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FLOWERING NEWSLETTER REVIEW

Flowering and trichome development share hormonal and transcription factor regulation

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Abstract

Gibberellins (GAs) and cytokinins (CKs) are plant hormones that act either synergistically or antagonistically during the regulation of different developmental processes. In *Arabidopsis thaliana*, GAs and CKs overlap in the positive regulation of processes such as the transition from the vegetative to the reproductive phase and the development of epidermal adaxial trichomes. Despite the fact that both developmental processes originate in the rosette leaves, they occur separately in time and space. Here we review how, as genetic and molecular mechanisms are being unraveled, both processes might be closely related. Additionally, this shared genetic network is not only dependent on GA and CK hormone signaling but is also strictly controlled by specific clades of transcription factor families. Some key flowering genes also control other rosette leaf developmental processes such as adaxial trichome formation. Conversely, most of the trichome activator genes, which belong to the MYB, bHLH and C2H2 families, were found to positively control the floral transition. Furthermore, three MADS floral organ identity genes, which are able to convert leaves into floral structures, are also able to induce trichome proliferation in the flower. These data lead us to propose that the spatio-temporal regulation and integration of diverse signals control different developmental processes, such as floral induction and trichome formation, which are intimately connected through similar genetic pathways.

Key words: Cytokinis, Floral induction, Flower organs, Gibberellins, Hormone siganling, Trichome formation.

Introduction

Flowering is one of the most critical developmental steps to ensure species perpetuation. Floral induction must occur at an appropriate time of the year to ensure offspring survival. Early flowering may result in poor flower and seed production as plants do not recruit enough reserves for an energy-consuming process, while late flowering may lead to a robust plant, but perhaps may jeopardize fruit maturation. As the time for floral induction is critical, both late induction and precocious flowering should be avoided. Consequently, plants constantly monitor environmental and endogenous signals to control their growth (Penfield, 2008). When plants are not competent to flower, they are insensitive to inductive environmental factors, while after the juvenile-to-adult transition plants reach the competence to respond to those signals (Bergonzi *et al.*, 2013; Huijser and Schmid, 2011). Indeed, flowering is controlled by a complex network of

interdependent genetic pathways that monitor and respond to both endogenous and environmental signals. Endogenous factors include hormones such as gibberellin (GA) and cytokinin (CK) (Mutasa-Göttgens and Hedden, 2009; Huijser and Schmid, 2011) and the age of the plant (Huijser and Schmid, 2011). Among the major environmental effectors are photoperiod, light intensity/quality and seasonal/daily changes in temperature (Thomas, 2006; Andrés and Coupland, 2012; Song *et al.*, 2012, 2013).

Plant fitness is an essential factor that may directly affect the success of plant reproduction. Not only environmental conditions but also insects can endanger proper plant development, including flower reproductive success. Herbivorous insect attacks can substantially decrease plant survival (Marquis and Alexander, 1992). Due to the fact that plant-insect encounters are not predictable, plants generally do not show high levels of resistance. However, plant plasticity creates the ability to respond rapidly to damage and to divert resistance resources for overcoming that damage (Agrawal, 2000). This plasticity most probably arose because plants are not able to move; consequently they have developed multiple physiological defense responses. Leaf trichomes are among these physiological defenses. Trichomes are epidermal protuberances that protect plants from the attack of herbivorous insects and develop even when plants are growing under optimal conditions (Traw and Bergelson, 2003). Interestingly, plasticity allows plants to respond to insect attacks by increasing the number and density of trichomes in new growing leaves, stems and flowers (Agrawal, 2000; Traw and Bergelson, 2003).

In many plant species trichomes are glandular multicellular structures able to produce, distribute and store toxic substances for protecting the plant against insect attacks (Olsson *et al.*, 2009), however *Arabidopsis thaliana* trichomes are unicellular and non-glandular structures (Hülskamp *et al.*, 2004). Despite not being able to store toxic substances, Arabidopsis trichome morphology, with a big size and three sharp terminations that develop on the adaxial surface of rosette leaves, reduce the access of herbivorous insects to leaf surface (Mauricio, 2005). But trichomes defend the plant not only against insects but also from other external factors such as an excess of UV light or high temperatures (Szymanski *et al.*, 2000; Schellmann *et al.*, 2007).

Adaxial rosette trichome initiation and development processes involve a complex genetic network. These include a multimeric complex, known as trichome activator complex, formed by a R2R3 MYB protein GLABROUS1 (*GL1*), two redundant trichome formation bHLH proteins, GLABRA3 (*GL3*) and ENHANCER OF GLABRA3 (EGL3), and a WD40 repeat containing protein, TRANSPARENT TESTA GLABRA 1 (TTG1) (Fig. 1) (Zhao *et al.*, 2008; Zhou *et al.*, 2011). Mutations in *GL1*, *TTG1*, and both *GL3*/*EGL3* result in Arabidopsis plants with a significant loss of trichomes (Payne *et al.*, 2000; Zhou *et al.*, 2011). In addition to that, this complex has not only a role in trichome initiation but also in later trichome development, as mutations in these genes result in smaller and less branched trichomes (Payne *et al.*, 2000).

It is accepted that the competency to enter the trichome pathway is limited to a few epidermal cells. Once an epidermal precursor is specified to acquire trichome cell fate, a mechanism of lateral inhibition towards the surrounding epidermal cells initiates (Langdale, 1998; Kirik *et al*, 2004*a*) (Fig. 1). This lateral inhibition mechanism involves cell-to-cell communication. Indeed, trichome activation factors such as GL3 and TTG1 also turn on negative regulators of trichome initiation as CAPRICE (CPC) and ENHANCER OF TRIPTYCHON AND CAPRICE 1 (ETC1), which subsequently move into neighboring epidermal pavement cells to prevent trichome formation (Zhao *et al*, 2008; Balkunde *et al*, 2010, 2011) (Fig. 1). In addition, these trichome positive regulators GL3 and TTG1 are also able to move among cells (Bouyer *et al*, 2008; Savage *et al*, 2008). CPC and ETC1 are not the only trichome repressors in Arabidopsis, others have been described to act as trichome inhibitors contributing to an elaborated and well-regulated genetic network that determines which epidermal cell may – or may not –morphogenetically become a trichome (Langdale, 1998; Kirik *et al*, 2004*a*). Interestingly, most of this trichome repressors including CPC, ETC1, ETC2, ETC3, TRICHOMELESS 1 (TCL1), TCL2 and TRIPTYCHON (TRY), belong to the R3-MYB TF family (Wang and Chen, 2014) (Fig. 1). Although TRY is the predominant member controlling trichome clustering on adaxial surface of rosette leaves (Schnittger *et al.*, 1998; Schellmann *et al.*, 2002), CPC, ETC1, ETC2 and ETC3 also regulate trichome development on leaves (Wada *et al.*, 1997, 2002; Esch *et al.*, 2004; Kirik *et al.*, 2004*a*, *b*; Tominaga *et al.*, 2008). However, TCL1 and TCL2 control trichome development mainly on inflorescence stems and pedicels (Wang *et al.*, 2007; Gan *et al.*, 2011). But not all these R3-MYB members are regulated by the trichome activator complex (GL1-TTG1-GL3/EGL3). Only *TRY*, *CPC*, *ETC1* and *ETC3* expressions are controlled by this multimeric complex in the rosette leaf, while *TCL1*, *TCL2* and *TRY* are regulated by an independent trichome pathway mediated by *microRNA156* (*miR156*) and *SQUAMOSA PROMOTER BINDING PROTEIN LIKE* (*SPL*) at least on the inflorescence stems (Yu *et al.*, 2010; Xue *et al.*, 2014). miR156-targeted SPL transcription factors not only play important roles in determining trichome initiation on the abaxial side of the rosette leaf but also on stems (Yu *et al.*, 2010; Xue *et al.*, 2014). Curiously enough, these genes also play a key role in controlling flowering through the age-dependent genetic pathway (Yu *et al.*, 2010; Xue *et al.*, 2014).

In the past decades, strong efforts have been made in the model plant Arabidopsis to unravel the different molecular and genetic mechanisms that regulate diverse cellular differentiation programs. Different results revealed that the network of transcriptional regulators affecting trichome proliferation are themselves affected by two plant hormones, GA and CK (Fig. 1), both of which are able to control and integrate diverse biological processes that occur at different cell levels (Schellmann *et al.*, 2002; Gan *et al.*, 2007; Zhao *et al.*, 2008). GA and CK are phytohormones required throughout plant development that contribute to and overlap in some plant developmental processes but they also have opposite

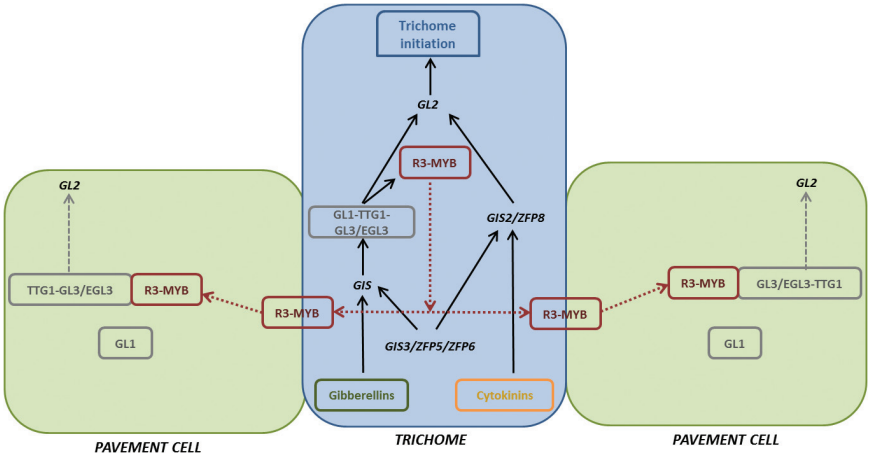

Fig. 1. Model for trichome and pavement cell fate specification in *Arabidopsis thaliana*. Trichome proliferation regulation is affected by gibberellins and cytokinins hormones through transcriptional regulation of the *GIS* clade genes: GIS, GIS2, and ZFP8. GIS2 and ZFP8 activate the trichome activator *GL2*, while GIS positively regulate some of the members of the trichome activation complex – *GL1, TTG1* and *GL3/EGL3* – that in turn activate *GL2* and, at the same time, R3-MYB repressor genes (black arrows). R3-MYB members that include CPC, ETC1, ETC2, ETC3, TCL1, TCL2 and TRY act as repressors of trichome initiation. Some of these R3-MYB move to the neighboring cells (dashed red lines) to prevent trichome formation, where they compete with GL1 for the interaction with GL3 and/or EGL3, thus limiting the activity of the trichome activation complex, and consequently decreasing *GL2* expression (dashed arrow).

roles in others (Zhang *et al.*, 2003). For instance, GA and CK act antagonistically in leaf formation and meristem maintenance and GA counteracts the CK effect in epidermal differentiation (Gan *et al.*, 2007). However, both hormones have synergistic effects on the constitutive induction of epidermal defensive trichomes, floral induction, valve margins and senescence suggesting that genetic interactions may be shared between these two hormonal signaling pathways (Chien and Sussex, 1996; Perazza *et al.*, 1998; Corbesier *et al.*, 2003; Traw and Bergelson, 2003; Gan *et al.*, 2007; D'Aloia *et al.*, 2011; Marsch-Martinez *et al.*, 2012; Pattanaik *et al.*, 2014). The fact that phytohormones play independent and overlapping functions may imply that the spatio-temporal pattern and integration of diverse signals through downstream regulators are of great importance. Two possible strategies have been described so far to explain plant hormone integration. The first one uses a centralized system of upstream hormone signaling integrators, such as the DELLA family, that are able to control plant growth in combination with hormones such as GA, auxin, ethylene and abscisic acid (Silverstone *et al.* 1998; Fu and Harberd, 2003; Achard *et al.*, 2006). The second strategy uses more specialized regulators such as transcription factors that may act downstream controlling the specific gene networks of different developmental processes, but without excluding an upstream regulation (Nemhauser *et al.*, 2006). This review will focus on how a small number of proteins may use one or both strategies for regulating upstream and downstream steps of floral induction and trichome formation by integrating the control of hormone signaling and diverse genetic networks.

Gibberellins and their positive role in flowering and trichome formation

GAs regulate different plant growth and developmental processes that span from seed germination to the control of last processes in the plant life cycle, such as senescence, leaf expansion, hypocotyl and stem elongation (Fig. 2) (Chien and Sussex, 1996; Perazza *et al.*, 1998; Davis, 2009). The GA biosynthetic pathway follows a complex regulatory network that leads to the final production of the GA bioactive form, GA_4 (Mitchum *et al.*, 2006). Most of the genes encoding enzymes of the GA biosynthetic pathway have been well studied (Olszewski *et al.*, 2002). For example, *GA3OXIDASE 1* (*GA3OX1*) and *GA3OX2* encode enzymes that transform GA_9 into the bioactive GA_4, but there are other important enzymes, such as *GA2OXIDASE*, which catabolizes an excess of GA_4 (Mitchum *et al.*, 2006). Therefore, a proper balance between the biosynthetic and catabolic enzymes is of essential importance for keeping a correct amount of GA.

In Arabidopsis, bioactive GAs promote floral induction as well as some other aspects of flower development, such as petal, stamen and viable pollen formation (Koornneef and van der Veen, 1980). GAs are also mobile signals that travel from the leaves to the shoot apical meristem (SAM) to induce the florigen *FLOWERING LOCUS T* (*FT*) and *SUPRESSOR OF OVEREXPRESSION OF CONSTANS1* (*SOC1*) in order to trigger flowering (Fig. 3) (Corbesier *et al.*, 2007; Mathieu *et al.*, 2007). Flowering is induced by GA under both inductive long-days (LD) (16 h light/8 h dark) and non-inductive short-day (SD) (8 h light/16 h dark) conditions, although GAs have a stronger effect controlling floral induction under SD conditions (Wilson *et al.*, 1992; Blázquez *et al.*, 1998; Nilsson *et al.*, 1998). Under SD conditions, GA are able to activate the floral integrator *SOC1* and the floral meristem identity gene *LEAFY* (*LFY*) in the SAM (Blázquez *et al.*, 1998; Moon *et al.*, 2003) (Fig. 3). Trichome proliferation and branching are also among the processes controlled by GA (Smyth *et al.*, 1990; Dill and Sun, 2001). External GA applications increase trichome density in leaves and stems of Arabidopsis (Perazza *et al.*, 1998; Gan *et al.*, 2006).

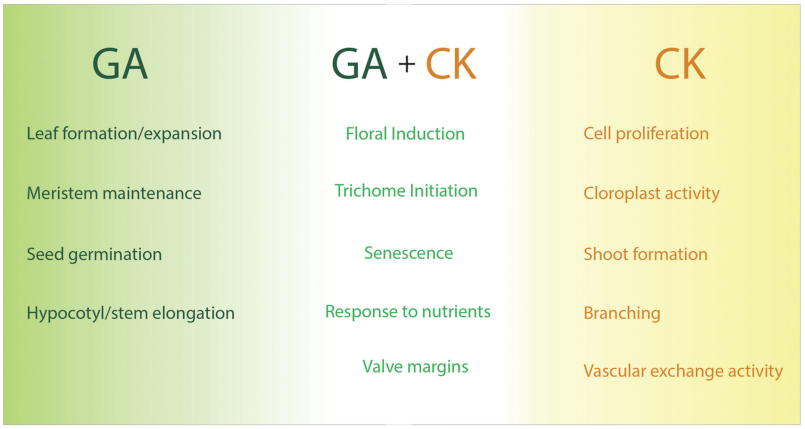

Fig. 2. Diagram showing GA- and CK-dependent overlapping and non-overlapping biological processes. GA and CK phytohormones regulate different plant growth and developmental processes that span from early stages during seed germination to the control of the final processes in the plant life cycle. Despite GA and CK acting antagonistically in several biological processes showed here, both hormones have synergistic effects on floral induction, trichome initiation, valve margins development, senescence and responses to nutrients availability.

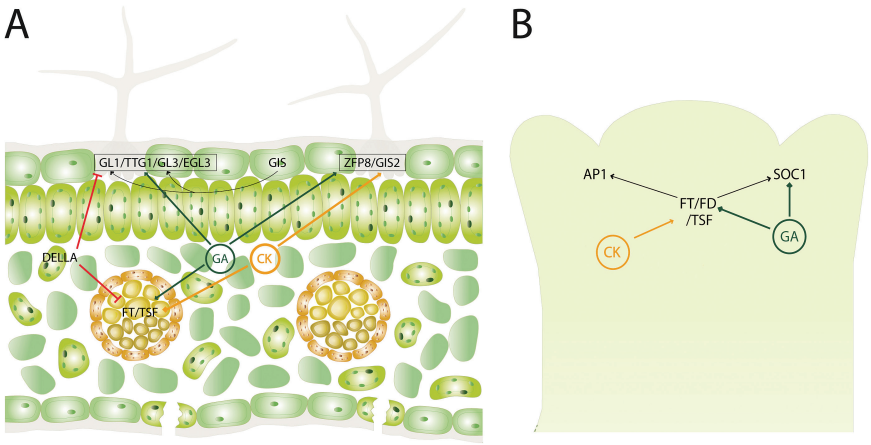

Fig. 3. The transcriptional regulatory network that affects floral and adaxial trichome induction at different organ, tissue and cell levels. (A) In rosette leaves, this complex network is partially controlled by GA and CK hormones that overlap in positively regulating the transcription of diverse trichome- and flowering-genes in either leaf mesophyll or epidermis. (B) Similar transcriptional regulation for the control of floral induction is found in the shoot apical meristem (SAM).

GA3OX1 and *GA3OX2* functions overlap during Arabidopsis development, showing functional redundancy not only in stimulating flowering but also in trichome development (Mitchum, 2006). *ga3ox1 ga3ox2* double mutant plants are semi-dwarf, late flowering and bear a reduced number of trichomes on rosette leaves, stems and flowers (Koornneef and van der Veen, 1980; Chiang *et al.*, 1995; Mitchum *et al.*, 2006). In general, mutant plants in which GA biosynthesis genes have been knocked down and are unable to produce normal GA levels, produce leaves with fewer trichomes (Chien and Sussex, 1996; Traw and Bergelson, 2003). In fact, when GA are exogenously sprayed on an Arabidopsis wild-type plant, rosette leaf adaxial trichome production is significantly increased (Chien and Sussex, 1996), while plants treated with GA biosynthesis inhibitors such as paclobutrazol and uniconazole are not able to produce trichomes (Chien and Sussex, 1996; Perazza *et al.*, 1998).

In Arabidopsis, functional redundancy in GA signalling has been attributed not only to the GA biosynthetic enzymes but also to DELLA proteins (Gallego-Bartolomé *et al.*, 2010). DELLA transcriptional regulators directly or indirectly repress the expression of GA-induced genes. The DELLA family encodes five members: *GIBBERELIC ACID INSENSITIVE* (*GAI*), *REPRESSOR OF gai-3* (*RGA*), and three *RGA-like* genes (*RGL1*, *RGL2* and *RGL3*) (Eckardt, 2002; Wen and Chang, 2002; Achard *et al.*, 2003). DELLA proteins not only repress GA signaling, but they also modulate GA homeostasis by regulating the expression of some GA biosynthetic enzymes such as *GA3OX1* and*GA20OXIDASE2*, and/or GA receptor genes such as *GIBBERELLIN INSENSITIVE DWARF 1a* (*GID1a*) and *GID1b* (Gallego-Bartolomé *et al.*, 2010). DELLA proteins act as repressors of GA-activated processes, consequently controlling floral induction. Among all the five members, *RGA* and *GAI* are the ones with a more important role in the transition to floral initiation (Dill and Sun, 2001; King *et al.*, 2001), while *RGA*, *RGL1* and *RGL2* have a more important role in flower and fruit development (Cheng *et al.*, 2004; Tyler *et al.*, 2004). The role of DELLA repressors in flowering control was determined by measuring the ability of different DELLA mutants

to rescue the strong phenotypes of the *ga1-3* mutant. The *ga1-3* mutant contains a large deletion in *GA REQUIRING 1* (*GA1*) gene, the enzyme that catalyzes the first committed step in GA biosynthesis (Sun and Kamiya, 1994). *rga* and *gai* null alleles are able to interact synergistically in order to rescue the normal vegetative growth and floral initiation in the *ga1*-3 mutant background (Dill and Sun, 2001; King *et al.*, 2001), indicating that *RGA* and *GAI* act as major floral transition repressors. However, some evidence shows that *RGA*, *RGL1*, and *RGL2* are also involved, to a lesser extent, in modulating flowering and floral development (Tyler *et al.*, 2004; Galvão *et al.*, 2012).

In addition, diverse plant species overexpressing DELLA proteins show dwarfism and delayed flowering (Dill *et al.*, 2004; Hamama *et al.*, 2012). It is known that DELLAs also regulate flower development by partly repressing the expression of floral homeotic genes such as *APETALA 3* (*AP3*), *PISTILLATA* (*PI*), and *AGAMOUS* (*AG*) (Yu *et al.*, 2004). Consequently, DELLA proteins are now universally considered as flowering inhibitors. Exogenous GA treatment is enough to restore the wild-type phenotype to *ga1-3* in terms of floral induction and flower development (Wilson *et al.*, 1992). Interestingly, this GA treatment is also able to restore the adaxial trichome number of glabrous *ga1-3* rosette leaves to wild-type levels (Smyth *et al.*, 1990). Later studies also show that DELLAs are directly involved in repressing trichome proliferation. Similar to members that control floral induction, *RGA* and *GAI*, play significant roles in trichome formation (Dill and Sun, 2001). *rga* and *gai* mutants are able to restore adaxial trichome initiation in the glabrous *ga1-3* mutant plants (Dill and Sun, 2001). Furthermore, several trichome activator transcription factor genes, including *GL1* and *GL3*, are induced in these plants, while contrarily *RGA* over-expression represses *GL1* and *GL3* expression (Fig. 3). Indeed, RGA and/or RGL2 proteins are able to interact with GL1, GL3 and EGL3 to repress the transcriptional function of this trichome activator complex (Qi *et al.*, 2014).

Cytokinins overlap with GA in floral induction and trichome formation

Cytokinins are involved in several aspects of plant growth and development. Firstly identified as factors that promote cell proliferation and shoot formation *in vitro*, CKs are found to activate cell-cycle genes in the leaf and interact with genetic regulators of stem cells in the SAM (Fig. 2) (Riou-Khamlichi *et al.*, 1999; Leibfried *et al.*, 2005). Additionally, CKs affect other important processes such as chloroplast or vascular exchange activity, branching and response to different nutrients as well as senescence (Fig. 2) (Yanai *et al.*, 2005; Gordon *et al.*, 2009). Decades ago, exogenous CK application was found to activate the floral transition of relatively old plants (Besnard-Wibaut, 1981; Dennis *et al.*, 1996). Later on, applications of CK in the form of benzylaminopurine (BAP) treatments using a hydroponic system have confirmed that CK are clearly involved in the floral transition (D'Aloia *et al.*, 2011). After BAP treatment, an up-regulation of *APETALA1* (*AP1*) expression, a marker of floral meristems, is detected; and indeed floral meristems are initiated two days later (D'Aloia *et al.*, 2011). CK have been proposed to act transmitting root-to-shoot signals during the floral transition (Kinet *et al.*, 1993; Havelange *et al.*, 2000). In fact, BAP application in the roots strongly promote floral induction in seven-week-old plants grown under SD conditions in the absence of other flowering stimulators such as extra GA, vernalization and/or LD photoperiod (D'Aloia *et al.*, 2011). At the histological level, an increase of CK levels is found in the SAM of Arabidopsis plants at the moment of flowering, suggesting that CKs might be real regulators of floral induction (Corbesier *et al.*, 2003).

CK biosynthetic enzymes have been well elucidated and are encoded by multigene families whose members are functionally redundant (Sakakibara *et al.*, 2006; Hirose *et al.*, 2008); this has always been an obstacle to genetically study in depth the role of CK in flowering. Luckily, physiological information has been obtained using genes that alter endogenous levels of CK, as *ALTERED MERISTEM PROGRAM 1* (*amp1*) overexpression results in early flowering plants (Werner *et al.*, 2006). Contrarily, when enzymes that degrade CK, such as *CYTOKININ OXIDASE/DEHYDROGENASE* (*CKX*), are overexpressed, Arabidopsis plants flower later than wild-type plants (Werner *et al.*, 2006). Genetically, CK applications are not able to activate the main florigen *FT*, but instead are able to promote the expression of its paralogue *TWIN SISTER of FT* (*TSF*) (Fig. 3) (D'Aloia *et al.*, 2011). As FT, TSF protein interacts with *FLOWERING LOCUS D* (*FD*) and is activated by *CONSTANS* (*CO*), therefore *TSF* acts redundantly with *FT* to promote flowering (Michaels *et al.*, 2005; Yamaguchi *et al.*, 2005; Mathieu *et al.*, 2007; Jang *et al.*, 2009). Furthermore, CKs are also able to activate, at least in the SAM, *SOC1* and *FD* (Fig. 3) (D'Aloia *et al.*, 2011). Indeed, it has been shown with BAP treatments on *tsf-1* and *soc1-2* that both genes are necessary for flowering in response to CK. Consequently, a model is proposed in which CKs activate *TSF* in the leaf, TSF moves to the SAM, and through interaction with FD, similarly to the action of FT, TSF induces the transcription of *SOC1* and *AP1* (Fig. 3) (D'Aloia *et al.*, 2011). Moreover, these results provide a clue of how redundant *FT* and *TSF* genes can be differentially regulated by distinct signals (D'Aloia *et al.*, 2011).

CKs are also able to stimulate trichome formation. Plants treated with BAP produce more trichomes on cauline leaves, stems and flowers (Maes *et al.*, 2008). The expression of many genes that act as trichome activators are stimulated by exogenous BAP not only on inflorescence organs but also to a lesser extent on the adaxial surface of rosette leaves (Gan *et al.*, 2007). Furthermore, interesting overlapping roles are found for some enzymes that degrade CK, such as *CKX*, which repress both floral induction and trichome initiation. When *CKX* is overexpressed a reduction in the number of flower trichomes and a late flowering are observed (Werner *et al.*, 2003).

However, phytohormones sometimes play antagonistic functions due to competition. Both GA and CK stimulate trichome formation and floral induction but, for

instance, exogenous GA applications may inhibit the effect of CK treatments as GAs are able to block CK signaling (Greenboim-Wainberg *et al.*, 2005). In contrast, exogenous CK applications increase the expression of genes that negatively regulate GA signaling (Brenner *et al.*, 2005). For example, this exhaustive control has been found to be essential for shoot meristem maintenance (Jasinski *et al.*, 2005; Yanai *et al.*, 2005). In the case of trichome proliferation, GA induction of trichomes is required throughout plant development; while CKs, although slightly affecting trichome formation in rosette leaves, are more specialized in trichome proliferation in upper inflorescences (Gan *et al.*, 2007).

Flowering-time genes affect trichome initiation

Leaves perceive light and other environmental conditions and, as mentioned, different genetic pathways that respond to environmental and endogenous status tightly control floral induction from the leaf. These genetic pathways have been extensively studied in Arabidopsis, and they converge in the activation of the so-called floral pathway integrators *FT* and *SOC1* that induce flowering from the leaf vascular tissue (Takada and Goto, 2003; Fornara *et al.*, 2010; Wellmer and Riechmann, 2010). FT protein, which is part of the florigen (Kardailsky *et al.*, 1999; Kobayashi *et al.*, 1999), travels from the leaf to the SAM, where it triggers flowering after interaction with FD (Fig. 3) (Corbesier *et al.*, 2007, Jaeger and Wigge, 2007; Lin *et al.*, 2007; Mathieu *et al.*, 2007; Tamaki *et al.*, 2007).

Epidermal trichomes are present on both adaxial and abaxial surfaces of rosette leaves in Arabidopsis. The number of trichomes growing on the adaxial surface reaches high numbers from the first true rosette leaf, and keeps increasing in new leaves through development. As mentioned, the main reason for that increase in adaxial trichomes is for protection against predators, excess of UV-light and transpiration, while the presence and utility of abaxial trichomes seems to be rather different. Abaxial trichomes are used as a marker for the juvenile-to-adult phase transition because they only develop in the adult rosette leaves but not in juvenile leaves (Chien and Sussex, 1996; Telfer *et al.*, 1997; Yu *et al.*, 2010). Adaxial trichome analyses have hardly been done in important floral activator mutant backgrounds, but some published results show that the number of abaxial trichomes, but not the time of appearance, of the late flowering *ft-1* and *soc1-2* mutants were clearly and significantly reduced (Willmann and Poethig, 2011). The double mutant *ft-1 soc1-2* produced even fewer trichomes than the single mutants (Willmann and Poethig, 2011), implying that those flowering activators may also have a role in the induction of trichome formation. Moreover, *FLOWERING LOCUS C* (*FLC*), a well-known MADS box gene that delays floral induction by repressing *FT* and *SOC1* (Hepworth *et al.*, 2002; Helliwell *et al.*, 2006; Searle *et al.*, 2006), also inhibit abaxial trichome formation. *flc* mutants show a significant increase in the abaxial trichome numbers independently of its role in flowering (Willmann and Poethig, 2011).

In addition to that, miR156-targeted *SPL* genes known to play key roles in the juvenile-to-adult transition as well as the plant phase transition towards flowering (Wang *et al.*, 2009; Wu *et al.*, 2009) have been found to control trichome initiation on the abaxial side of rosette leaves and stems (Yu *et al.*, 2010). They positively regulate the expression of some R3-MYB trichome repressors as *TCL1*, *TCL2* and *TRY* (Yu *et al.*, 2010; Xue *et al.* 2014). Not only miR156 but also the negative regulator of the GA signaling pathway, DELLAs, interact with SPLs to control flowering (Yu *et al.*, 2012). Therefore, and similarly to other flowering-time genes described in this review, SPLs affect other developmental processes that include trichome proliferation (Yu *et al.*, 2010; Xue *et al.* 2014).

And … all the way around: adaxial trichome activators affect floral transition

As previously described, GA and CK hormones play essential roles in trichome proliferation by positively controlling crucial downstream genes (Schellmann *et al.*, 2002; Gan *et al.*, 2006; Zhao *et al.*, 2008). The GA-dependent trichome pathway acts partially through *GLABROUS INFLORESCENCE STEMS* (*GIS*), which positively regulates the trichome activation complex formed by GL1, GL3, EGL3 and TTG1 (Fig. 1) (Payne *et al.*, 2000; Zhao *et al.*, 2008). On the other hand, the CK-dependent trichome pathway is controlled by *GLABROUS INFLORESCENCE STEMS2* (*GIS2*) and *ZINC FINGER PROTEIN* (*ZFP8*) (Fig. 1) (Gan *et al.*, 2007; Marsch-Martinez *et al*, 2012). Both pathways converge to activate *GLABROUS 2* (*GL2*), the universal trichome activator (Payne *et al.*, 2000) (Fig. 1).

Mutations in *GL1*, *TTG1* and both *GL3*/*EGL3* result in Arabidopsis plants with a significant loss of trichomes (Payne *et al.*, 2000; Zhou *et al.*, 2011). In addition to that, this complex has not only a role in trichome initiation but also in later trichome development, as mutations in these genes result in smaller and less branched trichomes (Payne *et al.*, 2000).

Trichome proliferation regulation affected by both hormones was first found to be activated through transcriptional regulation of the *GIS* clade, a clade that belongs to the extensive C2H2 transcription factor family (Tague and Goodman, 1995; Zhou *et al.*, 2013). GIS, GIS2 and ZFP8 – all members of the GIS clade – are able, collectively and individually, to positively regulate *GL1* (Gan, 2006, 2007; Ishida *et al.*, 2008), but they have diverged in their responses to developmental and hormonal signals, playing different roles in regulating trichome initiation on diverse plant organs (Gan *et al.*, 2006, 2007). Although playing a major role in controlling CK signaling, *GIS2* and *ZFP8* were found to partially integrate GA and CK to control trichome formation in inflorescence organs (Gan *et al.*, 2006, 2007).

Despite the fact that the regulation of trichome initiation has been extensively studied, recent data have identified new transcription factors that belong to the *GIS* clade, which may

play redundant roles in integrating GA and CK signaling, such as *ZINC FINGER PROTEIN 5* and *6* (*ZFP5* and *ZFP6*) and *GLABROUS INFLORESCENCE STEMS3* (*GIS3*) trichome activators (Zhou *et al.*, 2011, 2013; Sun *et al.*, 2015). Similar to the phenotypes of mutants in any of the genes of the trichome activator complex, loss of GIS-clade function leads to a decrease in trichome formation on the adaxial surface of rosette leaves and/or inflorescence organs. In addition, overexpression of any of these proteins generates a high density of trichomes (Tague and Goodman, 1995; Gan *et al.*, 2006, 2007; Zhou *et al.*, 2011, 2013; Sun *et al.*, 2015).

Interestingly, and in comparison with some of the floral activators and floral repressors that show clear trichome phenotypes, an equivalent situation is found in several trichome mutants. Compared with wild-type plants, a significant delay in flowering has been reported in all trichome activation mutants analyzed. *gl1*, *gl3, gis*, *gis2* and *zfp8* show a strong reduction in adaxial trichome production, some of them being almost glabrous, and all flower late (Yan *et al.*, 2012). Among them, the flowering time of the *gl1* mutant is the most delayed, with an average increase of 62.5% in the number of days to flowering relative to control plants (Yan *et al.*, 2012). The single mutants *gis*, *gis2* and *zfp8* show a clear late flowering, with increases of 44.15%, 57.88% and 51.67%, respectively, in the number of days to flowering compared with wild-type *Columbia* (*Col-0*) ecotype plants. The *gl3* mutant in a *Landsberg* erecta (*Ler*) background shows a similar phenotype, with an average of 56.45% more days needed to flower than *Ler* wild-type plants (Yan *et al.*, 2012). In contrast, plants overexpressing *GIS* and *GIS2*, which produce more trichomes, show early flowering in comparison to wild-type plants, with a 28.34% and 36.65% of reduction in the number of days needed to flower (Yan *et al.*, 2012). Additionally, some of the R3-MYBs trichome repressors that control trichome formation in a GL2-independent manner (Wang and Chen, 2014), as *TRY* and ETC3, have been found to play pleiotropic effects such as delaying flowering. Indeed, single *try* and *cpl3* mutants flower earlier with a decrease of 5.31% and 23.13% in the number of days, respectively (Tominaga *et al.*, 2008; Yan *et al.*, 2012).

Consequently, all these observations indicate that different developmental processes separated in time and space, i.e. adaxial trichome proliferation and floral induction, might be closely correlated and inter-connected through the CK and GA hormones (Fig. 3). Indeed, when publicly available high-throughput data was analyzed (www.ebi.ac.uk/arrayexpress) similar results were obtained. Data used included diverse microarrays from Arabidopsis plants treated with GA and CK as well as plants with mutated key-genes for flower transition, trichome initiation, GA-or CK-biosynthesis pathways; specifically mutants in the *FT*, *CO, SPINDLY* (*SPY*), *GA1*, *RESPONSE REGULATOR 1* (*ARR1*), *GL1*, *GL3* and *EGL3* genes. A Venn diagram of the differentially expressed (DE) genes among the different microarrays shows that there is a small but still significant number of genes that overlap at least among three out of the four aspects compared in this review (Fig. 4).

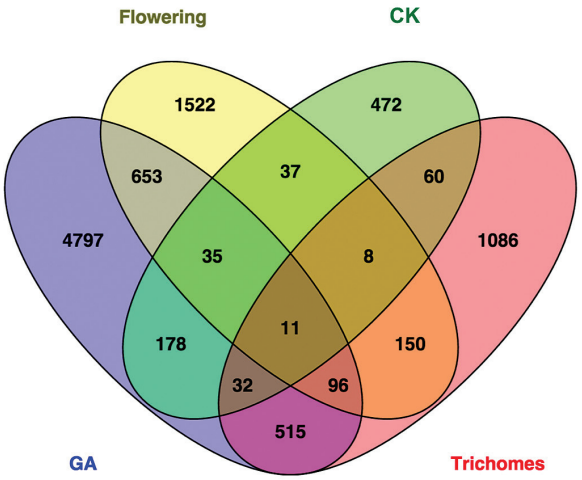

Fig. 4. Venn diagram showing the differentially expressed genes found among the diverse microarrays analyzed. High-throughput data used included microarrays from diverse Arabidopsis backgrounds that affect independently four biological processes: floral induction (yellow), trichome initiation (red), CK- (green) and GA-signaling (blue). A significant number of genes overlap at least among three out of the four aspects compared.

Floral organ identity genes repress inflorescence trichome initiation

This review is focused mainly on developmental processes that originate in the rosette leaves such as trichome initiation and flowering, but Arabidopsis trichomes are also present on inflorescence stems and flowers. In flowering species, floral organs, including sepals, petals, stamens and carpels are specified and controlled by floral organ identity genes (Bowman *et al.*, 1989; Coen and Meyerowitz, 1991; Pelaz *et al.*, 2000, 2001; Theissen, 2002; Ditta *et al.*, 2004). *AG*, a gene involved in stamen and carpel development (Yanofsky *et al.*, 1990; Drews *et al.*, 1991), has recently been found to be involved in repressing trichome proliferation on floral organs (Ó'Maoiléidigh *et al.*, 2013). Computational analyses using microarray data of early stage *ag* mutant flowers revealed that AG represses transcripts that encode proteins with several essential functions in rosette leaf development including trichome formation (Ó'Maoiléidigh *et al.*, 2013). Indeed, inducible artificial miRNA plant lines that silence *AG* (amiRAG) control trichome formation through direct regulation of some important trichome initiation genes, and show increased levels of the trichome initiation activators *GL1* and *ZFP8* (Larkin *et al.*, 1994; Schellmann *et al.*, 2002), while the trichome initiation repressors *CPC* and *TCL1* (Gan *et al.*, 2007; Wang *et al.*, 2007) are repressed (Ó'Maoiléidigh *et al.*, 2013). Phenotypical analyses showed that these amiRAG knockdown lines produce flowers with aberrant-shaped carpels that develop branched trichomes on their valves (Bowman *et al.*, 1989; Ó'Maoiléidigh *et al.*, 2013). The combinatorial function of AG, AP3 and PI proteins is widely known (Riechmann *et al.*, 1996; Honma and Goto, 2001; Theissen, 2002; Wuest *et al.*, 2012). ChIP-seq data analyses from AP3 and PI (Wuest *et al.*, 2012) revealed that both proteins are able to bind *in vivo* to the same trichome regulators targeted by AG, confirming

their combinatorial functions (Ó'Maoiléidigh *et al.*, 2013). Indeed, when all *AG, AP3* and *PI* are simultaneously knocked down, anthers of these mutant flowers develop branched and unbranched trichomes (Wuest *et al.*, 2012; Ó'Maoiléidigh *et al.*, 2013). Interestingly, these aberrant flowers, although slightly weaker, resemble those of plants overexpressing *GL1* trichome activator in the trichome repressor *try* mutant background (Schnittger *et al.*, 1998). *TRY* is able to control trichome initiation not only in rosette leaves but also in flowers (Schnittger *et al.*, 1998; Wellmer *et al.*, 2006). Similar to its GL2-independent function in leaves (Wang and Chen, 2014), TRY suppresses trichome proliferation in the flower independently of AG (Ó'Maoiléidigh *et al.*, 2013).

Conclusions

Using mutant analyses, gene expression studies and overlapping transcriptional regulatory interactions, great effort has been made to unravel the diverse molecular and genetic mechanisms that regulate different cellular differentiation programs in Arabidopsis. Data reveal that a network of transcriptional regulators is able to affect and be affected by GA and CK hormones at different organ, tissue and cell levels.

Indeed, in this review we show that the proper control of cell fate is of central importance and it is well coordinated in apparently distant developmental processes such as floral induction and epidermal trichome development. Both processes happen separately in time and most probably in space, but are interconnected, sharing a small genetic network on GA and CK hormone signaling. Several transcription factors belonging to the MYB, bHLH, C2H2, MADS families as well as DELLA proteins control both separated processes, floral transition and rosette leaf adaxial trichome proliferation, in response to different hormonal and developmental cues. Significant genetic interactions are shared between these two developmental processes. Here, we elucidate on how some important floral key activators and repressors control not only floral transition from the rosette leaf but also other rosette leaf developmental processes such as epidermal trichome formation. However, most of the analyzed trichome activator genes also positively control later developmental processes such as floral induction. In addition to that, as floral organs are essentially modified leaves through the action of different floral organ identity genes, these genes are also able to repress trichome proliferation in the flower. All these described transcription factors regulate floral induction and trichome formation processes by integrating diverse genetic networks and/or the control of hormone signaling. Therefore, while further investigation is necessary in order to dissect this complex regulatory network, these data lead us to suggest that the spatio-temporal regulation pattern and integration of signals of downstream regulators are of great importance; and consequently, different developmental processes separated in time, such as adaxial trichome proliferation and floral induction, might be closely correlated.

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Appendix

Expression information of the genes responding to GA, CK, flowering and trichome formation was obtained by the analysis of the following public microarray studies (http://www.ebi.ac.uk/arrayexpress/): E-GEOD-576,E-GEOD-7353,E-GEOD-8739,E-GEOD-8785,E-GEOD-12522,E-GEOD-12551,E-GEOD-39384,E-GEOD-44919,E-MEXP-344,E-MEXP-2270,E-MEXP-3362. For the datasets E-GEOD-7353, E-GEOD-8739, E-GEOD-8785, E-GEOD-12551 the lists of differentially expressed genes were taken directly from the published papers. E-GEOD-576 dataset was analyzed with the GEO2R tool from the NCBI with the default options. CEL files from E-GEOD-12522 and E-MEXP-2270 were downloaded; data were normalized with RMA using the R grma package (*R package version 2.40.0*). Then normalized data were used for differential expression test with the R package limma (Ritchie *et al.*, 2015). Probe expression values from the dataset E-MEXP-344 were analyzed with a *t*-test to identify the differentially expressed ones. Finally, E-GEOD-44919 and E-MEXP-3362 data were downloaded and limma was used to perform background correction (normexp), within normalization (loess) and between array normalization (quartile).

The differentially expressed genes coming from the four groups of experiments were joined and compared through a Venn diagram. An interactive tool for comparing lists with Venn diagrams was used (http://bioinfogp.cnb.csic.es/tools/venny/index.html).

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