are known to influence a large array of developmental processes in *Arabidopsis*, such as promoting the juvenile-to-adult phase transition by activating miR172, inducing flowering via activating *LEAFY* and the MADS box genes, inhibiting trichome initiation on floral organs through activating *TCL1*, as well as concertedly controlling male fertility.²¹⁻²⁴ Recently, the miR156/157-targeted SPLs have been shown to affect metabolic fluxes through the branched flavonoid biosynthetic pathway.⁴

Dihydroflavonols serve as common precursors of flavonols and anthocyanins and can be oxidized either by FLS to form flavonols or reduced by DFR to produce leucoanthocyanidins in the first dedicated step for anthocyanin biosynthesis (Fig. 1). Substrate competition between FLS and DFR controls metabolic flow in the flavonoid biosynthetic pathway. In *Arabidopsis* stems, anthocyanins accumulate in an acropetal manner, with the highest level at the junction between the stem and the rosette leaves. This pattern of anthocyanin distribution is controlled by miR156/157-targeted SPL genes.⁴ In the tissues with a high anthocyanin concentration, high levels of miR156/157 reduce the SPL activity and thus elevate the expression of anthocyanin biosynthetic genes.⁴ As a result, dihydroflavonols are directed into the anthocyanin branch. Contrarily, along the elongating stem of plants, gradually reduced miR156/157 levels result in progressively increased expression of SPL genes during plant development.⁴ As SPL levels rise, the expression of anthocyanin biosynthetic genes is more and more inhibited, leading to increased flavonol production by FLS.⁴ Enhanced flavonol accumulation is also observed in the overexpressors of *SPL9* or *SPL10*.⁴ Therefore, an antagonistic relationship exists between anthocyanin and flavonol biosynthesis in *Arabidopsis* stems. An increase in the ratio of flavonols to anthocyanins advances side by side with the transition from the formation of leaves to the formation of flowers on *Arabidopsis* shoots. At least one of the miR156/157 targets, SPL9, competes with TT8 for binding to anthocyanin-specific R2R3-MYBs (PAP1 and MYB113) to disrupt the MBW complex and thus negatively regulates anthocyanin biosynthesis via directly preventing the

expression of anthocyanin biosynthetic genes (*F3'H*, *DFR*, *BAN*, and *UGT75C1*).⁴ The molecular mechanism by which SPL9 controls the transcription of anthocyanin biosynthetic genes bears a striking similarity to that of MYBL2.

TT1 Interacts with TT2 and Positively Regulates PA Accumulation in Endothelial Cells of the Seed Coat

Development of the seed coat (also termed the testa) involves a complex process whereby the integuments of the ovule differentiate into 5 layers of specialized cells: 2 layers in the outer integument and 3 layers in the inner integument. During early stages of seed development, the innermost layer of the testa (also called the endothelium) and the seed base (micropyle and chalaza) synthesize the precursors of PAs.²⁵ These colorless precursors polymerize and oxidize to condensed tannins at later phases of seed development, giving a brown color to mature seeds.²⁵ Three regulatory proteins (TT2, TT8, and TTG1) form the MBW complex to regulate PA biosynthesis via activating the expression of LBGs (*DFR*, *LDOX*, *BAN*, and *TT12*).^{8,26,27} *TT2* expression is confined to PA-producing cells in the seed coat, whereas *TT8* and *TTG1* are expressed in both seeds and vegetative tissues.²⁶ Specific accumulation of PAs in the testa and at the seed base is conferred by the spatio-temporally restricted expression pattern of *TT2*.²⁶

TT1 encodes a WIP-type zinc finger protein that together with 5 other WIP proteins belongs to the subgroup A1d of the *Arabidopsis* zinc finger proteins.²⁸ Functional characterization of 3 WIPs (WIP2/NTT, WIP6/DOT5, and CmWIP1) reveals the involvement of this class of proteins in plant developmental processes.^{29,30} *TT1* is expressed in the endothelium of the seed coat and is required for the competence of endothelial cells to synthesize condensed tannins.³¹ *TT16* encodes the *ARABIDOPSIS* BSISTER (ABS) MADS domain protein and also exhibits endothelium-specific expression in the testa.² Although the endothelium layer of the *tt1* and *tt16* seeds lacks PA accumulation, the chalazal-micropylar area of these mutant seeds still produces PAs.^{2,3} These data suggest that PA biosynthesis at the seed base is not controlled by *TT1* and *TT16*. *TT1* is able to interact with *TT2* but not with *TT8* or *TTG1* and ectopic expression of *TT2* partially restores PA production in the *tt1* and *tt16* endothelial cells.³ These findings together indicate that *TT1* may organize the formation of the PA-specific MBW complex via associating with *TT2* and that the full activity of this complex requires the participation of *TT1*.

TCP3 Enhances Flavonoid Biosynthesis and Negatively Regulates Auxin Response via Interacting with R2R3-MYBs

The plant-specific TCP family of transcription factors is represented by the first 3 characterized members, TEOSINTE BRANCHED1 in maize (*Zea mays*), CYCLOIDEA (CYC) in *Antirrhinum majus*, and PROLIFERATING CELL NUCLEAR ANTIGEN FACTOR in rice (*Oryza sativa*).³² Among the 24 TCP proteins encoded by the *Arabidopsis* genome, 13 are classified as members of the class I/TCP-P and the other 11 TCPs fall into the class II/TCP-C, which is further subdivided into the CYC/TB1 and

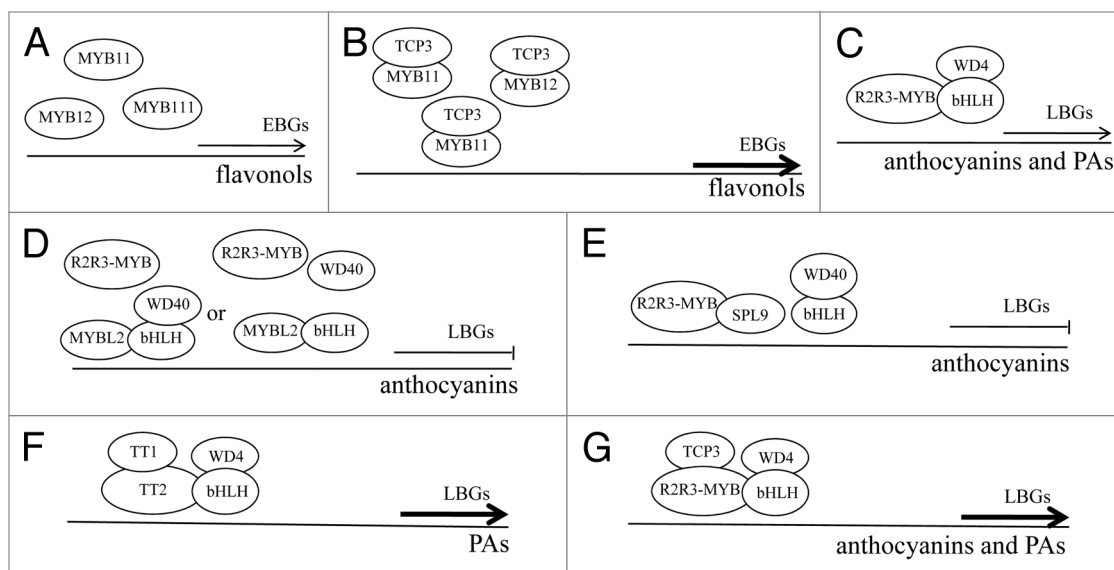


Figure 2. A schematic model for the fine-tuning of the flavonoid biosynthetic pathway. MYB11, MYB12, and MYB111 redundantly activate the expression of EBGs (A). TCP3 associates with these 3 R2R3-MYBs to stimulate the transcription of EBGs and thereby enhances flavonol production (B). The ternary R2R3-MYB/bHLH/WD40 (MBW) complex activates the expression of LBGs and thus controls the biosynthesis of anthocyanins and PAs (C). MYBL2 and SPL9 behave as negative fine-tuners of anthocyanin biosynthesis and disrupt the formation of the MBW complex via interacting competitively with bHLHs in the case of MYBL2 (D) or with R2R3-MYBs in the case of SPL9 (E). By contrast, TT1 acts as a positive fine-tuner of the PA biosynthesis in the endothelial cells of the testa (F) and TCP3 functions as a positive fine-tuner of both anthocyanin- and PA-specific MBW complexes (G). The 2 positive fine-tuners TT1 and TCP3 organize the formation of the MBW complex by synergistically associating with R2R3-MYBs. The counteracted or enhanced activity of the MBW complex reduces or heightens the biosynthesis of anthocyanins and PAs via influencing the expression of LBGs, respectively. Thin arrows indicate the transcription of LBGs and EBGs controlled by the ternary MBW complex and MYB11, MYB12, or MYB111, respectively. Hammers denote the inhibitory effects of MYBL2 or SPL9 on the transcription of LBGs. Thick arrows represent the heightened expression of EBGs or LBGs.

CINCINNATA (CIN) subgroups.^{32,33} TCP proteins have been demonstrated to control a multitude of plant biological processes, such as floral symmetry, plant architecture, the morphogenesis of lateral organs, leaf senescence, and defense response.³⁴⁻⁴⁴ In *Arabidopsis*, several TCP proteins are known to participate in developmental processes via regulating the biosynthetic pathways of plant hormones.⁴³⁻⁴⁶ *TCP1* directly activates *DWARF4* expression to promote brassinosteroid (BR) biosynthesis, thereby resulting in the longitudinal elongation of leaves and stems.^{45,46} The miRJA-targeted *CIN-TCPs* (*TCP2-4*, *TCP10*, and *TCP24*) operate redundantly to regulate leaf senescence and defense response via directly activating *LIPOXYGENASE2* (*LOX2*) expression to modulate jasmonic acid (JA) biosynthesis.^{43,44}

Combinatorial analysis of transgenic plants expressing the miRJA-resistant *mTCP3* and the dominant-negative *TCP3SRDX* has recently revealed a novel regulatory role for *TCP3* in enhancing flavonoid biosynthesis.¹² Seedlings and seeds of *mTCP3* plants hyperaccumulate flavonols, anthocyanins and PAs, whereas slightly reduced levels of these compounds are detected in *TCP3SRDX* plants.¹² R2R3-MYBs not only activate the transcription of EBGs but also participate in the formation of the MBW complex to control the expression of LBGs.^{8,14,27,47} *TCP3* interacts with R2R3-MYBs but neither with bHLHs nor with TTG1 and significantly strengthens the transcriptional activation capacity of TT8-bound R2R3-MYBs.¹² Heterodimerization of *TCP3* with MYB12 or MYB111 likely upregulates EBGs and hence enhances flavonol production. The interactions of *TCP3* with anthocyanin- and

PA-specific R2R3-MYBs suggest that *TCP3* acts in a manner similar to TT1 to promote flavonoid production via stabilizing the formation of the MBW complexes and thus stimulating the expression of LBGs. In agreement, *mTCP3* expression activates many enzymatic and regulatory genes involved in the early (*4CL*, *CHS/TT4*, *F3H/TT6*) and late steps (*DFR/TT3*, *LDOX/TT18*, *PAP1*) of the flavonoid pathway and downregulation of these respective genes is also detected in *TCP3SRDX* plants.¹² The failure to detect the interaction between *TCP3* and *GL1* is consistent with the lack of trichome phenotypes in transgenic plants, lending support to the specificity of *TCP3* interactions with flavonoid R2R3-MYBs. Interestingly, *TCP3* forms a heterodimer with MYBL2 in yeast cells and it is therefore also possible that *TCP3* reinforces the formation of the MBW complex via binding to MYBL2 and thus freeing bHLHs.¹²

Additionally, transgenic plants expressing *mTCP3* display altered leaf phyllotaxy, abnormal vasculature patterning, reduced apical dominance, impaired root development, and reduced organ size.¹² These developmental abnormalities are reminiscent of auxin-deficient or -insensitive mutants.⁴⁸⁻⁵⁰ Microarray analysis of *mTCP3* seedlings reveals many auxin-related genes with reduced expression levels, including the early auxin-responsive genes (*GH3.17* and *AUX/IAA29*), the auxin transporter protein genes (*PGP19*, *PGP1*, and *AUX1*) and the auxin receptor gene *TIR1*.¹² Contrarily, enhanced expression of several auxin-related genes (*AUX/IAA29*, *PARI*, and *PGP1*) is detectable in *TCP3SRDX* plants.¹² In conjunction with the data from studies of the auxin response

reporter *pDR5::GUS* and the auxin efflux carrier *pPIN1::PIN1-GFP*, morphological defects and transcriptome data of transgenic plants strongly indicate that *TCP3* negatively modulates auxin response, likely by weakening auxin transport capacity.

Endogenous flavonols, including quercetins and kaempferols, are considered to be negative regulators of cellular auxin efflux and polar auxin transport.⁵¹⁻⁵⁵ Altering in planta flavonol levels via applying exogenous flavonols, activating or inactivating the flavonoid pathway interferes with auxin transport capacity and thus affects many auxin-related biological processes.⁵¹⁻⁵⁶ Expression of *mTCP3* in wild type plants strengthens flavonol production and causes auxin-related developmental abnormalities.¹² The knockout mutant *tt4-11* does not produce any class of flavonoids^{57,58} and is therefore utilized to unveil the regulatory hierarchy of *TCP3* for these 2 biological processes. Phenotypic analysis of *mTCP3/tt4-11* plants demonstrates that the absence of flavonoid biosynthesis in the *tt4-11* mutant disables the auxin-related defects caused by expressing *mTCP3*.¹² Given this observation, compromised auxin response observed in *mTCP3* plants is thus due to heightened flavonol production. Taken together, these results indicate that *TCP3* promotes flavonol accumulation via binding to R2R3-MYBs and thus reduces auxin response likely by impairing auxin transport capacity.

Conclusions and Perspectives

Based on the data presented above, a model is proposed to elucidate how the aforementioned fine-tuners control flavonoid biosynthesis (Fig. 2). Three closely related R2R3-MYBs (MYB11, MYB12, and MYB111) redundantly activate the transcription of EBGs (Fig. 2A). *TCP3* interacts with these 3 R2R3-MYBs to stimulate the expression of EBGs and thus promotes flavonol production (Fig. 2B). The ternary MBW complex regulates the biosynthesis of anthocyanins and PAs via directly activating the late flavonoid biosynthetic steps (Fig. 2C). The negative fine-tuners of the flavonoid pathway disrupt the formation of the MBW complex via competitively interacting with bHLHs in the case of MYBL2 (Fig. 2D) or with R2R3-MYBs in the case of

SPL9 (Fig. 2E). By contrast, the positive fine-tuners, including TT1 and TCP3, organize the formation of the MBW complex by synergistically associating with R2R3-MYBs (Fig. 2F, G). The counteracted or enhanced activity of the MBW complex further reduces or enhances flavonoid biosynthesis via affecting the expression of LBGs, respectively. This fine-tuning of the flavonoid pathway is therefore achieved by competitive or synergistic protein interactions that disrupt or organize the formation of the MBW complex, allowing plants to respond to numerous developmental and environmental signals during growth and development.^{3,4,10-12} Intriguingly, 4 closely related R2R3-MYBs (MYB3, MYB4, MYB7, and MYB32) from the R2R3-MYB subgroup 4 may also act as fine-tuners of the flavonoid pathway in a manner similar to MYBL2.^{6,13} In addition, 3 LATERAL ORGAN BOUNDARY DOMAIN (LBD) proteins (LBD37, LBD38, and LBD39) operate upstream of *PAP1* and *PAP2* to negatively modulate anthocyanin production.⁵⁹ Activation of EBGs by *TT1* and *PAPs* as well as the positive feedback regulation of *TT8* expression by the MBW complex adds another layer of complexity to the regulatory mechanism of the flavonoid pathway.⁶⁰⁻⁶²

The flavonoid biosynthetic pathway has been one of the most intensively investigated metabolic systems in plants. Although numerous transcriptional regulators have been identified and characterized, many gaps still remain in our understanding of how this metabolic pathway is transcriptionally regulated in response to environmental and developmental signals. The availability of genomics data sets for model plant species, including *Arabidopsis*, rice, mosses, and *Medicago truncatula*, offers a good opportunity to investigate transcriptional control of flavonoid production from a completely new perspective. Advancing our knowledge of the flavonoid pathway will favor the development of new biotechnological tools for the generation of value-added plants with optimized flavonoid contents.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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