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Beyond YABBYs: a Focus on Versatility and Interactivity

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Abstract

The *YABBY* gene family encodes small plant-specific transcription factors. The first function described for these genes was their role in the establishment and equilibrium of the adaxial-abaxial axes in lateral organs of angiosperms, which includes leaves and leaf-derived organs, such as sepals, petals, stamens, and carpels, and specific floral organs such as ovule integuments and nectaries. From these discoveries, more studies investigating the participation of *YABBY* genes in other mechanisms of development and in maintenance of the life cycle of plants began to arise. The roles of *YABBY* genes in hormone biosynthesis and in the production of secondary metabolites were brought to light in addition to their contribution to the evolutionary history of the leaf blade and floral organs. The proteins of the YABBY family directly regulate the transcription of target genes or they are involved with protein-protein interactions that modulate the functions of other proteins. This review will approach some of the various functions performed by the YABBY family members, focusing on how diverse are the molecular pathways these transcription factors interact with. The wide range of these different interactions is an important aspect that directly contributes to the versatility of this family of transcription factors.

Keywords Gibberellin biosynthesis pathway · Leaf development · Protein-protein interaction · Secondary metabolite · Transcription factor

Abbreviations

AFO	*ABNORMAL FLORAL ORGANS*
AG	*AGAMOUS*
ARF	*AUXIN RESPONSE FACTOR*
DMAPP	dimethylallyl diphosphate
EST	expressed sequence tag
HMG-box	high mobility group box
CRC	*CRABS CLAW*
FIL	*FILAMENTOUS FLOWER*
GA	gibberellic acid
INO	*INNER NO OUTER*
IPP	isopentenyl diphosphate
KAN	*KANADI*
MEP	2- C-methyl-D-erythritol 4-phosphate pathway
MVA	mevalonate pathway
NZZ	*NOZZLE*
PGT	peltate glandular trichomes
SAM	shoot apical meristem
SPL	*SPOROCYTELESS*
YAB1	*YABBY1*
YAB2	*YABBY2*
YAB3	*YABBY3*
YAB4	*YABBY4*
YAB5	*YABBY5*
WUS	*WUSCHEL*

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Introduction

The *YABBY* gene family is specific to seed plants and encode a class of small transcription factors with two conserved domains: a C_2C_2 zinc-finger domain and a helix-loop-helix domain (YABBY domain) with sequences similar to the first two helices of the HMG-box motif (High Mobility Group box), responsible for the binding of transcription factors to DNA (Golz and Hudson 1999; Siegfried et al. 1999; Bowman 2000a). These genes are found in the angiosperms and gymnosperms and the evolutionary history of this family coincides with the origin of seed plants (Sarojam et al. 2010). These transcription factors are responsible for several development processes in plants, such as the establishment of adaxial-abaxial polarity, development of lateral organs,

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response to abiotic stress, modulators of gibberellin biosynthesis pathway, among other functions (Yang et al. 2016; Zhao et al. 2017; Zhang et al. 2019).

In dicots species these genes play a significant role in the establishment of the abaxial-adaxial polarity in plant organs such as leaves and leaf-derived organs, being responsible to specify the fate of abaxial cells (Siegfried et al. 1999; Bowman 2000b; Bowman et al. 2002). The establishment of polarity is fundamental for development and growth of the plant leaf blade and leaf-derived organs (McConnel and Barton 1998; Eshed et al. 2001). *Arabidopsis* genome contains six *YABBY* genes: *YABBY1*/*FILAMENTOUS FLOWER*/*ABNORMAL FLORAL ORGANS* (*YAB1*/*FIL*/*AFO*), *YABBY2* (*YAB2*), *YABBY3* (*YAB3*), *YABBY4*/*INNER NO OUTER* (*YAB4*/*INO*), *YABBY5* (*YAB5*) and *CRABS CLAW* (*CRC*) (Fig. 1b and c) (Bowman 2000a; Kumaran et al. 2002). In angiosperms, these genes are organized into five subfamilies: FIL + YAB3, YAB2, INO, YAB5 and CRC (Yamada et al. 2011; Finet et al. 2016). *FIL*, *YAB2*, *YAB3* and *YAB5* genes are expressed on the abaxial surfaces of leaves and tissues of floral organs primordium - except in ovules - such as sepals, petals, stamens, carpels and also in the floral meristem (Fig. 1c) (Sawa et al. 1999; Siegfried et al. 1999). *CRC* is expressed in carpels and nectars (Bowman and Smyth 1999) and *INO* expressed in the outer integument of the ovules (Fig. 1b) (Golz and Hudson 1999).

Overexpression or reduction of *FIL*, *YAB2*, *YAB3* and *YAB5* genes expression causes changes in size and shape of the leaf blade and floral organs, giving rise to filamentous structures (Sawa et al. 1999; Eshed et al. 2004). In transgenic *Arabidopsis*, the overexpression of *FIL* gene results in filamentous leaf structures with abaxial characteristics and loss of adaxial characteristics (Sawa et al. 1999). Loss of polarity in *fil* mutant and the *fil-5 yab3-1* double mutants gave rise to floral organs with filamentous structures of radial symmetry and leaves with a mixture of abaxial and ectopic adaxial cells (Siegfried et al. 1999). Cases of quadruple mutants of the *YABBY* vegetative genes (*fil-8 yab2-1 yab3-2 yab5-1*) resulted loss of the leaf blade and originated adaxialized filamentous organs in which the *WUS* (*WUSCHEL*) gene is expressed, reactivating the shoot program (Sarojam et al. 2010). These findings and others researches have led some authors to propose that the role of *YABBY* family genes in leaf blade development derived from an ancestral shoot-specific network (Floyd and Bowman 2010; Sarojam et al. 2010). Loss of function mutations in *CRC* genes cause malformation in the structure of gynoecium and floral nectaries do not develop (Alvarez and Smyth 1999; Bowman and Smyth 1999). In *Arabidopsis*, the gynoecium of *crc* mutants are wider and shorter and the carpels do not fuse in the apex region of the ovary (Alvarez and Smyth 1999), in addition, there is no specification and development of floral nectaries at the base of stamens (Bowman and Smyth 1999). *INO* gene is responsible for the development of the outer integument of ovules and in mutant plants *ino* the absence of the outer integument is responsible for the malformation of ovules (Villanueva et al. 1999).

The abaxial expression of the *YABBY* genes is not a rule in angiosperms, although it occurs in many dicot species, such as *Arabidopsis* (Bowman 2000a), *Antirrhinum* (Golz et al. 2004), tomato (Kim et al. 2003) and tobacco (Foster et al. 2002). In *Amborella trichopoda*, a basal species of

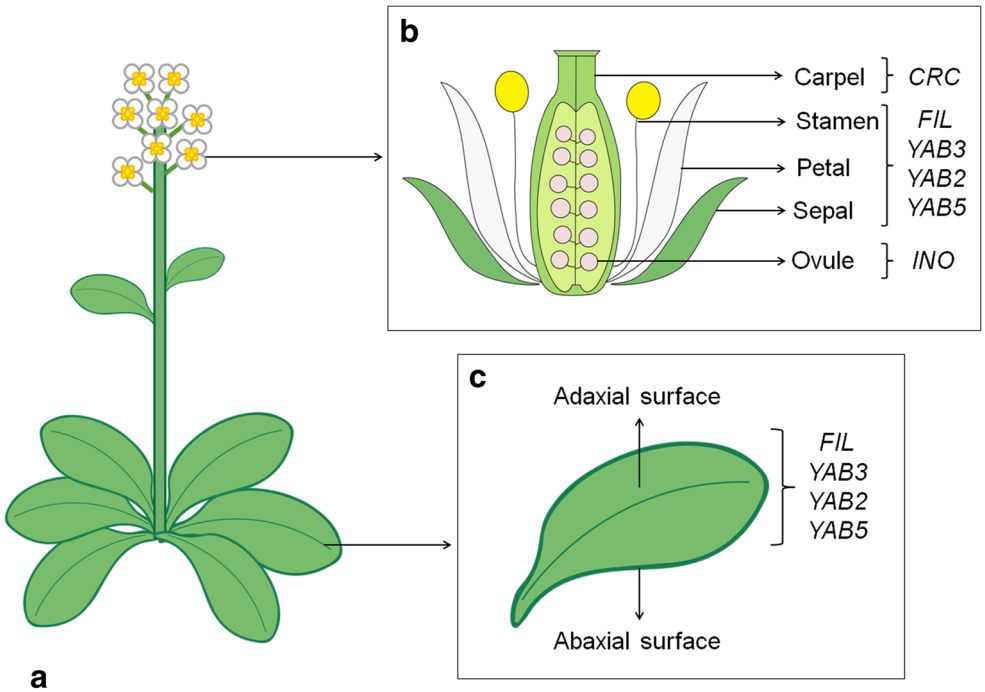

Fig. 1 A. Schematic drawing of (**a**) *thaliana* plant. (**b**) Longitudinal section of flower indicating YABBY genes expressed in floral organs. (**c**) YABBY genes expressed in leaves. Based from Sawa et al. (1999); Siegfried et al. (1999); Eshed et al. (2004)

angiosperm ("ANITA grade"), the *AmbF1* (*Amborella FIL-like-1)* gene, homologous to the *YAB2* in *Arabidopsis*, is expressed in the adaxial tissue of the carpel and leaf (Yamada et al. 2004). In *Passiflora edulis*, analysis of the expression pattern by *in situ* hybridization was performed using expressed sequence tags (ESTs) (Cutri and Dornelas 2012). The results showed that the transcript PACEPE3005G07, which has high similarity to the *FIL* sequence of *Arabidopsis*, is expressed on the adaxial side of the leaf primordia and on the adaxial side of all floral primordia during the initial development of the floral meristems (Cutri and Dornelas 2012). In monocot species the expression occurs in the adaxial surface (Sarojam et al. 2010). In the case of the *zyb9* and *zyb14* genes of maize, homologous to the *FIL* and *YAB3* genes of *Arabidopsis*, their expression occurs in the adaxial surface of leaf primordia (Juarez et al. 2004). In rice, the expression of *OsYABBY1*, belonging to the YAB2 clade, is related to the differentiation of specific types of cells and not in polar expression (Jang et al. 2004; Toriba et al. 2007). These findings suggest that in monocots the YABBY family developed new functions (Yang et al. 2016).

There are many studies of the role played by the *YABBY* genes in the development of the lateral organs focusing on the establishment of adaxial-abaxial polarity in the most varied angiosperms species. However, the number of studies related to the other functions that these transcription factors play in the most varied developmental processes of plants during their life cycle have increased significantly. For example, in soybean, some *YABBY* members participate in abiotic stress responses such as salt, drought and abscisic acid (ABA) (Zhao et al. 2017). In pineapple, there are also *YABBY* genes related to responses to salt stress (Li et al. 2019). In rice, genes that participate in the biosynthesis pathway of the gibberellin hormone have been reported (Dai et al. 2007; Yang et al. 2016). In *Artemisia annua, AaYABBY5* acts as a regulator of expression of genes that participate in the artemisinin biosynthesis pathway, an effective compound used to treat malaria (Kayani et al. 2019). These and other studies show the versatility and great importance of this family and how these studies contribute to the most diverse aspects of research carried out on seed plants, which may be of ecological, evolutionary or economic interest. Thus, this review aims to compile some of the diverse functions that the YABBY family plays focusing on the types of interactions that occur with these transcription factors, such as protein-protein, DNA-protein interaction and their role in hormone and secondary metabolite biosynthesis pathways.

DNA-protein Interaction in Leaf Development Mechanisms

Leaves of the seed plants are lateral organs that develop from shoot apical meristem (SAM) and play a crucial role in plant life as they are the main structures responsible for the photosynthetic process. The flat structure of the leaves requires a balance between the adaxial and abaxial surfaces and a limitation of the leaf margin (Eshed et al. 2004). Thus, the participation of several genes, including the *YABBY*s, is essential. Analysis of complete genomes of land plants species failed to identify *YABBY* genes sequences in moss and lycophytes species (Floyd and Bowman 2010). In contrast, the presence of these genes in gymnosperms and angiosperms species shows that the evolutionary history of the YABBY family coincides with the origin of seed plants (Yamada et al. 2011; Finet et al. 2016). While the YABBY family is organized into five subfamilies in angiosperms, in gymnosperms the homologous genes are organized into four different clades (A, B, C and D clades) (Finet et al. 2016). Research focused on phylogenetic analysis of YABBYs in seed plants showed two possible topologies in phylogenetic reconstructions: (1) angiosperms and gymnosperms in two different distinct monophyletic clades, suggesting a single gene as the common ancestor of seed plants; (2) two paraphyletic clades, in which some sequences of gymnosperms YABBYs are grouped with those of angiosperms, suggesting at least two genes as the common ancestor (Yamada et al. 2011; Bartholmes et al. 2012; Finet et al. 2016). Although it is not yet known which of these two evolutionary scenarios is the real one, these data provide important details for understanding how YABBYs evolved simultaneously with seed plants. Furthermore, discoveries about the role that YABBYs play in the establishment and development of leaves, in specification and expansion of the leaf blade, as well as in the regulation of SAM genes, led some authors to propose that these transcription factors are responsible for the origin of a leaf-specific network from the transformation of ancestral shoot-specific network (Floyd and Bowman 2010; Sarojam et al. 2010). Hereafter, these functions will be discussed focusing on DNA-protein interactions between YABBY transcription factors and other genes.

The morphology of the leaf structure is directly linked to the formation of axes during its development. From the relative position of SAM, the adaxial-abaxial polarities are defined during the development of the leaf primordium (Goldshmidt et al. 2008; Fukushima and Hasebe 2014) and the establishment of these axes is controlled by a gene network and hormonal signals (Bar and Ori 2014). In *Arabidopsis*, the KANADI and YABBY transcriptional factors family are the main determinants of the leaf blade's abaxial identity (Husbands et al. 2009). On the other hand, adaxial identity is determined by expressing the transcription factors of HD-ZIP Class III (HD-ZIPIII), such as the *REVOLUTA* (*REV*), *PHABULOSA* (*PHB*) and *PHAVOLUTA* (*PHV*) genes, and MYB family, more specifically the *ASYMMETRIC LEAF* genes (*AS1* and *AS2*) (Emery et al. 2003; Moon and Hake 2011). The regulation of these

genes between them, positively or negatively, is responsible for initiating and maintaining the balance between the adaxial and abaxial surfaces of leaves (Moon and Hake 2011; Fukushima and Hasebe 2014). The pattern of *YABBYs* expression on the abaxial surface during leaf development was recorded not only in species of eudicots and some monocots, but also in species of gymnosperms and basal angiosperms. In *Ginkgo biloba*, *GbiYABC* (clade C with an expression pattern similar to *FIL*/*YAB3*) is expressed on the abaxial surface of leaf primordia, and its expression seems to complement the expression of the *GbiC3HDZ1* (HD-ZIP Class III) (Floyd and Bowman 2010; Finet et al. 2016). In *Cabomba caroliniana* ("ANITA grade"), *CcFIL* and *CcYAB5* are expressed in a similar way in the abaxial tissues of leaf primordia, in addition the expression of these genes occurs mutually with *CabC3HDZ1* (co-orthologist of *PHB* and *PHV*) (Yamada et al. 2011). The mutual expression of the *YABBY* and *HD-ZIPIII* genes during the leaf development in seed plants may indicate an ancestral expression pattern established as part of a new mechanism acquired to transform the shoot-specific network into a leaf-specific network (Tomescu 2009; Yamada et al. 2011; Finet et al. 2016).

Leaf primordium is derived out of the peripheral zone (PZ) of the SAM, from the recruitment of mitotic cells from the central zone (CZ) (Bowman and Eshed 2000; Goldshimdt et al. 2008). CZ activity is maintained by the expression of several genes, among them we can highlight *WUSCHEL* (*WUS*), *CLAVATA3* (*CLV3*) and *KNOTTED1*-like homeobox (*KNOX*) (Bowman and Eshed 2000). A crucial point for the establishment and initiation of the leaf primordium is the downregulation of *KNOX* genes in SAM (Bowman and Eshed 2000). *SHOOTMERISTEMLESS* (*STM*), *BREVIPEDICELLUS* (*BP* or *KNAT1*) and *KNAT2* genes, members of the KNOX family, are expressed in CZ and downregulated in PZ (Piazza et al. 2005; Bar and Ori 2014). During the leaf development, since establishment and initiation of the leaf primordium, the YABBYs play a bifunctional role acting as positive and negative regulators in the expression of different genes, including genes that are expressed in SAM (Kumaran et al. 2002; Goldshmidt et al. 2008; Bonaccorso et al. 2012). FIL and YAB3 play fundamental roles in regulating SAM markers genes (Goldshmidt et al. 2008; Sarojam et al. 2010). These transcription factors act as negative regulators of the *KNOX* genes (Fig. 2) (Kumaran et al. 2002; Piazza et al. 2005). In *Arabidopsis* transgenic plants for loss of function mutants *fil-8* and *yab3-2*, the *STM*, *BP* and *KNAT2* genes are expressed ectopically in the leaves (Kumaran et al. 2002), giving rise to defective leaves and aberrant phyllotaxis (Goldshmidt et al. 2008). The study performed by Goldshmidt et al. (2008) revealed that expression of *FIL* and *YAB3* in the primordia domain emits a signal that is mediated to the domain of gene expression in CZ. This non-autonomously signal performs effects on the expression of genes expressed in CZ, including *WUS* and *CLV3*, responsible for the maintenance and organization of SAM, reflecting directly in the establishment of the relative position of leaf primordium development domain. Furthermore, the loss of function of *YABBY* genes is also capable of reestablishing the expression of the *WUS*, responsible for establishing the SAM. As shown by Sarojam et al. (2010), in plants for the loss of function *fil-8 yab2-1 yab3-2 yab5-1* mutant, the leaves gave rise to adaxialized filamentous structures in which SAM was established in the tips through the activation of *WUS*.

The bifunctional role that YABBY transcription factors play as positive and negative regulators in the expression of different genes is essential for the establishment of adaxial-abaxial axes and leaf blade expansion (Eshed et al. 2004; Moon and Hake 2011; Bonaccorso et al. 2012). It is from the juxtaposition of adaxial and abaxial cells that the leaf blade is established and its expansion is regulated by the activity of polarity genes (McConnell and Barton 1998; Eshed et al. 2004). *FIL* and *YAB3* are positively regulated by KANADIs (KAN) and AUXIN RESPONSE FACTOR (ARF) during the development of the leaf blade in *Arabidopsis* (Eshed et al. 2004). Similarly, FIL and YAB3 positively regulate the expression of *KAN1* and *ARF4* in a positive feedback loop (Bonaccorso et al. 2012). Bonaccorso et al. (2012) found, in studies with transgenic *Arabidopsis* plants, that the expression of *KAN1* and *ARF4* increased in 35S::FIL:GR plants combined with the dexamethasone/cycloheximide (DEX/CHX) treatment. These results demonstrate that FIL acts downstream of *KAN1*, a gene that encodes another essential transcription factor in the establishment of identity and maintenance of abaxial cells and leaf blade expansion (Emery et al. 2003; Eshed et al. 2004). The expansion of the leaf blade depends on the antagonistic mutual expression between KANADI and PHB-like genes, and in *kanadi* mutants for loss of function (*kan1*, *kan2* and *kan3*), the leaves exhibit a severe loss of polarity (Eshed et al. 2004). The positive feedback loop between *YABBY* and *KANADI* genes is a key point in the establishment and maintenance of the leaf blade, since these transcription factors act as negative regulators of the adaxial identity genes, ensuring that they are not expressed in abaxial cells (Fig. 3) (Eshed et al. 2001; Bowman et al. 2002; Moon and Hake 2011). YABBY transcription factors are also involved in positive regulation of *CINCINNATA*-class *TCP* genes, which encode a transcription factors family that also plays a fundamental role in leaf blade development (Martín-Trillo and Cubas 2010). In transgenic *Arabidopsis* plants for the YABBY complex mutants, most TCP genes are not activated, failing to establish the leaf blade growth system (Sarojam et al. 2010).

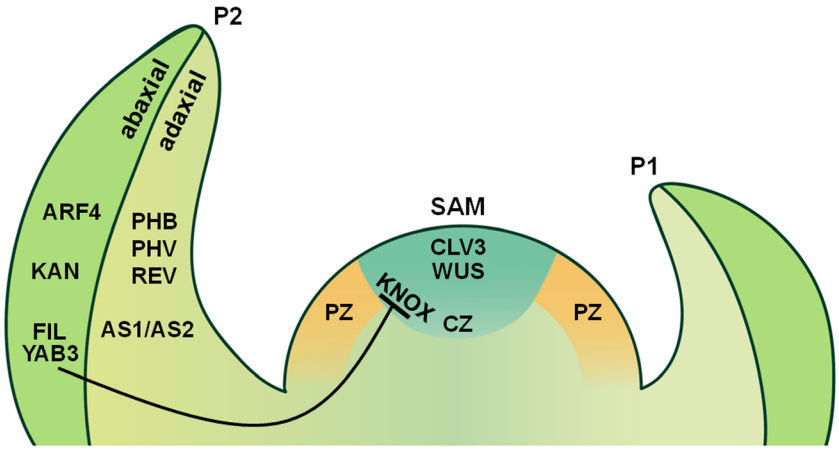

Fig. 2 Establishment and initiation of the leaf primordium in shoot apical meristem. The expression of *WUS*, *CLAV3* and *KNOX* is responsible for maintaining the CZ. YABBY transcription factors act as negative regulators of *KNOX* expression in SAM. *KNOX* repression is the starting point for the establishment of the leaf primordium derived from the PZ. YABBY, KANADI and ARF4 are responsible for establishing abaxial identity, while HD-ZIPIII (PHB, PHV and REV) and AS1/AS2 for adaxial identity. CZ, central zone; PZ, peripheral zone; P1, primordium 1; P2, primordium 2; SAM, shoot apical meristem. Adapted from Bowman and Eshed (2000); Moon and Hake (2011); Piazza et al. (2005)

Protein-protein Interaction Affecting the Development of Ovules and Carpels

A major factor for the evolutionary success of angiosperms was the emergence of flowers, ensuring greater efficiency in reproduction. Through pollination, carried out by biotic or abiotic vectors, the flowers give rise to fruits and consequently to seeds, which guarantee the propagation of the species. The complexity of these reproductive organs occurs through several regulatory mechanisms involving many transcription factors. Among these, we highlight two members of the YABBY family: CRC and INO (Bowman and Smyth 1999; Villanueva et al. 1999). In *Arabidopsis*, CRC is necessary for specification and development of nectary and carpels (Bowman and Smyth 1999; Golz and Hudson 1999), while INO is essential for the development of ovules, more specifically in the determination of abaxial polarity and development of the outer integument (Fig. 3) (Villanueva et al. 1999; Meister et al. 2002). *INO* is expressed in abaxial cells surface of the outer integument and the loss of its function results in the absence of the integument and, consequently, in interruption of the development of gametophytes (Sawa et al. 1999; Siegfried et al. 1999). Generally, the transcription factors with an HMG-box or a zinc-finger domain are known for their ability to form homo- and heterodimers (Sanchez-Giraldo et al. 2015). This ability is attributed to members of the YABBY family that have these two domains conserved.

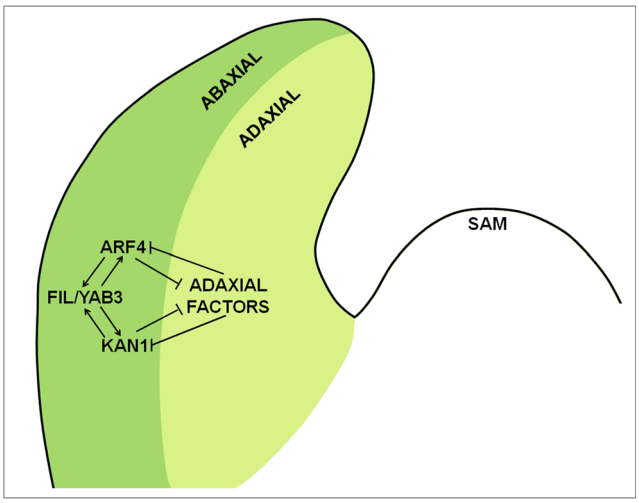

Fig. 3 Establishment and maintenance of adaxial-abaxial polarity in leaf development. The simultaneous antagonistic expression of adaxial-abaxial identity genes is responsible for the establishment of leaf blade polarities. KAN1 and ARF4 are positive regulators of *FIL/YAB* in a positive feedback loop. Adaptedfrom Bonaccorso et al. (2012)

The mature ovules of *Arabidopsis* have three distinct elements, distinguished along the proximal-distal axis: funiculus, chalaza and nucellus (Villanueva et al. 1999; Sieber et al. 2004a, b), representing excellent models of pattern formation in plants (Gasser et al. 1998; Chevalier et al. 2002). Several ovule development studies reported the importance of the NOZZLE/SPOROCYTELESS (NZZ/SPL) transcription factor in this process (Yang et al. 1999; Balasubramanian and Schneitz 2000; Sieber et al. 2004b; Wei et al. 2015; Liu et al. 2018). NZZ/SPL is a key component in regulating the formation of the proximal-distal pattern and cell proliferation during ovule development (Figs. 4 and 5) (Schiefthaler et al. 1999; Balasubramanian and Schneitz 2002; Sieber et al. 2004a). The development of the nucellus in the primordium of the ovule, the identity of the chalaza, the cell proliferation in the funiculus and the development of the integuments depend on NZZ (Balasubramanian and Schneltz 2000). Sieber et al. (2004b), using a yeast two-hybrid system, showed the

interaction of NZZ and INO proteins in vivo. The results showed that NZZ binds to INO through the recognition of the two conserved domains in the YABBY family (Zinc-finger and HMG-like domain "YABBY"). This result indicates that the NZZ-INO interaction is responsible for the coordinated formation of the proximal-distal and adaxial-abaxial axis in the development of the ovules, since the first is established before the specification of the second, which begins with the development of the outer integument in the chalaza (Villanueva et al. 1999). In *Cucumis sativus*, the SPL-INO in vivo interaction was also reported when analyzed in a yeast two-hybrid system, which made it possible to conclude about the interaction of these proteins during the development of the ovule integument (Liu et al. 2018). The results of these studies demonstrate that the regulation mechanism through the NZZ/SPL-INO interaction seems to be preserved in the development of the ovule integuments.

Another important transcription factor that acts in the development of the outer integument in *Arabidopsis* is LEUNIG (LUG) (Franks et al. 2002), that acts as a corepressor that depends on direct interaction with INO (Stahle et al. 2009; Simon et al. 2017). In yeast two-hybrid assays it was detected that interaction between INO and LUG happens in the N-terminal region, which includes the zinc finger domain (Simon et al. 2017). During the specification of the identity of stamens and carpels in *Arabidopsis*, LUG interacts with the transcriptional corepressor SEUSS (SEU), in a negative regulation mechanism, so that AGAMOUS (AG) is expressed only in the center of the floral meristem (Franks et al. 2002). The homeotic gene *AG* encodes a transcription factor responsible for the development of stamens and carpels (Yanofsky et al. 1990). Similar to *LUG*, *SEU* is also expressed in ovule cells during its development and its protein has no DNA-binding motifs (Bao et al. 2010). The role of SEU during the ovule integument development depends on the interaction with INO, through the N-terminal and C-terminal regions, as demonstrated by yeast two-hybrid assays (Simon et al. 2017).

The ovules are stored in carpels and, after fertilization, they give rise to seeds. The number of carpels varies between species and in the presence of two or more the process of fusing these organs is essential for the gynecium to form properly (Bowman et al. 1999). In dicot species, as in *A. thaliana*, the CRC transcription factor is one of the most important in the nectaries development and in the growth and fusion processes of carpels, in addition to being involved in the termination of the floral meristem (Bowman and Smyth 1999; Gross et al. 2018). In *Antirrhinum* STYLOSA (STY), LUG ortholog, interact physically with SEUSS LIKE (SLK) and members of the YABBY family, suggesting that in *Arabidopsis* there may be a protein complex formed SEU-CRC-LUG-FIL that acts in the development of gynecium (Azhakanandam et al. 2008). In *A. thaliana* CRC forms homodimers and interacts with INO, as demonstrated by in vivo assays (living yeast cells) performed by Gross et al. (2018), during the development of floral organs. The interaction between YABBY proteins and other proteins is essential in ovules and carpels development.

Interactions with the Gibberellin Pathway

Plant hormones, known as phytohormones, are essential organic compounds for the development and growth of plants. Phytohormones act in small doses, yet maintaining the main role as regulating several plant life-cycle processes together with a genetic program (Gray 2004). This section focuses on the interaction of YABBYs transcription factors in the gibberellic acid biosynthesis pathway. Gibberellic acid (GAs) are responsible for a number of these processes, including leaf expansion, stem elongation, seed germination and flower development (Silverstone et al. 1997; Cheng et al. 2004; Yamaguchi 2008). Either overexpression of genes responsible for suppressing other GA-biosynthesis transcription genes or loss of function mutants of the genes that synthesize GA results in semi-dwarf or dwarf phenotype specimens

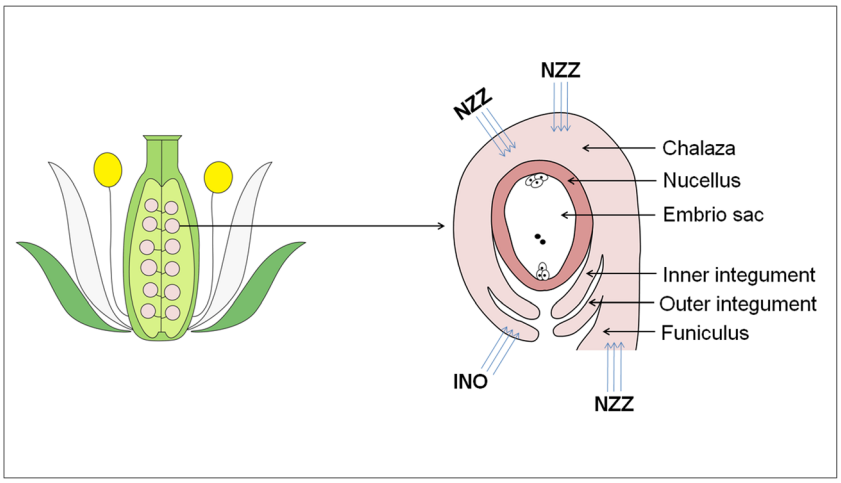

Fig. 4 Representation of the organization of *A. thaliana* mature ovule tissues. INO and NZZ are essential for the development of ovules. INO is responsible for determining the abaxial polarity of the ovule outer integument. NZZ acts on the development of nucellus, the identity of chalaza and cell proliferation of the funiculus. Adapted from Sieber et al. (2004a)

(Fukazawa et al. 2000; Hirano et al. 2012; Yamaguchi 2008). Currently, 136 gibberellins are known in nature, although only some of them are biologically active and thus involved in plant development and growth processes, such as GA1, GA3, GA4 and GA7 (Yamaguchi 2008; Hedden 2019). GA12 is the first to be synthesized by plants, despite being biologically inactive (Hedden and Phillips 2000; Sun 2008). Dioxigenase enzymes are necessary in the active GA-production chain as oxidation-catalyzers. The main ones being GA20oxidase (GA20ox) and GA3oxidase (GA3ox), producing GA1 and GA4 (Olszewski et al. 2002; Yamaguchi 2008). Although GA1 and GA4 are active, they may become inactive by the enzyme GA2oxidase (GA2ox) (Hedden and Phillips 2000; Olszewski et al. 2002).

Different factors are responsible for regulating the metabolism of gibberellins, such as light, tissue types, stage of development and response to GA through homeostasis mechanisms (Hedden and Phillips 2000). Changes in the levels of GA accumulation in plant cells act as signaling pathways in two regulatory mechanisms: (1) regulating the expression of GA responsive genes through the activity or degradation of the DELLA protein that binds to the promoters of these genes (Hirano et al. 2012; McGinnis et al. 2003); (2) regulating the genes involved in gibberellin biosynthesis through the inactivation of the *GA20ox* and *GA3ox* genes and in the activation of *GA2ox* (Hedden and Phillips 2000; Yamaguchi 2008).

Studies carried out on *Arabidopsis* and rice by Murase et al. (2008) and Shimada et al. (2008), showed that, in low concentrations of GA, the transcription repressor DELLA (SRL1 in rice) keeps the gibberellin-responsive genes repressed. In high concentrations of GA, it binds to the GIBBERELLIN INSENSITIVE DWARF1 (GID1) receptor that interacts with DELLA, acting as a marker for the SCF^{GID2} ubiquitination complex to bind to DELLA and activate its degradation by 26S proteasome. With the degradation of DELLA, the transcription of the GA-regulated genes is activated. Analysis of the DELLA protein showed that it does not have a DNA binding domain, raising the hypothesis that other transcription factors act as an intermediate protein between DELLA and the DNA sequence (Harberd et al. 2009; Hauvermale et al. 2012).

In *Oryza sativa* rice species, the family YABBY is formed by eight members (Toriba et al. 2007). A study by Yang et al. (2016) in this species showed, through immunoprecipitation experiments with antibodies of proteins isolated from plants, that the transcription factor OsYABBY4 acts in the modulation of the gibberellin pathway. OsYABBY4 functions as an intermediate protein between SLR1 and the DNA sequence of the promoter region of gibberellin-responsive genes, repressing its expression in the absence of GA (Fig. 6a). In its presence, it binds to the GID1 receptor interacting with SLR1, replacing the OsYABBY binding. This interaction signals SLR1 for the SCF^{GID2} ubiquitination complex to bind to it and activate its degradation by 26S proteasome. The GA-GID1-SLR1 interaction releases the OsYABBY4 binding of the gene promoter, activating its expression (Fig. 6b).

In the same study by Yang et al. (2016), OsYABBY4 was described as a negative regulator of *GA20ox2* expression for gibberellin biosynthesis. Through functional studies, it was shown that OsYABBY4 binds to the promoters of *SLR1* and *GA20ox2* and suppresses its expression. These are not the only reports of YABBY transcription factors acting as modulators in the gibberellin biosynthesis pathway in rice. The work developed by Dai et al. (2007) with transgenic plants reports functions performed by YABBY1 (YAB1) in the biosynthesis of gibberellin in the same species. The results obtained in this work showed that the overexpression of *YAB1* resulted in plants with semi-dwarf phenotypes due to the

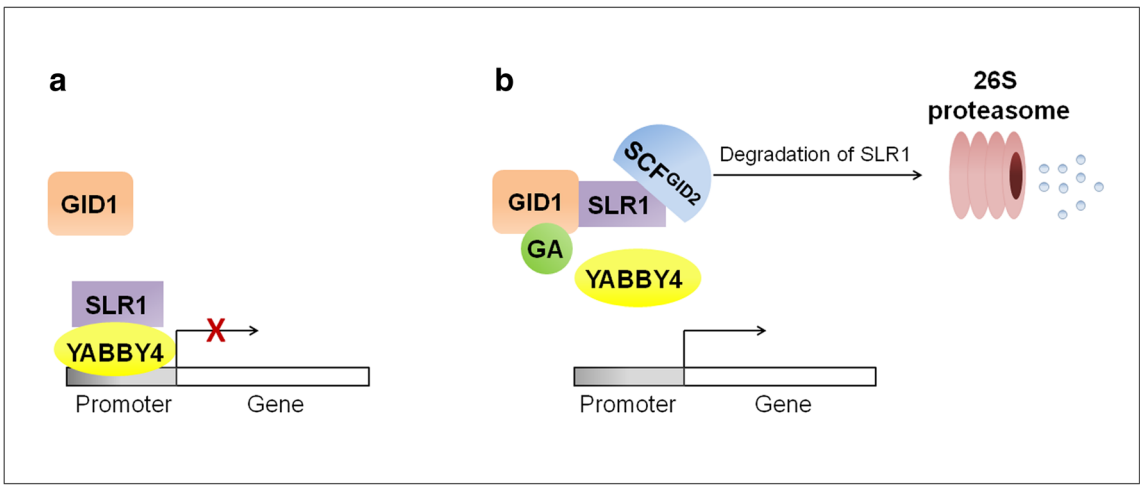

Fig. 5 **a** Interaction between OsYABBY4 and SLR1 in the absence of GA, suppressing gene expression. **b** GA-GID1-SLR1 interaction, activating the labeling of SLR1 by the SCFGID2 ubiquitination complex and consequently its degradation by the 26S proteasome. The interaction between GA-GID1 and SLR1 releases the bond between OsYABBY4 and the promoter sequence, activating gene expression. Adapted from Yang et al. (2016)

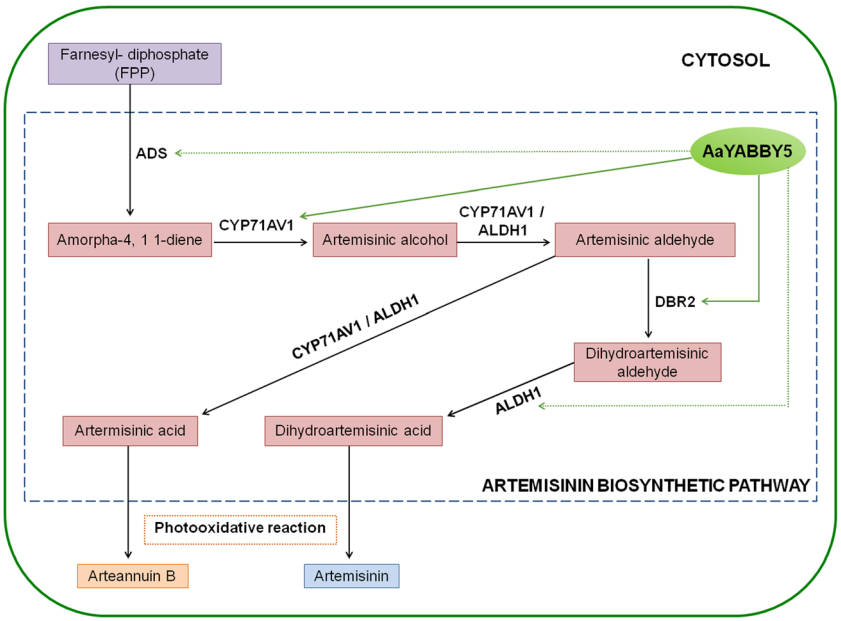

Fig. 6 Artemisinin biosynthesis pathway in *Artemisia annua*. AaYABBY5 transcription factor acts in the artemisin biosynthesis pathway as a positive regulator, as indicated by the green arrows. Simple arrows indicate that regulation occurs directly through the binding of AaYABBY5 to *CYP71AV1* e *DBR2* genes promoter. The dashed lines indicate an indirect regulation of AaYABBY5 in the expression of *ADH1* and *ALDH1* genes. ADS, amorpha-4, 1 1-diene synthase; ADH1, alcohol dehydrogenase 1; ALDH1, aldehyde dehydrogenase 1; CYP71AV1, cytochrome P450 monooxygenase; DBR2, double-bond reductase. Adapted from Kayani et al. (2019)

binding of YAB1 in the promoter of *GA3ox2*, a gibberellin biosynthesis gene, repressing its expression. In addition, it has been shown that *YAB1* expression is responsive to GA, being activated in the presence of gibberellin and suppressed in its absence. The compilation of all these results demonstrates the great importance that YABBY members have in the gibberellin biosynthesis pathway in rice. In addition, they demonstrate the versatility that the YABBY family has since the same transcription factor performs DNA-protein and protein-protein interactions within the same pathway.

Interactions with Secondary Metabolite Pathways

The YABBY transcription factors also act in isoprenoid biosynthesis pathways. Terpenes, also known as isoprenoids, are a group of natural compounds produced by all forms of life. Currently, more than 55,000 isoprenoid molecules have been discovered, most of which are produced by plants (Thulasiram et al. 2007). In plants, terpenes are classified as primary and secondary metabolites. Primary metabolites constitute a group of compounds, which are essential for the development and growth of plants, such as: phytohormones cytokinins, gibberellins and abscisic acid that act as regulators of plant development; the carotenoids, chlorophylls and plastoquinones related to the photosynthesis process; and the ubiquinone that acts in the respiration process (Theis and Lerdau et al. 2003; Rodríguez-Concepción 2014; Vranová et al. 2012). The secondary metabolites are synthesized in some families and species of plants, forming a group with thousands of hundreds of compounds composed by oils, volatiles and pigments (Rodríguez-Concepción 2014; Pulido et al. 2012). This group has a wide variety of functions involved in different mechanisms of interaction between plants and the environment, such as plant-plant and insect-plant communication, defense against herbivores and pathogens and attraction of pollinating agents and seed dispersers (Theis and Lerdau 2003; Aharoni et al. 2006; Vanovrá et al. 2013).

The five-carbon (C5) isomers dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP) are the universal precursors of all isoprenoids and their biosynthesis can take place in two different ways: the mevalonate (MVA) pathway in the cytosol and the 2- C-methyl-D-erythritol 4-phosphate (MEP) pathway in plastids (Bouvier et al. 2005; Vranová et al. 2012; Tetali 2019). In general, terpenes are grouped and named after the size of the isoprene molecules chain that comprises them and the wide variety of chemical structures of these compounds is interpreted as a crucial factor in the diversification of their functions (Bouvier et al. 2005; Aharoni et al. 2006; Vranová et al. 2013; Tetali 2019). The continuous process of gene evolution to produce new compounds also has a key role in the different types of functions that terpenes perform (Pichersky and Gang 2000). It is estimated that 15–25% of genes in plants are responsible for the biosynthesis of secondary metabolites, including isoprenoids, flavonoids and alkaloids (Bouvier et al. 2005). Studies that aim to identify and characterize the genes involved in secondary metabolites pathways are extremely important for the development of new techniques involved in the production of compounds with high economic value, such as in the production of drugs, cosmetics, fragrances, food, pesticides, biomaterials and others (Aharoni et al. 2006; Bohlmann and Keeling 2008; Vranová et al. 2013). Here we will focus on the YABBY role in regulating genes that participate in the biosynthesis pathways of terpenes in the species *Artemisia annua* and *Mentha spicata*.

Arteminisin is a sesquiterpene lactone produced in the aerial parts of *Artemisia annua* which has great economic value because of its effectiveness as a therapeutic agent against malaria, an infectious disease caused by the parasitic protozoan *Plasmodium falciparum* (Abdin et al. 2003; Weathers et al. 2006). In addition, it is also used to treat hepatitis B (Romero et al. 2006), as an anticancer (Nam et al. 2007) and against parasitic helminths (Keiser and Utzinger 2007). Although artemisinin is naturally synthesized by *A. annua*, its production is relatively low, varying between 0.1-1% of the dry leaf weight (Abdin et al. 2003). The necessity for large-scale production has motivated many studies to focus on the identification of enzymes that act in the artemisinin synthesis as a basis for the application of molecular engineering techniques (Weathers et al. 2006). The four main enzymes that act in the artemisinin biosynthesis pathway are: amorpha-4,11-diene synthase (*ADS*) (Bouwmeester et al. 1999); cytochrome P450 monooxygenase (*CYP71AV1*) (Ro et al. 2006; Teoh et al. 2006); double-bond reductase 2 (*DBR2*) (Zhang et al. 2008); and aldehyde dehydrogenase 1 (*ALDH1*) (Teoh et al. 2009). In *A. annua*, isopentenyl diphosphate (IPP) is produced by MVA pathway and the MEP pathway produces IPP and its dimethylallyl diphosphate (DMAPP) isomer (Towler and Weathers 2007). In the cytosol, one molecule of DMAPP and two of IPP are used to produce farnesyl diphosphate (FPP), a precursor to the biosynthesis of artemisinin (Ma et al. 2017). The ADS enzyme converts FPP to amorpha-4,11-diene which in the next stage will be oxidized to produce artemisinic alcohol and artemisinic aldehyde, respectively, in the presence of CYP71AV1 and ALDH1 (Bouwmeester et al. 1999; Ro et al. 2006; Teoh et al. 2006). Two products are derived from artemisinic aldehyde, dihydroartemisinic aldehyde (DHAA) catalyzed by DBR2 (Zhang et al. 2008) and artemisinic acid (AA) in the presence of CYP71AV1 and ALDH1 (Teoh et al. 2009). DHAA and AA undergo photo-oxidative reactions producing arteannuin B and artemisinin, respectively (Brown and Sy 2004; Brown and Sy 2007).

Through analyzes of *A. annua* whole-genome and phylogenetic analysis, Kayani et al. (2019) identified a homologous gene of MsYABBY5, named AaYABBY5, characterized as a negative regulator of monoterpenes in *Mentha spicata* (Wang et al. 2016). Still in this study, the activity of *AaYABBY5* as a regulator of genes encoding enzymes that act in the artemisinin biosynthesis pathway was analyzed and reported through the application of different techniques, such as the dual-luciferase reporter (Dual-LUC) and Yeast One Hybrid assays, in addition to quantitative analysis Real-Time PCR (qPCR) and high-performance liquid chromatography (HPLC) using transgenic plants for the overexpression of *AaYABBY5* and *AaYABBY5* antisense plants. The Dual-LUC reporter assays recorded an increase in the activity of the *ADS*, *CYP71AV1*, *DBR2* and *ALDH1* promoters, but only *CYP71AV1* and *DBR2* demonstrated a direct link to AaYABBY5 through the Yeast One Hybrid assays. The qPCR analysis showed that in plants with *AaYABBY5* overexpression, *ADS*, *CYP71AV1*, *DBR2* and *ALDH1* genes had a significant increase in its expression, while in antisense plants the expression decreased significantly. In addition, HPLC results showed an increase in the concentration of artemisinin in overexpressed *AaYABBY5* plants and a decrease in concentration in antisense plants. In this way, the authors were able to prove that AaYABBY5 regulates positively the genes that encode the enzymes that act in the artemisinin biosynthesis (Fig. 6). The role of YABBY members as positive regulators in secondary metabolite pathways was also reported in *A. thaliana*, in which FIL acts as a positive regulator in anthocyanins biosynthesis, pigments that belong to the flavonoid group (Boter et al. 2015) and activation of genes involved in the glucosinolates production (Douglas et al. 2017).

Plants of the genus *Mentha*, family Lamiaceae, are sources of essential oils of great economic value because they are used on large scale by the pharmaceutical, food and cosmetics industries (Sinha et al. 2013). These essential oils, more specifically the monoterpenes limonene and carvone, are secondary metabolites synthesized by the MEP pathway (Turner and Croteau, 2004; Jin et al. 2014). Production of these monoterpenes occurs in small-specialized structures, called peltate glandular trichomes (PGT), found on the surfaces of aerial parts of plants of the genus *Mentha* (Jin et al. 2014; Wang 2014). In the species *Mentha spicata*, known as spearmint, PGT are found on the adaxial and abaxial surfaces of the leaves and are responsible not only for the production of monoterpenes, but also for storing them (Wang 2014). The study developed by Wang et al. 2016 with *M. spicata* showed that a YABBY member, called *MsYABBY5*, is preferentially expressed in PGT and is involved in the biosynthesis of terpenes in the species. Through the use of transgenic plants that overexpress *MsYABBY5* and silenced it, using the RNA interference (RNAi) technique, changes in terpene levels have been reported. In overexpressed plants the levels of terpenes decreased, while in silenced plants the levels increased, suggesting that the transcription factor *MsYABBY5* acts as a possible repressor in the biosynthesis pathway of these terpenes. This work also reported a reduction in the production of secondary metabolites in *Ocimum basilicum* (basil) and *Nicotiana sylvestris* in view of the ectopic expression of *MsYABBY5*.

Conclusions

The first function described in the literature performed by YABBY members was their essential role as regulators of identity and establishment of the abaxial face during the development of lateral organs in angiosperms. The balance between the adaxial-abaxial axes is a crucial point at the origin of the leaf blade. Although this is a well-preserved function in

dicot species, as in *A. thaliana*, there is a divergence of functions between monocot species, as seen in *O. sativa* - whose genes are expressed on the adaxial surface of the leaves. From these discoveries, studies aimed at the participation of YABBY members in various mechanisms of development and maintenance of the life cycle of plants, in both gymnosperms and angiosperms, took a large proportion. The compilation of these works described in the literature shows the versatility of this family, not only in the different functions they play but also in the way in which the interactions of these transcription factors occur - whether they are directly linked to DNA or the interaction is between one or more proteins. In addition to the importance they play in the evolutionary history of the appearance of leaves, these small transcription factors are also responsible for the biggest factor in the evolutionary success of angiosperms, as they are essential in the development of floral organs, such as ovules and carpels. YABBY transcription factors are crucial not only at different points in the evolutionary history of plants, but also in vital mechanisms for development and maintenance of the species, as well as in the participation of the gibberellin hormone pathway. The discovery of the participation of YABBY members in secondary metabolite biosynthesis pathway, as in artemisinin biosynthesis, used in the production of an antimalarial drug, and in the production of other isoprenoids, as occurs in species of the genus *Mentha*, demonstrate how the studies of this gene family are also essential in the development of compounds of great economic value in the most diverse branches of industries, such as pharmaceutical and food. New studies on the identification and characterization of YABBYs in new species, from the sequencing of genomes, studies of gene expression, in addition to studies of protein-protein interactions and others, are extremely important in the discovery of new functions and contributions of this very versatile small transcription factors family.

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