Plants express genes that encode enzymes that catalyse reactions to form plant secondary metabolites in specific cell types. However, the mechanisms of how plants decide their cellular metabolic fate and how cells diversify and specialise their specific secondary metabolites remains largely unknown. Additionally, whether and how an established metabolic program impacts genome-wide reprogramming of plant gene expression is unclear. We recently isolated PAP1-programmed anthocyanin-producing (red) and -free (white) cells from Arabidopsis thaliana; our previous studies have indicated that the PAP1 expression level is similar between these two different cell types. Transcriptional analysis showed that the red cells contain the TTG1-GL3/TT8-PAP1 regulatory complex, which controls anthocyanin biosynthesis; in contrast, the white cells and the wild-type cells lack this entire complex. These data indicate that different regulatory programming underlies the different metabolic states of these cells. In addition, our previous transcriptomic comparison indicated that there is a clear difference in the gene expression profiles of the red and wild-type cells, which is probably a consequence of cell-specific reprogramming. Based on these observations, in this report we discuss the potential mechanisms that underlie the programming and reprogramming of gene expression involved in anthocyanin biosynthesis.

Introduction

More than two hundred thousand structurally diverse plant secondary metabolites (PSMs, plant natural products) have been reported in the plant kingdom. In general, PSMs provide diverse functions such as protection against herbivores and pathogens and attraction of pollinators and seed dispersers. Because they are biosynthesised from primary metabolites (e.g., amino acids), PSMs have been concisely categorised into nitrogen-containing secondary metabolites (alkaloids, glucosinolates, cyanogenic glycosides, amines and non-protein amino acids), terpenoids, and phenolics. An obvious biosynthetic property of PSMs is that their genes are expressed in a family-, plant-, tissue-, cell- or time-specific manner. Phytoalexins are also PSMs as a rapidly expressed result of plant-microbial interactions. PSMs are biosynthesised in pathways that are catalysed by enzymes encoded by genes, and these metabolic pathways are regulated by transcription factors. In a previous review, Vom Endt et al. asked the important question of what regulates the regulators. Some recent studies have provided relevant evidence and attempted to answer this question. For example, treatment of suspension-cultured Medicago truncatula cells with either jasmonic acid or yeast extract induces the expression of genes that encode for transcription factors that can reprogram secondary metabolism. However, exactly how specific metabolic fates of plant cells are determined and how specific metabolic pathways are memorised by plant cells remain unknown. The answers to these two questions will increase our understanding of PSM biosynthesis and metabolic engineering.

Anthocyanins are a group of natural pink/red/blue/purple pigments that are widely produced in the plant kingdom.
Anthocyanin pigments are an ideal model for studying the complex process of natural product biosynthesis in plants. There are three common types of anthocyanins that are classified based on their core chromophore structure: cyanin, delphinin, and pelargonin. The main anthocyanin molecules that are biosynthesised in *A. thaliana* are cyanins derived from cyanidin. Beginning with phenylalanine, there are nine enzymes involved in this pathway that are essential for the biosynthesis of red anthocyanidin pigment in *A. thaliana* (Fig. 1B). Of these nine enzymes, phenylalanine amino-lyase (PAL), cinnamate-4-hydroxylase (C4H), and 4-coumaroyl: CoA-ligase (4CL) are also required for the biosynthesis of other phenylpropanoids. Chalcone synthase (CHS), chalcone isomerase (CHI), flavanone-3-hydroxylase (F3H), and flavonoid 3'-hydroxylase (F3' H) are normally referred to as the early flavonoid pathway enzymes, whereas dihydroflavonol 4-reductase (DFR) and anthocyanidin synthase (also called leucoanthocyanidin dioxygenase, LDOX) are normally referred to as the late anthocyanin pathway enzymes. The glycotransferases (GT) add sugars to anthocyanidins, which diversifies the anthocyanin structure. Flavonoid 3'5'-hydroxylase (F3'5'H) is another enzyme that is required for delphinin production. To produce anthocyanins, the expression of genes that code for these enzymes is essential. Correspondingly, mutations in these genes (e.g., *tt3*, a DFR mutant) cause the loss of anthocyanin expression in plant tissue.

Although numerous regulators (Fig. 1) from Arabidopsis (e.g., PAP1, GL3 and TTG1) and the C gene from maize have been functionally characterised, how these regulators are themselves regulated remains unknown. We recently developed anthocyanin-producing Arabidopsis cells and tobacco cells that are programmed by the expression of PAP1 to study these unknown mechanisms. These two systems are ideal models for understanding how PAP1, an R2R3-MYB transcription factor, programs anthocyanin biosynthesis in cells and how PAP1 function is in turn regulated by other factors. Based on our recent work, the goal of this addendum is to provide insight into the programming and reprogramming mechanisms that determine the cellular metabolic fate of anthocyanin biosynthesis in *A. thaliana*.

**Figure 1.** A scheme showing the differentiation of red and white PAP1-programmed Arabidopsis cells and the regulation of metabolism toward anthocyanin biosynthesis in the red cells. (A) The white box illustrates the dedifferentiation of cells from a PAP1-programmed purple seedling with anthocyanin accumulation in the epidermal cells; the acquisition of calli with different accumulation patterns of anthocyanins; re-differentiation of red and white cells; and a RT-PCR image showing the expression of PAP1 in both the white and red cells. The thin arrows indicate experimental procedures that were performed to differentiate cells from leaves. (B) The light blue box presents the components that are required for the development of an anthocyanin biosynthesis metabolic fate in red cells; these include 10 pathway genes, the TTG1-GL3/TT8-PAP1 regulatory complex we recently described and factors that potentially control the regulatory complex. The wide black arrows indicate regulatory activation, and the question marks indicate unknowns. (C) The light green box illustrates the process of establishing and maintaining a particular metabolic fate, which involves the genome-wide reprogramming of metabolic gene expression. The thick black arrows between boxes A and C indicate that the establishment of a metabolic fate can lead to the reprogramming of gene expression. Our previous study showed that the red cells have reprogrammed gene expression.

**Differentiation of PAP1-Based Programming into Anthocyanin Biosynthesis in Arabidopsis Cells**

Previous studies have shown that PAP1 is a master activator of anthocyanin biosynthesis in *A. thaliana*. However, PAP1 regulation in vivo is restricted to specific cell types. "pap1-D" plants overexpress the
**PAPI** gene under the control of a 35S promoter with four enhancers. Previous studies have shown that **PAPI** overexpression either activates or increases the expression of the most of genes encoding the nine enzymes and GTs described above that catalyse the formation of anthocyanins in plants. However, **PAPI** overexpression does not lead to anthocyanin production in all plant cells. **PAPI** activation of anthocyanin biosynthesis is strongly restricted to certain cell types, e.g., epidermal and hypodermal cells of leaves, as well as parenchymal cells in and around the vascular bundles of leaf veins. Interestingly, **PAPI** overexpression does not lead to the formation of anthocyanins in trichomes, which contrasts with the results for ectopic expression of **PAPI** in tobacco plants. Thus, these data indicate that **PAPI** function and subsequent anthocyanin biosynthesis in trichomes is differentially regulated, even in similar cell types.

**PAPI** regulation is restricted to specific cell types in vitro. We recently described the metabolic engineering of anthocyanin production in Arabidopsis cells from **pap1**-**D** plants that were transcriptionally programmed by overexpression of the **PAPI** gene encoding MYB75. To obtain **PAPI**-programmed cells that produce anthocyanins, we screened multiple lighting conditions and a large number of media consisting of multiple combinations of phytohormones, inorganic nutrients and organic nutrients. Newly induced cells that were dedifferentiated from red leaf explants produced low levels of anthocyanins. Red cells (Fig. 1A) with high levels of anthocyanins were obtained from media containing very low levels of nitrogen source. We observed that although the cellular **PAPI** expression level was high, the selected cells had anthocyanin accumulation patterns that ranged from low to high (Fig. 1A), which indicates that **PAPI** regulation differs in various parts of the callus. Recently, we isolated white (e.g., NRC7) and red cell lines (RC7) from a single explant (Fig. 1A). We performed RT-PCR assays to determine whether **PAPI** was also over expressed in the white cells. The results showed that the **PAPI** expression level is very similar between the NRC7 and RC7 cell lines (Fig. 1A). This indicates that the posttranscriptional status of PAPI must differ because although both cell types overexpress PAPI, only the red cells biosynthesise anthocyanins. **PAPI** regulation in engineered cells requires additional regulators, and the generation and characterisation of numerous knockout mutants has increased our knowledge of anthocyanin biosynthesis regulation in Arabidopsis. Previous reports have indicated that the WBM (WD-40/bHLH/MYB) complexes are likely to control anthocyanin biosynthesis. The WBM complexes in Arabidopsis seedlings are TTG1/WD-40/GL3/bHLH-PAPI/MYB75, TTG1-GL3-PAP2/MYB90, TTG1 -GL3-MYB113 and/or 114. In seeds, the most likely regulatory complex is the TTG1-TT8/bHLH- TT2/MYB complex located in the endothelium. In our engineered red cells that were programmed by **PAPI**, microarray and RT-PCR analyses indicated that **PAPI**, GL3, TT8 and TTG1 were all expressed; however, **PAPI** expression was not detected and there were low expression levels of GL3 and TT8 in the wild-type control cells. We also recently analysed the expression levels of these genes in **PAPI**-programmed white cells (NRC7, Fig. 1A). The GL3 expression level was extremely low, and TT8 expression was not detected (Table 1, PCR image data not shown). These results indicate that low or no expression of these two genes may lead to no anthocyanin production in the white cells, which supports the hypothesis that **PAPI** regulation may be dependent on GL3 and/or TT8. These experiments also show that there are different regulatory programs in these two types of metabolic cells.

**Table 1.** TTG1-GL3/TT8-PAPI1 complex gene expression in PAPI1-programmed anthocyanin-producing (RC7) cells, PAPI1-programmed anthocyanin-free (NRC7) cells and wild-type (WT) cells

| Cell type | TTG1 | GL3 | TT8 | PAPI1 |
|-----------|------|-----|-----|-------|
| RC7       | +    | +   | +   | +     |
| NRC7      | +    | d   | -   | +     |
| WT        | +    | -   | -   | -     |

“+”: expression; “-”: no expression; “d”: at the limit of detection.

**Metabolic Cell Fate and Gene Expression Reprogramming**

Little is known about the mechanisms that determine cellular metabolic fate and plant secondary metabolism. As described above, **PAPI**-based programming is strongly restricted to specific cell types; however, the mechanisms underlying this observation are unclear. Here, we hypothesise that this difference in cellular metabolic fate toward anthocyanin biosynthesis programmed by a WBM complex is controlled by epigenetics. Our engineered red cells are an ideal model for studying the differentiation of metabolic fate toward anthocyanin biosynthesis. In our experiment, we isolated red and white cells from PAPI-programmed leaves (Fig. 1A). We hypothesised that the red cells (Fig. 1A) inherited their epigenetic modifications from the epidermal and hypodermal cells of leaves or parenchymal cells in the vascular bundles of the leaf veins, which have active **PAPI**-based programming promoting anthocyanin production. In contrast, we hypothesised that the white cells (NRC7, Fig. 1A) originate from mesophyll cells or other cell types that do not produce anthocyanins. In addition, we hypothesised that although the in vitro cultured red cells morphologically differ from the in planta anthocyanin-producing cells (e.g., epidermal cells) in leaves, the red cells inherit their “metabolic context” from their somatic “mother” cells. Furthermore, we suggest that the engineered white cells (e.g., NRC7, Fig. 1A) lack the metabolic context and epigenetic modifications required for anthocyanin production. The most direct evidence is the expression of TTG1, TT8 and GL3 (GLABRA3) in the red cells. TTG1 may be a genetic marker for an epidermal cellular and metabolic fate in Arabidopsis tissue. TTG1 is an essential component of the WBM complexes that regulate anthocyanin biosynthesis described above. Additionally, TTG1 is globally involved in determining the fate of epidermal cells, including pavement cells and trichomes. TTG1 recruitment may trigger the development of plant tissue into epidermis. Similarly, GL3 may be another
marker gene. GL3 is specifically expressed in the epidermis of Arabidopsis tissues. In our experiments, we observed that GL3 was expressed in the red cells but not in the wild-type control cells. Recently, we showed that trace expression occurs in PAP1-programmed white cells (PCR data not shown). TT8 may be yet another marker gene, although it has been reported to regulate anthocyanin and proanthocyanidin biosynthesis in the seed coat. In our experiments, TT8 expression was detected in the red cells but not in the wild-type control or PAP1-programmed white cells.

The morphological differences between the in vitro cultured cells and epidermal cells can be explained by their EGL3 expression pattern. Previous studies have shown that EGL3 (Enhancer of GL3) plays a role in the determination of pavement cell fate, and EGL3 gene deletion results in abnormal epidermis. However, additional studies have reported that EGL3 does not play a role in anthocyanin production. In our engineered red and control cells, EGL3 expression was not detected. Therefore, although these engineered red cells do not inherit epidermal cell morphology, they contain the epigenetic modifications that promote anthocyanin biosynthesis.

One appropriate explanation for metabolic fate differentiation between similar cell types is different epigenetics. Although there are few studies describing plant epigenetics related to metabolic differentiation, knowledge regarding how a plant determines cell fate during vegetative and reproductive growth bears on the likelihood of epigenetic differences in various metabolic cell types. The Polycomb (PcG) and trithorax (trxG) groups are two protein families that are evolutionarily conserved in the fungal, animal, and plant kingdoms. These proteins have been shown to help determine plant cell development. In general, these two groups of proteins are antagonistically expressed at specific times during organismal development and at various transitions. The PcG proteins repress homeotic gene (HOX gene) expression, whereas the trxG proteins activate and maintain the expression of HOX genes, thereby promoting development and differentiation. Currently, the main PcG protein members identified in Arabidopsis include MEA (MEDEA), CLF (CRULY LEAF), SWN (SWINGER), FIE (FERTILIZATION INDEPENDENT ENDOSPERM), MS1 (MULTICOPY SUPPRESSOR OF IRA1), FIS2 (FERTILIZATION-DEPENDENT SEED 2), EMF2 (EMBRYONIC FLOWER 2), and VRN2 (VERNALIZATION 2). Other potential members include VRN1 (VERNALIZATION 1) and VIN3 (VERNALIZATION INSENSITIVE 3). These proteins form different types of Polycomb Repressive Complex 2s (PRC2s), including FIS PRC2-like, EMF PRC2-like, and VRN PRC2-like complexes. Several recent reviews have summarized and discussed their functions.

One of the main functions of PRC2 is to catalyse the trimethylation of histone H3 at lysine 27 (H3K27me3), which leads to the reversible repression of gene expression. PRC2 also catalyses the trimethylation of histone H3 at lysine 9 (H3K9me3), which results in long-term repression of gene expression. The trxG proteins identified in Arabidopsis include ATX1 (Arabidopsis Trithorax 1), UTL1 (ULTRAPETALA 1), PKL (PRICKLE), and EFS (EARLY FLOWERING IN SHORT DAYS). ATX1 catalyses the trimethylation of histone H3 at lysine 4 (H3K4me3), which activates and maintains the expression of genes involved in flower development. In our experiments, we mined microarray data and found that in the both the red and control cells, MEA, CLF, SWN, FIE, MS1, EMF2, VRN2 and VRN1 were expressed. In addition to the PcG members, EFS (a trxG member) was also expressed. However, FIS2 was not expressed. When we performed our microarray analysis, the ATX1 probe was not available on the Affymetrix ATH1 microarray; thus, we could not analyse ATX1 expression.

Interestingly, the MEA expression level was nearly 1.8-fold lower in the red cells compared to the wild-type control cells (false discovery rate, FDR, 0.02). In contrast to MEA, the VRN1 expression level was nearly 1.5-fold higher in the red cells than in the control cells (FDR, 0.02). MEA, which is a self-controlling protein and an essential component of the FIS PRC2 complex, has been shown to regulate seed development. Additionally, increased MEA expression has been proposed to cause callus formation (de-differentiation) on elf sun double mutant leaves when grown on plant tissue culture medium. Thus, it seems likely that MEA expression was associated with the leaf callus formation observed in our experiments. However, it is unclear whether these PRC 2-like complexes control the expression or function of the TTT1-G1-GL3/TT8-PAP1 complex. Future studies are needed to analyse these possible interactions, and such data will provide a more thorough understanding of the mechanisms involved in programming plant gene expression towards the biosynthesis of anthocyanins.

It is likely that established metabolic cells reprogram gene expression. However, there is little information regarding the reprogramming of gene expression in programmed cells towards anthocyanin biosynthesis or that of other metabolites. In general, the biosynthesis of many plant secondary metabolites is very responsive to biotic and abiotic stimuli. For example, phytoalexins are produced after transient reprogramming of gene expression in plant tissues in response to pathogens or other external signals. Evidence from a number of sources has shown that plant cells can rapidly program gene transcription profiles in response to elicitors, pathogen attacks, and nutrients such as nitrogen. However, whether the elicited programming can reprogram gene expression and can be inherited by progeny cells remains unclear.

In our experiment, the red cells programmed by PAPI expression are an ideal model for studying the genome-wide reprogramming of gene expression. As previously reported, when we used 0.05 as a false discovery rate, we found that the expression profiles of nearly 6.5% of the genes in the Arabidopsis genome were altered in the red cells, which indicates that metabolic engineering for anthocyanins led to genome-wide reprogramming. However, the mechanisms that are responsible for this reprogramming are unknown. We hypothesise...
that the overexpression of PAPI alters the epigenetic context of the red cells, and that the progeny cells inherit this alteration during long-term subculture under optimized conditions. Interestingly, anthocyanin formation in the red cells is regulated by additional factors such as plant hormones and nitrogen concentration (data not shown). These observations indicate that anthocyanin biosynthesis as programmed by PAPI is reversible.

Conclusion

Our studies regarding PAPI-programmed anthocyanin biosynthesis and our genome-wide gene expression analysis have shown that the TTG1-GL3/TT8-PAP1 regulatory complex plays a key role in this process. The presence of this regulatory complex in Arabidopsis cells appears to promote anthocyanin production in vitro. Furthermore, genome-wide gene expression analyses of the red and wild-type cells showed that these cells have different transcriptomes, which likely mediates their different reprogrammed phenotypes. Our data provide fundamental information about the mechanisms whereby plant secondary metabolism is programmed and reprogrammed. Furthermore, these studies suggest that regulatory programming may eventually be applied to engineer medicinally and nutritionally significant metabolites.

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