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HYPOTHESIS

SPECIAL ISSUE: PLANT CELL BIOLOGY

Emerging role of the plant ERF transcription factors in coordinating wound defense responses and repair

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ABSTRACT

Plants react to wounding through the activation of both defense and repair pathways, but how these two responses are coordinated is unclear. Here, we put forward the hypothesis that diverse members of the subfamily X of the plant-specific ethylene response factor (ERF) transcription factors coordinate stress signaling with the activation of wound repair mechanisms. Moreover, we highlight the observation that tissue repair is strongly boosted through the formation of a heterodimeric protein complex that comprises ERF and transcription factors of the GRAS domain type. This interaction turns ERFs into highly potent and stress-responsive activators of cell proliferation. The potency to induce stem cell identity suggests that these heterodimeric transcription factor complexes could become valuable tools to increase crop regeneration and transformation efficiency.

KEY WORDS: Plant, Stem cell, Wound repair, Regeneration, Callus

Introduction

Plants have evolved many different strategies to cope with distinct types of biotic and abiotic stresses, as well as with injury through wounding. These strategies have likely been developed because of their immobile lifestyle. Wounding threatens plant survival, especially if it occurs in the stem that holds the vascular tissue that is used for the transport of nutrients and water, as the stem connects the shoot and leaves with the flowers and fruits (Melnyk, 2017). Additionally, wounds represent possible entry sites for pathogens. At the cellular level, plants respond to wounding by activation of their defense systems (Savatin et al., 2014). Physiological responses include the repair and reinforcement of the cell wall and the activation of wound-signaling pathways. This occurs through induction of both local and systemic defense-related proteins and activation of hormones related to wounding, such as ethylene and jasmonic acid (JA) (León et al., 2001; Sasaki et al., 2002). In parallel, the plant initiates mechanisms of wound healing, which often imply a local reactivation of cell division (Heyman et al., 2016; Sena et al., 2009).

Whereas the signaling cascades used by plants to prevent infection following wounding have been well documented, how these pathways communicate with cell repair mechanisms is unclear. Based on recent findings, we speculate below that the unique subgroup X of transcription factors of the ethylene response factor (ERF) family coordinates stress signaling with wound healing. Moreover, we highlight that – at least for the process of wound healing – the activity of these transcription factors is fine-tuned and controlled through their heterodimerization with transcription factors of a distinct protein family. This heterodimerization turns the ERFs into highly potent cell division activators. Finally, we discuss the use of these heterodimeric transcription factors to improve plant regeneration.

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The ERF family of transcription factors

The *Arabidopsis thaliana* genome encodes more than 65 gene transcription factor families, with some comprising over 100 family members (Mitsuda and Ohme-Takagi, 2009; Riaño-Pachón et al., 2007). Among these different families, the ERF family of plant-specific transcription factors constitutes one of the largest (Nakano et al., 2006). The discovery of the ERF family is connected to the characterization of the homeotic *APETALA2* (*AP2*) gene, a putative nuclear protein that harbors an essential 68-amino-acid repeat motif that was designated the AP2 domain and contains DNA-binding activity (Jofuku et al., 1994; Ohme-Takagi and Shinshi, 1995). The gene was identified through its ability to promote the establishment of the floral meristem: mutations in this locus result in the transformation of sepals into leaves, and petals into stamenoid organs that produce pollen, or even cause sepals to be transformed into carpels which bear the ovules (Bowman et al., 1989; Bowman et al., 1991; Kunst et al., 1989). Since then, the number of identified AP2-type genes increased noticeably across the plant kingdom, counting 147 in *Arabidopsis thaliana* and up to 210 in *Zea mays* (Guo et al., 2016; Lata et al., 2014; Liu et al., 2013; Nakano et al., 2006; Rao et al., 2015).

The *Arabidopsis thaliana* ERF family can be subdivided into four main groups: AP2 (18 members), RAV (six members), ethylene-responsive element binding (EREB)-dehydration-responsive element-binding (DREB) proteins (122 members), and a group with the single member APETALA 2 FAMILY PROTEIN INVOLVED IN SALICYLIC ACID MEDIATED DISEASE DEFENSE 1 (Nakano et al., 2006). The 18 members of the AP2 subgroup are hallmarked by the presence of two AP2 domains (Fig. 1A). Besides AP2 itself, PLETHORA (PLT) proteins comprise a well-studied subfamily of the AP2-type transcription factors. The PLT transcription factors were originally identified as essential regulators that control stem cell activity in the *Arabidopsis thaliana* root (Aida et al., 2004; Santuari et al., 2016). Additionally, PLTs orchestrate phyllo- and rhizo-taxis during plant development (Hofhuis et al., 2013; Prasad et al., 2011); together with AINTEGUMENTA (ANT), another AP2-type transcription factor, they control shoot apical meristem function (Mudunkothge and Krizek, 2012; Nole-Wilson et al., 2005). Thus, the AP2 subfamily contains several key regulators that control different developmental processes during plant growth.

RAV-type transcription factors respond transcriptionally to touch-related stimuli (Kagaya and Hattori, 2009). In contrast to the AP2-type transcription factors, RAVs possess a single AP2 domain and a second conserved DNA-binding domain, which is

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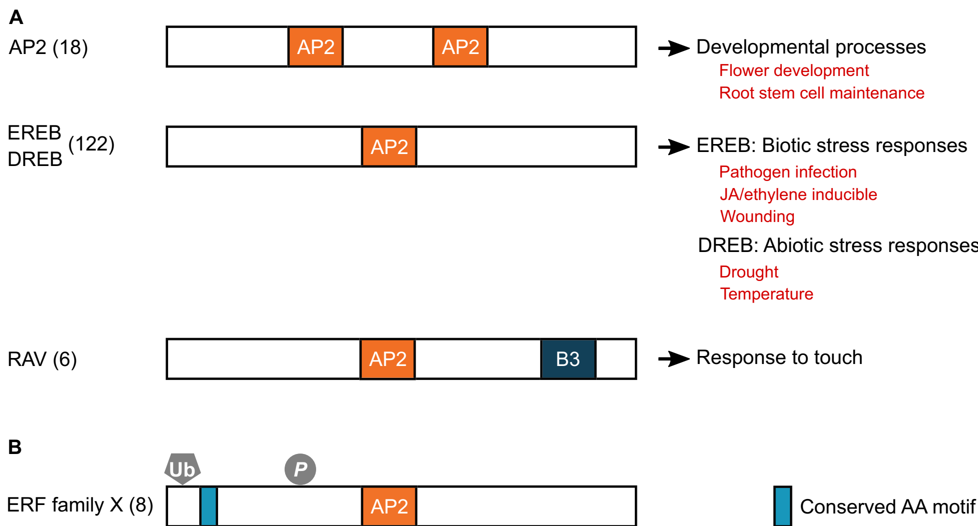

Fig. 1. Schematic overview of the structural organization of the different ERF subfamilies. (A) Plants have three major groups of ERF transcriptions factors: AP2, EREB/DREB, and RAV. The number of respective family members in *Arabidopsis thaliana* is listed in brackets. Conserved amino acid motifs (AP2 and B3) that mark the different groups are indicated. Developmental and stress processes controlled by the different ERF classes are listed on the right. (B) Schematic representation of the ERF subfamily X protein members, including the subfamily-specific conserved motif and possible posttranslational modification sites. AA, Amino Acid; *P*, phosphorylation site as described for ERF110 (Li et al., 2012); Ub, ubiquitylation site as reported for ERF115 (Walton et al., 2016).

located at their C-terminus and designated B3 (Fig. 1A) (Kagaya et al., 1999). A single AP2 domain can also be found in the members of the EREB proteins (Fig. 1A), which were identified as factors that mediate the ethylene response through recognition of the consensus GCC-motif within target gene promoters (Fujimoto et al., 2000; Ohme-Takagi and Shinshi, 1995). The DREB subfamily within the EREB class is defined by their ability to activate target gene expression upon dehydration (Ingram and Bartels, 1996; Kizis et al., 2001). As suggested by their name, DREB transcription factors control the expression of genes that hold a drought-responsive *cis*-acting element, although also they regulate low temperature- and cold-responsive genes (Baker et al., 1994; Jiang et al., 1996; Liu et al., 1998).

The EREB-DREB subfamily X

Phylogenetic clustering of the 122 *Arabidopsis* EREB-DREB members led to their classification into 12 subgroups, namely I to X, VI-L and Xb-L (Nakano et al., 2006). Here, we review the features of the members of the X subfamily (ERF108 to ERF115), whose hallmark is a conserved N-terminal sequence (Figs 1B and 2) and discuss their participation in wound signaling and tissue repair.

ERF108

ERF108, also known as RELATED TO APETALA2.6 (RAP2.6), was identified as a transcription factor that can be induced by JA (Wang et al., 2008), which is in line with studies that demonstrate that its transcription is induced by pathogens (Fig. 3) (He et al., 2004). In order to find novel components that are involved in wound signal perception and JA signaling, a screen for mutants that display constitutive *ERF108* expression was performed and resulted in the identification of a mutation in the *MECHANOSENSITIVE CHANNEL OF SMALL CONDUCTANCE-LIKE 10* (*MSL10*) gene (Zou et al., 2016). This mutant displays characteristic features of the JA response, such as accumulation of anthocyanin pigments and shorter petioles. These results corroborated the observation that *ERF108* is a target of the JA signaling pathway. Apart from JA, other stress signals, such as abscisic acid (ABA), heat, drought, sorbitol and salt, significantly induce *ERF108* expression (Krishnaswamy et al.,

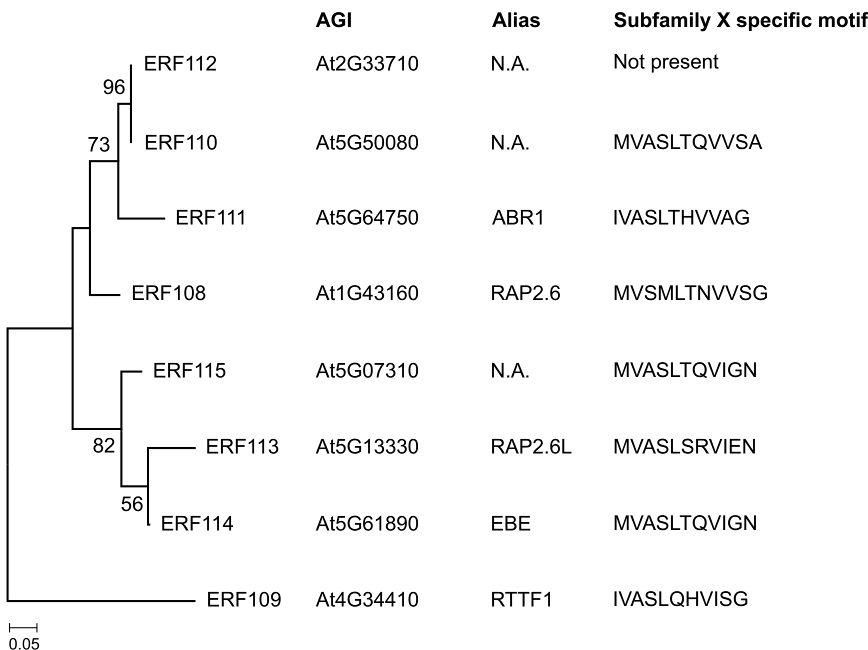

Fig. 2. Phylogenetic tree of the *Arabidopsis thaliana* ERF subfamily X. The phylogenetic tree was constructed using the Maximum Likelihood Method (cpREV+G, 500 bootstrap iterations; only bootstrap values>50 are shown) with Mega software (v5.1), based on a multiple sequence alignment (generated with Clustal Omega) of the AP2 domains of ERF family X protein members. For each family member, the *Arabidopsis* Genome Initiative (AGI) locus code, the alternative gene name (alias), and the subfamily conserved amino acid motif is given. N.A., not applicable.

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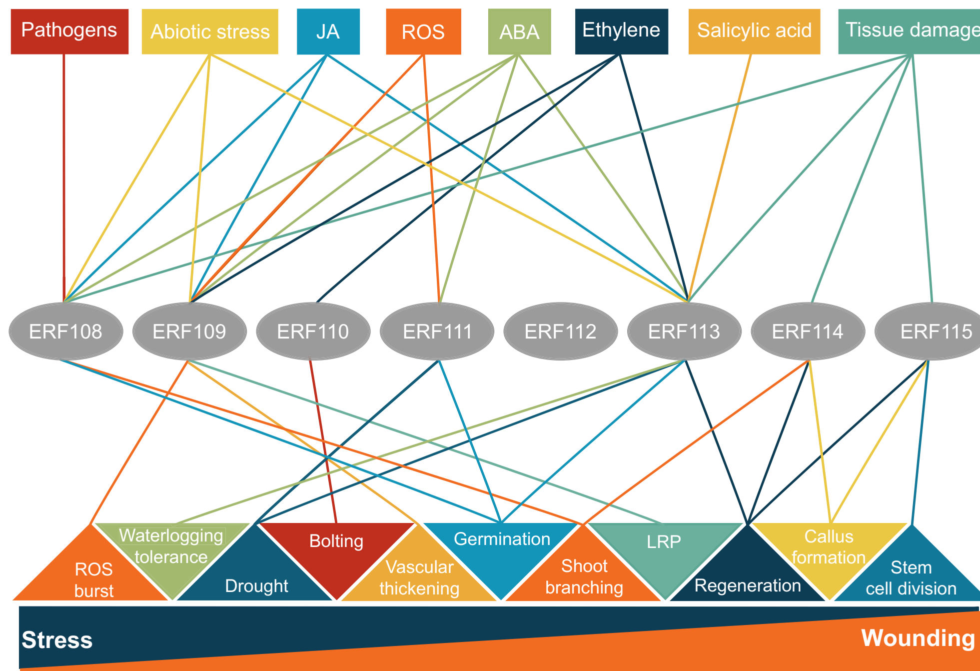

Fig. 3. Overview of the ERF X subfamily members and their function in wound response and tissue repair. Lines connect the different ERF members with upstream activating cues and downstream events. The distinct ERF subfamily members respond to a diverse set of wound-induced stimuli: pathogen attacks, abiotic stress signals (such as cold), jasmonic acid (JA), reactive oxygen species (ROS), abscisic acid (ABA), ethylene, salicylic acid (SA) and tissue damage. Downstream events include the activation of a ROS burst, resistance to waterlogging and drought, bolting time control, activation of vascular thickening, shoot branching, lateral root primordia (LRP) initiation, tissue regeneration following wounding, spontaneous callus formation and root stem cell proliferation. Note that for ERF112 no upstream activating cue or downstream function is appointed, as no such data are available to date. The color scale at the bottom indicates the putative gradation of involvement of the ERF family members in stress (blue) and wounding (orange) response.

2011; Zhu et al., 2010). Upon overexpression of *ERF108*, plants develop more secondary branches and are dwarfed. Moreover, these transgenic plants display hypersensitivity to ABA and osmotic stress during seed germination and early seedling growth stages. Thus, it appears that *ERF108* represents a stress-inducible transcript required for stress adaptation. Interestingly, ERF108 is phylogenetically related to the tobacco WOUND-RESPONSIVE AP2-LIKE FACTOR 1 (WRAF1) and WRAF2 proteins. Both bind the vascular system-specific and wound-responsive *cis*-acting element (VWRE) that has been mapped within the promoter of the wound-induced *tpoxN1* peroxidase gene (Sasaki et al., 2006; Sasaki et al., 2007). This indirectly suggests that ERF108 might also participate in wound healing (Fig. 3).

ERF109

ERF109 is also known as REDOX RESPONSIVE TRANSCRIPTION FACTOR 1 (RRTF1) (Khandelwal et al., 2008). Similar to *ERF108*, *ERF109* expression is induced by many different abiotic stresses: salt, drought, cold, ultraviolet B, heat, osmotic stress, as well as hormones such as ABA and JA (Fig. 3) (Gadjev et al., 2006; Matsui et al., 2008; Toufighi et al., 2005; Wang et al., 2008). Its transcription is mediated in part by WRKY transcription factors, in particular WRKY18, WRKY40, and WRKY60, which are induced in response to ABA and abiotic stresses (Chen et al., 2010; Pandey et al., 2010). In accordance with this, the transcriptional activation of *ERF109* by high levels of light and hydrogen peroxide (H_2O_2) is almost completely abolished in the respective triple *wrky* knockout.

Not only does *ERF109* gene expression become activated in response to reactive oxygen species (ROS) that result from stress stimuli; its gene product promotes ROS accumulation, which suggests that ERF109 participates in the generation of an oxidative burst (Fig. 3) (Matsuo et al., 2015). In addition, *ERF109* overexpression lines show symptoms of photoinhibition and photobleaching under medium- and high-light conditions, and enhanced susceptibility to the plant pathogen *Alternaria brassicae*. These symptoms can be weakened by the application of antioxidants or free radical scavengers, which suggests that the constant high ROS levels in the *ERF109*-overexpressing plants render them more sensitive to abiotic and biotic stress. These data fit the hypothesis that ERF109 plays a role in controlling the balance of ROS (Matsuo et al., 2015). Correspondingly, *erf109* knockout lines accumulate less H_2O_2 and ROS compared to control plants (Matsuo et al., 2015). Strikingly, although *ERF108* and *ERF109* appear to be strongly co-expressed over a wide set of different conditions, no elevated H_2O_2 and ROS were seen in *ERF108* overexpression lines, which indicates that these ERFs have a distinct role in stress response.

Experimental data link *ERF109* not only to stress signaling, but to developmental programs as well. Knockout plants display less lateral root primordia, whereas overexpression lines show significantly more of them. Moreover, wild-type, but not *erf109* mutant roots, display an increase in the number of lateral roots following JA treatment, which suggests that ERF109 plays a role in JA-dependent initiation of lateral root development (Fig. 3). Interestingly, *ERF109* overexpression lines display a number of phenotypes that resemble the overproduction of auxin, such as a long hypocotyl, and longer and more root hairs. Correspondingly, these lines contain significantly higher auxin levels, likely owing to the increased expression of the *ASA1* and *YUC2* auxin biosynthesis genes (Cai et al., 2014).

Apart from the control of the number of lateral roots, ERF109 activity has also been linked to radial vascular thickening through control of vascular cell division. The PHLOEM INTERCALATED

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WITH XYLEM (PXY) receptor is a signaling component that mediates vascular cell division, but surprisingly, the *pxy* knockout does not display a clear vascular cell division phenotype (Etchells et al., 2012). A transcriptomic analysis combined with genetic data revealed that the lack of such a phenotype is due to a compensatory effect through the upregulation of a number of ERF transcription factors, including *ERF109*. Accordingly, although both the *pxy* and *erf109* single mutants do not display an obvious phenotype, the double mutant shows a clear reduction in vascular cell number (Fig. 3). Moreover, it has been found that vascular expression of *ERF109* is controlled by ethylene signaling, which fits the observation that ethylene promotes radial growth (Etchells et al., 2012). In conclusion, although being primarily identified as a gene responsive to stress, more recent data indicate that, similar to *ERF108*, *ERF109* might also play a role in morphogenetic changes that help to adapt to stress conditions.

ERF110

ERF110 is one of the least-studied ERFs of the subfamily and appears to be controlled by ethylene at both the transcriptional and posttranscriptional level (Fig. 3). At the gene level, its expression appears to be promoted by ethylene, whereas at the protein level, ERF110 was found to be phosphorylated and this is counteracted by ethylene signaling (Fig. 1B) (Li et al., 2012). This phosphorylation has been linked to the bolting time of the plant, as the delayed bolting phenotype of ethylene mutants can be rescued by overexpression of the wild-type *ERF110* gene, but not its allele coding for a phospho-mutant (Fig. 3) (Zhu et al., 2013). Interestingly, the transcriptional activation of the above-mentioned *tpoxN1* peroxidase gene by the WRAF1 and WRAF2 tobacco ERF108-like proteins upon wounding also depends on protein phosphorylation. This indicates that phosphorylation might be a general mechanism to control the activity of the X subclass of ERF transcription factors at the posttranslational level (Sasaki et al., 2002).

ERF111

ERF111, also called ABSCISIC ACID REPRESSOR 1 (ABR1), is another family member that is controlled by phosphorylation. Its phosphorylation is mediated in a Ca^{2+}-dependent manner by the CBL9-CIPK3 module [the CALCINEURIN-B-LIKE 9 calcium-binding protein (CBL9) in complex with the CBL-interacting serine/threonine-protein kinase 3 (CIPK3)] that controls cold and ABA signal transduction (Kim et al., 2003). This observation fits with the role of ERF111 as an inhibitor of ABA responses during seed germination (Pandey et al., 2005; Sanyal et al., 2017) (Fig. 3). In addition, identical seed germination phenotypes for ABA treatment of *cbl9*, *cipk3* and *erf111* mutant plants strongly suggest that the CBL9-CIPK3 module and ERF111 operate in the same pathway. Conversely, overexpression of *ERF111* results in a drought-sensitive phenotype, whereas *ERF111*-knockout mutants display drought tolerance (Fig. 3) (Sanyal et al., 2017).

ERF111 transcription appears to be under control of multiple transcriptional regulators, including the ABA-responsive zinc finger transcription factor Yin Yang 1 (YY1) and the multiprotein bridging factor 1 (MBF1) (Li et al., 2016; Zou et al., 2016). The latter represents a highly conserved transcriptional co-activator that regulates diverse physiological processes (Jindra et al., 2004; Liu et al., 2003). For example, the constitutive overexpression of *MBF1* enhances abiotic stress tolerance, including heat and salt (Kim et al., 2007; Suzuki et al., 2008; Suzuki et al., 2005). The *Arabidopsis* genome encodes three *MBF1* genes, and the triple knockout displays increased sensitivity to H_2O_2 and a significant diminution of seed germination (Arce et al., 2010). Compared to wild-type plants, *ERF111* transcript levels are reduced in the triple knockout, which indicates that MBF1s regulate expression of the *ERF111* gene.

ERF113

ERF113, also known as *RELATED TO APETALA2.6L* (*RAP2.6L*), is another ERF family member that is induced by salt stress and drought (Fig. 3). Additionally, *ERF113* transcription is responsive to JA, salicylic acid, ABA and ethylene (Krishnaswamy et al., 2011). Correspondingly, *ERF113* overexpression confers resistance to stresses that activate these hormones. For instance, overexpression of *ERF113* triggers stomatal closure and enhances waterlogging tolerance (Liu et al., 2012), but it also results in a reduced germination rate. In addition to the response to hormonal cues, ERF113 activity can further be linked to developmental processes, such as shoot regeneration from root explants and ovule development (Che et al., 2006; Sun et al., 2010) (Fig. 3). Additionally, ERF113 plays a role in tissue recovery following stem incision or grafting (Asahina et al., 2011). Not only is *ERF113* strongly induced after incision at the lower regions of the cut gap, but plants that express a dominant-negative allele of *ERF113* also display tissue reunion defects (Asahina et al., 2011); following incision, the pith cells that surround the cut site randomly divide and elongate intrusively toward the cut surface. These responses are strongly diminished in the *erf113* mutant, which suggests that ERF113 has a role in promoting cell division that is induced by wounding (Fig. 3). Expression of *ERF113* at the cut site coincides with the expression of the *LOX2* gene, a component of the pathway for the biosynthesis of JA. Similarly, the *ERF113* gene is upregulated upon JA methyl ester administration, suggesting that JA is a primary trigger for *ERF113* induction following wounding (Asahina et al., 2011).

ERF114

ERF114 is also known as ERF BUD ENHANCER (EBE) because of the observed axillary bud outgrowth upon its overexpression. Similar to ERF113, ERF114 activity has been linked with tissue regeneration (Mehrnia et al., 2013). Not only is its expression strongly induced following wounding and coincides with callus formation at the cut sites, but a further prominent feature observed for *ERF114* overexpression plants is neoplasia in the form of tissue that is similar to green callus, and it is often produced at wound sites. Moreover, it has been observed that explants which overexpress *ERF114* increase their rates of callus production when cultured on callus-inducing medium (Mehrnia et al., 2013). Taken together, the data indicate that ERF114 might play a role in wound healing through control of the ratio between auxin and cytokinin, which is known to be important for control of apical dominance and callus formation (Fig. 3).

ERF115

ERF115 was biochemically identified and characterized as a target of the anaphase-promoting complex/cyclosome (APC/C), which is an E3 ubiquitin ligase complex that targets cell division rate-limiting proteins, such as cyclins, for destruction (Heyman et al., 2013). Correspondingly, an ubiquitylation site was mapped at the N-terminus of ERF115 (Fig. 1B) (Walton et al., 2016). Within the plant root meristem, *ERF115* expression appears to be confined to the stem cell niche (SCN) that, in *Arabidopsis*, is a well-organized structure. The SCN consists of a single tier of stem cells, which gives rise to the distinct tissue layers that surround a group of cells with a low proliferation rate, called the quiescent center (Heyman

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et al., 2014). *ERF115* transcription thereby appears to specifically mark dividing quiescent center cells, because *ERF115* overexpression stimulates these cells to divide. This illustrates that ERF115 is a rate-limiting factor for the proliferation of quiescent center cells that is constrained in its activity through the targeted destruction by the APC/C (Heyman et al., 2013). Strikingly, when roots are exposed to mild stress conditions, such as elevated temperatures, *ERF115* is transcriptionally activated. This activation likely results in an increase in ERF115 protein abundance to a level at which it escapes the repressive action of the APC/C, triggering a round of quiescent center cell division and so generating new stem cells that replenish the older or stressed ones (Heyman et al., 2013).

Under more-severe stress settings, such as under conditions that induce DNA damage or root tip damage, *ERF115* is strongly expressed in meristematic cells that are positioned immediately next to dying ones; this suggests a more general role in root tissue replenishment (Heyman et al., 2016) (Fig. 3). Upon the death of cells, the neighboring cells instantly express *ERF115*, which is followed by the induction of regenerative cell divisions. A putative downstream target of ERF115 is the *PHYTOSULFOKINE 5* (*PSK5*) precursor gene which encodes a peptide hormone that was originally identified by its ability to promote proliferation of plant cells within low-density cultures (Matsubayashi and Sakagami, 1996). Thus, it appears that ERF115 is part of a mechanism that allows the replacement of damaged stem cells by new ones, thereby contributing to the reconstitution and longevity of the plant SCN (Heyman et al., 2014). Recently, *ERF115* expression has been reported to be induced by salinity and to play a role in salt stress tolerance (Krishnamurthy et al., 2017); however, whether these observations are directly linked to salt-induced cell death remains to be investigated.

Control of activity of ERF by the GRAS domain transcription factor family

Recently, both ERF114 and ERF115 were found to heterodimerize with members of the GRAS-domain-containing transcription factor family (Heyman et al., 2016). GRAS transcription factors derive their name from the first three members cloned [GAI, RGA, and SCARECROW (SCR)]. The *Arabidopsis* genome encodes 33 members that can phylogenetically be categorized into distinct functional classes of divergent but mainly developmental processes, most of them related to stem cell and meristem organization (Bolle, 2004; Pysh et al., 1999; Tian et al., 2004). Among these, members of the SCR branch play a role in radial pattern formation within the root and shoot meristem. The LATERAL SUPPRESSOR branch controls auxillary meristem maintenance (Greb et al., 2003; Li et al., 2003; Schumacher et al., 1999), whereas HAIRY MERISTEM members prevent stem cells from differentiating (Engstrom et al., 2011; Stuurman et al., 2002; Zhou et al., 2015). Rather than controlling meristem function, members of the DELLA branch act as negative regulators of gibberellic acid signal transduction, which in turn controls a variety of developmental processes (Cao et al., 2005; Cheng et al., 2004; Dill and Sun, 2001; King et al., 2001; Lee et al., 2002; Piskurewicz and Lopez-Molina, 2009; Tyler et al., 2004).

The GRAS domain transcription factors that associate with ERF114 and ERF115 belong to the PAT1 branch, which has five members in *Arabidopsis* [PAT1, and the scarecrow-like proteins 1-21 (SCL1, SCL5, SCL13 and SCL21)] (Heyman et al., 2016; Torres-Galea et al., 2013). Upon their interaction, PAT1 is able to dramatically boost the regenerative capacities of ERF115, as illustrated by the spontaneous generation of callus tissue in plants co-overexpressing *ERF115* and *PAT1* (Heyman et al., 2016). In line with this, *pat1* mutants display a reduced frequency in root tip regeneration that is similar to that of *ERF115*-deficient plants. PAT1 and its closest homolog SCL21 were originally identified as components that act positively on the phytochrome A (PhyA)-dependent light-signaling pathway (Bolle et al., 2000; Torres-Galea et al., 2013). PhyA predominates in dark-grown seedlings and represents the primary sensor for far-red light. Upon exposure to far-red light, PhyA is degraded; this results in the activation of the so-called de-etiolation process, which includes an inhibition of hypocotyl elongation. Similar to *phyA* mutants, *PAT1*- and *SCL21*-deficient plants fail to inhibit hypocotyl elongation under far-red light. Likewise, *scl21* mutants display a reduced germination following a far-red light pulse (Torres-Galea et al., 2013; Torres-Galea et al., 2006). By contrast, *SCL13* knockdowns display a red light-specific hypocotyl elongation phenotype, which suggests that this protein interacts with a red-light receptor, most likely phytochrome B (Torres-Galea et al., 2006). How these light phenotypes connect to the callus-inducing properties of PAT1 and SCL21 is currently unclear. Different reports have identified crosstalk networks that involve phytochrome, hormonal and abiotic stimuli, such as brassinosteroids, auxin and various stresses that result from dehydration or wounding (Auge et al., 2012; Robson et al., 2010; Sandhu et al., 2012). Cytokinins also play a role in a number of light-regulated processes, including de-etiolation (Schmülling, 2004). Accordingly, *PAT1* was identified as a gene with a rapid response to cytokinin (Brenner et al., 2005). Therefore, it cannot be excluded that the observed light-responsive phenotype of the GRAS domain mutants might somehow tie in with a change in hormone balance, although more experimental data are required to solve this issue.

Through domain mapping, the motif within the ERF115 protein that is responsible for the interaction with PAT1 branch members has been pinpointed to the subfamily-specific conserved motif present in all ERF subfamily X members, with the exception of ERF112 (Fig. 2). Despite this family-specific motif, ERF114 and ERF115 appear to not be the only ERF transcription factors to heterodimerize with GRAS proteins; the DELLA protein GAI was shown to interact with the ERF transcription factor RAP2.3, and, in doing so, GAI impairs the transcriptional activity of RAP2.3 on its target promoters (Marín-de la Rosa et al., 2014). Similarly, in a study on chitin-induced transcription factors ERF5 was shown to interact with SCL13. However, the biological significance of this interaction was not analyzed (Son et al., 2012). It remains to be investigated whether the dimerization between members of the ERF and GRAS domain transcription factors is a general phenomenon, and how precisely they affect the activity of each other. Whereas ERF proteins have been shown to directly bind DNA through their AP2 domain (Ohme-Takagi and Shinshi, 1995), no such evidence is available for GRAS proteins, which, therefore, have been suggested to rather operate as transcription cofactors (Hirano et al., 2017). Moreover, both in *Arabidopsis* and *Brassica napus*, GRAS proteins have been reported to interact with histone deacetylases, which are known for their transcriptional regulation activity through histone modification (Gao et al., 2004, 2015; Zhou et al., 2005). It is therefore tempting to speculate that the ERF provides target gene specificity, whereas the GRAS interaction partner controls the regulation of its transcription by recruiting histone-modifying enzymes (Fig. 4).

Conclusions

Up to now, the subfamily X of EREB-DREB transcription factors had been mainly linked to either stress signaling or regeneration

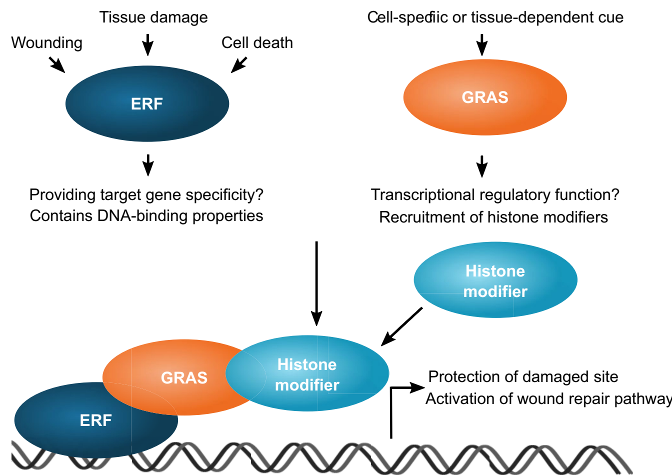

Fig. 4. Model for cooperative activity of the ERF–GRAS heterodimer. The ERF proteins accumulate in cells in response to wounding, tissue damage or cell death to form a heterodimeric complex with a GRAS transcription factor, whose expression is mainly determined by positional or tissue-dependent cues. The presence of a DNA-binding motif within the ERFs suggests that they determine target gene specificity. The GRAS factors lack DNA-binding properties, and are hypothesized to act as transcriptional co-regulators, possibly through the recruitment of histone-modifying enzymes.

processes, but the increasing available data summarized here suggest that the members of this specific family might rather play a dual role in both of these. In doing so, these ERFs offer an elegant way to simultaneously protect injured sites and initiate their healing. Whereas ERF108 and ERF109 have been predominantly linked to JA and ABA stress signaling, data that was obtained on their tobacco orthologs suggest that they also have a role in wound repair (Sasaki et al., 2006, 2007). By contrast, whereas ERF113 and ERF115 had been demonstrated to be required for tissue repair, they have been additionally linked to JA signaling and salinity stress, respectively (Asahina et al., 2011; Krishnamurthy et al., 2017). Moreover, the fact that a target gene for ERF115 is *PSK5* suggests an additional role in pathogen recognition, as plants that are defective for the PHYTOSULFOKINE RECEPTOR1 (PSKR1) display hypersensitivity toward necrotrophic fungal infection (Mosher et al., 2013). Moreover, *ERF115* transcription has been found to be instantly induced in cells that surround dying cells, but whether this involves the activity of stress hormones still needs to be defined. The identification of the upstream regulators will surely help to resolve this question. Likewise, the identification of target genes for the different ERFs might help to pinpoint their relative contribution to wound protection versus repair for each of them. An intriguing question is whether the different transcription factors operate redundantly, or whether each of them can be attributed to specific wounding response and repair processes. Here, a study of the co-expression networks of the different transcription factor genes could contribute to the identification of distinct processes controlled by the various ERF–GRAS complexes. However, the final picture might be even more complex, given the posttranscriptional control of the ERFs through ubiquitylation and phosphorylation, as well as their heterodimerization with GRAS domain transcription factors (Heyman et al., 2016; Li et al., 2012; Walton et al., 2016). ERF115 binds at least two different GRAS family members, PAT1 and SCL21 (Heyman et al., 2016). It would be interesting to know whether the ERF115–PAT1 and ERF115–SCL21 complexes respond to the same upstream signals and activate the same target genes. Finally, preliminary data also suggest an interplay between at least some of the ERF subfamily X members and the WOUND INDUCED DEDIFFERENTIATION (WIND) proteins, being ERF-type transcription factors themselves (Heyman et al., 2016; Ikeuchi et al., 2017). *WIND1* is rapidly induced upon tissue wounding and stimulates cells to dedifferentiate and proliferate to form callus, which precedes tissue regeneration (Iwase et al., 2011a), whereas ectopic overexpression of all four *WIND* family members induces callus formation (Iwase et al., 2011b). Although *WIND1* was recently identified as a putative ERF115 target gene, the mechanisms controlling interplay between the different ERF subfamilies remain elusive.

Knowledge of the nature of the ERF–GRAS complexes that possess capacities to induce cell division might be important to improve transformation efficiency. Cereals have been cultivated for over 9000 years. During this period, their yield quality and quantity has been optimized through breeding. Genetic engineering tools allow further improvement of crop plants, but grasses appear to be very recalcitrant to *in vitro* culturing, which is an essential step during transformation techniques (Namasivayam, 2007). Most of the crop transformation protocols that are available today are of low efficiency, genotype-dependent and often work only on non-commercial low-yield cultivars. Thus, there is a need for a generic factor that can increase the *in vitro* culture competence of plants where this is traditionally difficult. For efficient transformation, the tissue and developmental stage of the explant is crucial: only cells that possess high cell division capacities are capable of regeneration, which explains the use of embryonic plant tissues in crop transformation protocols. Indeed, whereas in many dicotyledon plants cell division can be induced as a wounding response in leaf segments, cereal leaf segments lack the appropriate wound-healing response (Hiei et al., 2014). A recent breakthrough study reported that when the morphogenic genes *WUSCHEL2* and *BABYBOOM* were expressed in maize, successful transformation from various explants, such as mature embryos and seedlings, was achieved in inbred maize lines that had previously been difficult to transform (Lowe et al., 2016). Transformation efficiencies that were similarly increased were also reported for rice, sorghum and sugarcane, which indicate that expressing transcription factors that control regeneration processes can make it possible to genetically modify difficult to transform monocot species and varieties (Lowe et al., 2016). Because of the involvement of ERF and GRAS family transcription factors in regeneration and developmental processes and their stem cell-inducing potential, they might be ideal candidates to improve the transformation efficiency of various crops. Further research on ERF–GRAS transcription factor interactions could shed light on mechanisms governing both plant regeneration and defense responses, and might produce valuable tools for agricultural biotechnology.

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