

1 **Short title:** Group VII Ethylene Response Factors

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6 **Title:**

7 **Group VII Ethylene Response Factors in Arabidopsis: regulation and physiological roles**

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19 **One sentence summary:** The role of ERF-VII TFs in higher plants is to coordinate their signature response to
20 oxygen deficiency, but additional layers of modulation of ERF-VII activity enrich their regulatory range.

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23 The Ethylene Response Factor (ERF) family of plant-specific transcription factors (TFs) comprises
24 a large number of elements with diversified functions in terms of hormone responses, development,
25 and biotic and abiotic stress responses (Dey and Corina Vlot, 2015; Licausi et al., 2013). Of these,
26 group VII ERFs form a phylogenetic cluster (Nakano et al., 2006), which is conserved across
27 angiosperms (Licausi et al., 2011). One universal function attributed to ERF-VII TFs in higher
28 plants is to coordinate their signature response to oxygen deficiency, which consists in the

29 accumulation and enhanced selective translation of a core set of transcripts (Mustroph et al. 2009
30 and 2010; Branco-Price et al., 2008). These transcripts are responsible for reshaping cell
31 metabolism for sustained energy production, energy saving, the protection of subcellular
32 components and the detoxification of harmful anaerobic metabolism products.

33 The relationship between ERF-VII members from various plant species and their tolerance to low
34 oxygen (hypoxia) stresses has been widely reported. Different rice types rely on *ERF-VII* genes to
35 develop contrasting strategies of underwater growth arrest (Xu et al., 2006) or shoot elongation
36 (Hattori et al., 2009), which equally ensure stress endurance. ERF-VIIs are exploited to i) convert
37 the signal arising from ethylene entrapment in submerged tissues into the gibberellin-mediated
38 regulation of carbohydrate metabolism (Fukao and Bailey-Serres, 2008; Hattori et al., 2011; van
39 Veen et al., 2013); ii) protect plants from concurrent redox stress; and iii) prepare them for post-
40 submergence dehydration by enhancing ABA sensitivity (Bailey-Serres et al., 2012). Additionally,
41 the over-expression and stabilization of ERF-VII proteins can enhance hypoxia survival in
42 *Arabidopsis thaliana* and barley (Hinz et al., 2010; Licausi et al., 2010a; Gibbs et al., 2011;
43 Mendiondo et al., 2016).

44 The molecular mechanisms by which varying oxygen levels regulate the activity of the ERF-VII
45 factors have been most extensively investigated in *Arabidopsis* (Fig. 1), where the subfamily is
46 composed of three highly expressed (*AtRAP2.2/2.3/2.12*, “RAP-type”) and two hypoxia-inducible
47 *ERF-VII* genes (*AtHRE1/2*, “HRE-type”) (Licausi et al., 2010a). The feed-back repression of
48 RAP2.12 by the anaerobic transcription factor HRA1 suggests that the ERF-VII activity is tightly
49 modulated to grant transcriptional flexibility in response to fluctuations in oxygen availability
50 (Giuntoli et al., 2014). With the noticeable exception of OsSub1A, ERF-VIIs are directly regulated
51 by oxygen, in that their protein half-life is determined by an oxygen-dependent mechanism of
52 proteasomal degradation, which prevents their nuclear accumulation in the presence of oxygen
53 (Gibbs et al., 2011; Licausi et al., 2011). RAP-type factors seem to operate as redundant activators
54 of the anaerobic response (Bui et al., 2015; Papdi et al., 2015; Gasch et al., 2016). One of them,
55 RAP2.12, has been shown to be stored at an inactive site (the plasma membrane) under aerobic
56 conditions and to move to the nucleus after short-term hypoxia (Kosmacz et al., 2015). This
57 mechanism is believed to ensure plant cells a fast response to oxygen shortages.

58 Although the direct regulation of the ERF-VIIs by oxygen has been revealed, submergence is a
59 complex stress and its regulation has not been fully understood. In fact, the flooding response in
60 plants entails the integration of manifold stimuli, represented by hormone signals, reactive oxygen

61 species (ROS) signatures, carbohydrate levels, redox indicators, pH variations and second
62 messengers. In addition to perceiving changes in oxygen levels, ERF-VIIs are expected to collect
63 part of such vast signaling network. For instance, the proteasomal turnover of RAP-type AtERF-
64 VIIs has been proposed to be mediated by an additional, oxygen-independent mechanism brought
65 about by the RING finger E3 ligases SINAT1 and SINAT2 (Welsch et al., 2007; Papdi et al., 2015;
66 Fig. 1). Since SINAT1/2 are bridged to starvation and autophagy (Qi et al., 2017), perception of low
67 nutrient conditions, established upon oxygen deprivation, could hypothetically converge on ERF-
68 VII regulation through the SINAT pathway.

69 An overview of ERF-VII functions has been made by Gibbs et al. (2015). In this update, we
70 highlight the most recent findings regarding N-terminal modifying mechanisms, DNA binding
71 properties and protein interactions of the Arabidopsis ERF-VII factors. We also highlight the
72 perspective that additional layers of regulation, beyond their oxygen sensitivity, might contribute to
73 expand the range of their physiological functions.

74 **CONVERGENCE OF REGULATORY MECHANISMS AT THE ERF-VII PROTEIN N- 75 TERMINI**

76 **Plant cysteine oxidases**

77 Phylogenetic analysis of ERF-VII orthologous proteins in higher plants highlighted the existence of
78 a highly conserved N-terminal NH₂-MCGGAIL-COOH sequence (Licausi et al., 2011). Initial
79 recognition of plant ERF-VII proteins as potential oxygen-sensitive substrates entailed the finding
80 that this consensus contains a redox-sensitive cysteine, in such a position as to be amenable to
81 recognition by a specialized proteolytic pathway, known as the Arg-Cys/N-end rule pathway
82 (NERP) for proteasomal degradation (Gibbs et al., 2011; Licausi et al., 2011). A sequence of
83 orderly reactions involves ERF-VII proteins (Box 1). Mature ERF-VII proteins expose an N-
84 terminal cysteine (Cys2), which functions as a degradation signature (“N-degron”) targeting these
85 proteins to the 26S proteasome, upon sequential recruitment of arginyl transferase and E3 ubiquitin
86 ligase enzymes (Bachmair et al., 1986; Varshavsky 2011). In Arabidopsis, the latter enzymatic
87 functions are represented by ATE1/2 and PRT6 proteins, respectively (Fig. 1).

88 The existence of a conserved oxygen-dependent N-degron on the ERF-VII factors represents a
89 promising link between cellular oxygen levels and those coordinated transcriptional adjustments
90 that constitute the hallmark of plant hypoxic responses. Despite this, only recently has light been
91 shed on the mechanism by which the Arg-Cys/N-end rule is initiated in response to oxygen. A

92 family of plant-specific metalloproteins, named plant cysteine oxidases (PCOs), has been found to
93 be related to Cys2 oxidation in ERF-VII proteins. *PCOs* encompass five members in Arabidopsis,
94 two of which (*PCO1/2*) are part of the core response to low oxygen (Mustroph et al., 2009 and
95 2010). Genetic dissection of the Arg-Cys/N-end rule pathway has demonstrated that *PCO1/2* act
96 upstream of *ATE1/2* and *PRT6* to redundantly repress anaerobic gene induction under hypoxia. In
97 line with this, individual over-expression of either gene determines lower tolerance to submergence
98 (Weits et al., 2014). In the plant, PCO enzymes impact on ERF-VII protein levels, in that the
99 stability of AtRAP2.12 correlates negatively with *PCO1/2* expression (Weits et al., 2014). In
100 addition, *in vitro* evidence suggests that PCOs influence ERF-VII *in vivo* turnover by direct Cys2
101 oxidation. Purified recombinant PCO enzymes consume molecular oxygen in the presence of either
102 L-Cys or synthetic peptides corresponding to AtRAP2.12 N-terminus (Weits et al., 2014), and
103 catalyze the reaction of N-terminal Cys to Cys-sulfinic acid (CysO₂) (White et al., 2017). A
104 recombinant plant ATE1 enzyme can also conjugate arginine to a synthetic NH₂-CGGAIISDFI-
105 COOH peptide, derived from the AtRAP2.12 N-terminus, only in the presence of both PCO and
106 oxygen. This thus provides proof for the generation of an active oxygen-sensitive N-degron on such
107 substrates (White et al., 2017).

108 These milestone studies lay the foundation for a model of plant O₂-sensor switch *in vivo*. Plant
109 PCOs qualify as the first cysteinyl dioxygenase enzymes discovered, since before that date only
110 bacterial and mammalian cysteine dioxygenases (CDOs) had been known, which promote free L-
111 Cys conversion, contributing to its homeostasis to prevent cytotoxicity (Dominy et al., 2006; Ye et
112 al., 2007). In animals, the existence of enzymatic activities mediating N-terminal cysteine oxidation
113 is debated (Kwon et al., 2002; Hu et al., 2005). Therefore, the recent findings regarding PCOs have
114 opened a fascinating perspective on the diversification of the Arg/N-end rule pathway among
115 kingdoms. Despite the connection established between cysteine oxidation and N-terminal protein
116 arginylation (Hu et al., 2005), knowledge regarding the targets of the specialized Arg-Cys/NERP
117 branch in mammals is limited to the RGS4/5 proteins (Lee et al., 2005), regulating cardiac G-
118 protein signaling (Lee et al., 2012), and to the proapoptotic protein BRCA1 (Piatkov et al., 2012).
119 Unlike plants, no target of this pathway has been associated with hypoxic responses, which instead
120 rely on an unrelated, albeit functionally parallel, mechanism regulating the oxygen-sensitive TF
121 HIF α (Jaakkola et al., 2001). It is tempting to speculate that the specific evolution of an enzymatic
122 control point for cysteine oxidation in the plant kingdom, represented by PCOs, enabled plants to
123 couple the N-end rule with oxygen sensing.

124 Cysteine oxidases are non-heme iron-dependent oxygenases, which make use of a coordinated iron
125 ion to activate oxygen during catalysis, forming a putative Fe(III)-superoxo intermediate (White
126 and Flashman, 2016). Given this enzymatic requirement, PCOs qualify as a potential convergence
127 point between iron and low oxygen signaling. There is a partial overlap in the transcriptional
128 adjustments between low Fe and hypoxia, possibly as a consequence of a higher energy demand,
129 due to a compensatory increase in iron uptake, which enhances the mitochondrial activity (López-
130 Millán et al., 2000; Vigani, 2012). Hypoxia also stimulates the expression of Fe deficiency genes,
131 with the involvement of the ethylene-responsive TFs EIN3/EIL1 (García et al., 2014; Lucena et al.,
132 2015). In turn, it has further been shown that ethylene-mediated iron homeostasis involves
133 EIN3/EIL1 interaction with the subunit Med25 of Mediator (a large multiprotein complex that
134 bridges *cis*-element-bound TFs and the basal transcriptional machinery; Dolan and Chapple, 2017)
135 (Yang et al., 2014). In the human body, the oxygen-sensing pathway contributes to iron
136 homeostasis and deficiency responses with the action of HIF prolyl hydroxylase (P4Hs) enzymes
137 (Salahudeen and Bruick, 2009; Anderson et al., 2013; Siegert et al., 2015). P4Hs are non-heme Fe-
138 and 2-OG-dependent oxygenases that work as sensors for oxygen in metazoans, in the same way as
139 the phylogenetically unrelated PCOs do in plants. While a role in iron responses has been proposed
140 for plant P4H homologs (Vigani et al., 2013), no connection has yet been proposed between these
141 processes and PCOs. Given the impaired metal uptake capability by waterlogged root systems
142 (Martínez-Cuenca et al., 2015), a mechanism might have been evolved in plants to integrate the
143 perception of hypoxia with intracellular metal ion homeostasis. Hypothetically, PCO activity could
144 be regulated through metal ion switching at its active site, thereby providing a proxy for the
145 intracellular Fe status, which has been proposed as being estimated from its balance with other
146 transition metal ions (Kobayashi and Nishizawa, 2014).

147 PCOs also represent a potential node in the interplay between O₂ signaling and ROS homeostasis.
148 In mammalian cells, ROS, produced during hypoxia by the malfunctioning of Complex III at the
149 mETC, indirectly impact on HIF α stability, by inhibiting the activity of P4Hs (Chandel et al., 2000;
150 Bell et al., 2007). It would therefore be interesting to investigate whether a similar mechanism acted
151 on the functionally equivalent PCO enzymes.

152 **N-terminal cysteine modifications**

153 Cys2 in ERF-VII TFs is a regulatory cysteine (Formenko et al., 2010; Couturier et al., 2013). Its
154 thiol group is highly susceptible to oxidation (Reddie and Carrol, 2008) by oxygen, ROS and RNS
155 (reactive nitrogen species), it can be used in a variety of redox reactions (Giles et al., 2003), and can

156 undergo additional enzymatic modifications, such as S-acylation and N-acetylation (Polevoda and
157 Sherman, 2003). Therefore, Cys2 has the potential to accept diversified signaling pathways,
158 promoting the integration of manifold stimuli, and might have been selected accordingly (Marino
159 and Gladyshev, 2010).

160 Low H₂O₂ concentrations, compatible with the signaling range, promote Cys oxidation to Cys-
161 sulfenic acid (CysO) (Schieber and Chandel, 2014). CysO can be reverted to thiolate by disulfide
162 reductases, thioredoxin and glutaredoxin, or act as an intermediate for disulfide bond formation
163 (Poole, 2015). Instead, higher H₂O₂ levels, generated under ROS stress, can push oxidation to Cys-
164 sulfinic (CysO₂) or irreversibly further to Cys-sulfonic forms (CysO₃) (Schieber and Chandel, 2014;
165 Fig. 1). Once viewed as a transient species in disulfide bond production, CysO has been found to be
166 significant for catalysis and protein functionality (Gupta and Carrol, 2014). Thiol-disulfide
167 transitions, on the other hand, are frequently associated with redox regulation in plants. For
168 instance, intra- or intermolecular Cys-Cys formation is believed to determine the nuclear
169 localization of the redox TF HSFA8 in response to H₂O₂ (Giesguth et al., 2015). Despite the fact
170 that redox-sensitive non-clustered cysteines have been identified and examined in plant
171 transcription factors before (Schmidt and Schippers, 2015), they have never been found to belong to
172 MC-proteins. The fact that the conversion of a synthetic RAP2.12-derived peptide released CysO₂
173 as the sole reaction product *in vitro* (White et al., 2017) does not rule out that additional,
174 biologically significant, oxo-species may be formed by the ERF-VII N-termini in the cellular
175 environment and contribute to their half-life, localization, or function.

176 In the case of the mammalian GTPase-activating proteins RGS4/5, a non-enzymatic S-nitrosylation
177 reaction has been proposed to precede Cys2 oxidation. The biological chemistry of S-
178 nitrosocysteine has not yet been fully clarified (Gould et al., 2013). Although *in vitro* PCO can
179 process Cys2 in the absence of NO, i.e. without previous S-nitrosylation (White et al., 2017), a role
180 for NO in the degradation of the ERF-VIIs has been observed *in vivo*. In fact, NO has been shown
181 to promote an N-end rule pathway-dependent proteolysis of full-length ERF-VII factors, as well as
182 artificial ERF-VII-derived Arg-Cys/NERP substrates (MC-GUS, UBI-C-GUS) in Arabidopsis and
183 barley (Gibbs et al., 2014; Vicente et al., 2017). However, the mechanism connecting NO to ERF-
184 VII stability still needs to be revealed (Gibbs et al., 2015) (Fig. 1).

185 Exposure of an amino-terminal Cys is a requisite for implementing N-end rule reactions. Thus even
186 prior to Cys2 modification, regulation of the N-terminal methionine cleavage could represent a
187 general mechanism affecting MC-protein stability. Human MetAP2 activity responds to the

188 cytosolic redox state through the thioredoxin-dependent conversion of a Cys₂₂₈-Cys₄₄₈ disulfide
189 bond (Chiu et al., 2014). Such evidence provides a potential link between cellular ROS content and,
190 ultimately, the availability of MC-proteins for N-end rule pathway-mediated degradation.

191 The functions of ERF-VII Cys2 might be extended by the covalent attachment of lipid moieties
192 (lipidation). This process has emerged as a major regulatory mechanism in a variety of subcellular
193 responses in animals, yeast and, more recently, plants. In fact, the conjugation of a hydrophobic
194 moiety can have a strong impact on the structure, interaction and, primarily, membrane targeting of
195 soluble proteins (Aicart-Ramos et al., 2011; Hemsey, 2015). Cysteines can establish dynamic
196 thioester bonds with fatty acids (S-acylation), by the action of endomembrane-associated protein
197 S-acyltransferase (PAT) and palmitoyl thioesterase enzymes (Hang and Linder, 2011).

198 Cys2 palmitoylation has been demonstrated for human RGS proteins (De Vries et al., 1996). Cys2
199 mutation does not affect RGS4 direct association with phospholipid bilayers (Srinivasa et al., 1998),
200 which is in fact due to the folding of its N-terminus in an alpha-helical structure (Bernstein et al.,
201 2000). However, Cys2 palmitoylation is crucial for RGS4 and RGS16 activity, possibly by
202 affecting their affinity for G α target subunits (Druey et al., 1999; Tu et al., 1999).

203 AtRAP2.12 has been found to reside at the plasma membrane in aerobic leaf cells (Fig. 1), unless its
204 N-terminal domain is ablated (Licausi et al., 2011; Giuntoli et al., 2017). In turn, ERF-VII
205 association with the plasma membrane is believed to depend on acyl-CoA binding proteins
206 (ACBPs), according to the observed interaction between members of the two families (Li and Chye,
207 2004; Li et al., 2008; Licausi et al., 2011). During hypoxia, AtRAP2.12 is quickly displaced from
208 the plasma membrane towards the nucleus (Kosmacz et al., 2015). Given that the regulation of fatty
209 acid profiles has been associated with hypoxic stress (Klinkenberg et al., 2004; Xie et al., 2015a;
210 Xie et al., 2015b), the evidence available can be the basis of a speculative model of hypoxia
211 sensing, in which the dynamic acylation state of the ERF-VII TFs collects indirect low oxygen
212 signals to regulate their intracellular trafficking and activity.

213

214 **LATEST INSIGHTS INTO THE TRANSCRIPTION FACTOR PROPERTIES OF THE** 215 **ERF-VIIs**

216 Long-standing efforts have focused the quest for DNA regulatory elements that enable plants to
217 coordinate the activation of low-oxygen responsive promoters, under the assumption that co-

218 expressed promoters should share common features, thus mediating their recognition by the
219 transcriptional machinery (Rombauts et al., 2003).

220 *In vitro* DNA binding assays associate ERF family members with GCC-box motifs (5'-AGCCGCC-
221 3') (Ohme-Takagi and Shinshi, 1995; Hao et al., 1998), which have been traced out in many genes
222 induced by ethylene, pathogenesis, wounding, or jasmonate (Brown et al., 2003; Zarei et al., 2011).
223 However, the fact that GCC-boxes have not been recognized as part of the anaerobic response
224 promoter element (known as ARE; Olive et al., 1990) raised the question as to whether group VII
225 ERFs had a different DNA binding affinity. AtRAP2.2 was isolated as an interactor of the unrelated
226 5'-ATCTA-3' motif, claimed to contain the minimum determinant for ERF-VII DNA binding
227 (Welsch et al., 2007). Although present in the 5'-upstream sequence of many anaerobic genes
228 (Licausi et al., 2010b), evidence presented by Gasch et al. (2016) indicates that this motif is not
229 likely to be responsible for their activation by the anaerobic TFs.

230 A promising candidate as a functional anaerobic promoter element in plants was recently revealed.
231 Phylogenetically related core anaerobic genes from 25 species were compared, and clustering of the
232 detected DNA motif patterns resulted in nine conserved consensus sequences (Gasch et al., 2016).
233 Of these, a 12 bp-long bipartite motif composed of GC- and GT-rich halves was validated as a
234 regulator of the anaerobic targets *LBD41* and *PCO1* from Arabidopsis and named Hypoxia
235 Responsive Promoter Element (HRPE) (Fig. 1). The resemblance of HRPE to the previously
236 annotated ARE sequence from maize, and the demonstration that RAP-type ERF-VIIs were able to
237 bind a synthetic ARE promoter, suggest that an actual connection point has been found between the
238 long-sought after plant hypoxia response element and the ethylene responsive factors.

239 Two of the other conserved motif clusters matched known regulatory elements, namely the ABA-
240 responsive element (ABRE) and the GCC-box. The detection of ABRE, which harbours a G-box
241 element, complies with previous reports on the involvement of G-box binding bZIP factors in the
242 regulation of the *ADH* promoter (McKendree and Ferl, 1992; Meier and Grissem, 1994; de
243 Bruxelles et al., 1996). The enrichment of core anaerobic promoters with GCC-boxes also suggests
244 that the ERF-VII factors retained the ability to bind this canonical motif. The experimental reports
245 on the relationship between ERF-VIIs and GCC-boxes are not all in agreement. A direct interaction
246 was identified between AtRAP2.3 and a GCC-box-containing promoter region of the *ABI5* gene
247 (Gibbs et al., 2014), and RAP2.3 was able to transactivate a synthetic promoter containing tandem
248 GCC-box copies from *HOOKLESS1* (Marín-de la Rosa et al., 2014). However, a yeast-1-hybrid
249 experiment failed to detect an interaction between AtRAP2.2 and a prey construct composed of

250 tandem copies of a GCC-box, when flanking nucleotides from the Arabidopsis *PDF1.2* promoter
251 were included (Ou et al., 2011). Finally, the binding of AtHRE2 to a synthetic GCC-box probe was
252 shown to occur *in vitro* by Lee et al. (2015).

253 The mechanism of ERF-VII interaction with HRPE still awaits an experimental description. Unlike
254 RAP-type proteins, HRE1 and HRE2 have not proven capable of activating natural anaerobic
255 promoters (Bui et al., 2015). Their inability to associate with HRPE (Gasch et al., 2016) points to a
256 deficiency in DNA binding by either HRE1 or HRE2, despite the presence of a fully conserved
257 AP2/ERF domain (Nakano et al., 2006). This would imply more specific needs for HRPE
258 recognition than those provided by this well-characterized DNA-binding domain. In other words,
259 additional protein domains, exclusively present on RAP-type ERF-VIIs, might be necessary for the
260 interaction with HRPE. One hypothesis is that the AP2/ERF domain might contact the GC-rich
261 region of HRPE (Yang et al., 2009), whereas neighboring amino-acids would mediate the
262 interaction with the GT portion.

263 Specific DNA-binding properties might underlie the functional diversification reported for the
264 Arabidopsis ERF-VII factors under hypoxia. Here, HREs are needed to sustain anaerobic gene
265 expression, but are not essential for the initiation of transcriptional responses (Licausi et al., 2010a).
266 Rather than associating with target promoters, HREs may contribute a transcriptional activation
267 function to - still unresolved - protein complexes that form after a primary, RAP-type dependent,
268 response to low oxygen. In fact, HREs share a conserved C-terminal hydrophobic motif with the
269 other ERF-VII factors, called CMVII-8 (Van Veen et al., 2014). CMVII-8 is sufficient to confer
270 transactivation properties, when fused to a GAL4 DNA-binding domain (Bui et al., 2015) or
271 evaluated inside native AtRAP2.2/12 proteins (Licausi et al., 2011). Thus, ERF-VIIs generally
272 qualify as activators.

273 The isolation of RAP2.12 as a partner of the Med25 subunit of the Mediator complex suggests that
274 the recruitment of RNA polymerase II by the ERF-VIIs occurs through their interaction with
275 particular Mediator (Med) proteins (Ou et al., 2011). The degree of specialization of Med proteins,
276 in terms of TF interaction preferences, is assumed to be low, because of the limited number of Med
277 subunits encoded by the proteome (the approximate proportion in Arabidopsis is 30 as against more
278 than 1500 TFs). However, the observation that individual mutated subunits produce particular –
279 although pleiotropic – phenotypes implies the existence of specific functions (Samanta and Thakur,
280 2015). Med25 has emerged as a master regulator in plants (Kazan, 2017), involved in hormone

281 signaling, iron homeostasis, flowering regulation and abiotic stress responses. Whether or not it
282 plays a role in hypoxic responses still needs to be investigated.

283

284 **EXPANDING ROLES OF ERF-VII FAMILY FACTORS**

285 Growing evidence supports ERF-VII involvement in transcriptional adjustments that go beyond the
286 activation of a set of conserved hypoxia-responsive genes (Mustroph et al., 2010). The recent
287 literature links these proteins to developmental processes controlled by ABA, ethylene and
288 gibberellin, to abiotic stress tolerance and resistance to fungal attack. Participation of the ERF-VII
289 in some of these physiological phenomena might in principle be enabled by the existence of
290 hypoxic microenvironments in plant tissues. On the other hand, ERF-VII functionality seems to be
291 expanded through additional, low oxygen-independent, mechanisms which subtract these TFs from
292 aerobic degradation and confer them condition-, tissue- or cell-specific stability, expression and
293 activity.

294 **ERF-VII involvement in ROS- and NO-dependent responses**

295 ERF-VIIs can impact on plant responses under various abiotic and biotic stress conditions with
296 oxidative stress components. In Arabidopsis, RAP-type ERF-VIIs participate in oxidative and
297 osmotic stress tolerance (Papdi et al., 2015), *AtRAP2.2* expression is positively correlated with plant
298 resistance to the necrotrophic fungus *Botrytis cinerea* (Zhao et al., 2012), and AtHRE2 contributes
299 to salinity and osmotic stress tolerance (Park et al., 2011). Ectopic expression of ERF-VII
300 homologous sequences in several plant species triggers protective responses against dehydration,
301 salt, mannitol, heavy metals, heat, as well as against a wide range of tested pathogens (reviewed in
302 Gibbs et al., 2015). Constitutive *ERF-VII* gene expression relates to more sustained activation of
303 ROS scavenging reactions, and, conversely, mutations inside the gene family lead to elevated ROS
304 under stress. Therefore, prompt and sustained ROS scavenging is believed to account for the
305 positive impact of ERF-VII over-expression in those conditions entailing oxidative stress (Ogawa et
306 al., 2005; Tang et al., 2005; Park et al., 2011; Yao et al., 2017; Vicente et al., 2017).

307 ROS production is enhanced under low oxygen conditions (Steffens et al., 2013). Thus, the same
308 protective mechanisms can act as an integral part of the ERF-VII dependent response strategy to
309 hypoxia. Improved ROS management has been associated with superior submergence tolerance in
310 maize and *Brachypodium distachyon* (Campbell et al., 2015; Rivera-Contreras et al., 2016), while

311 the activation of antioxidant responses in the post-hypoxic phase is crucial for survival in
312 Arabidopsis (Paradiso et al., 2016; Yuan et al., 2017). Interestingly, a target of RAP-type ERF-VIIs,
313 namely *HYPOXIA RESPONSIVE UNIVERSAL STRESS PROTEIN1 (HRU1)*, has been shown to
314 coordinate oxygen sensing by PCO/RAP2.12 with H₂O₂ production by NADPH oxidases,
315 indicating that there is a network connecting diverse signaling pathways downstream of ERF-VII
316 targets (Gonzali et al. 2015). At the same time, ERF-VII involvement in the regulation of stress
317 responses occurring under oxygen-replete conditions implies that the post-translational system
318 controlling their stability depending on oxygen is intertwined with additional regulatory
319 mechanisms. The Arg-Cys/NERP has recently been proved to promote Arabidopsis and barley
320 tolerance to salinity, drought and heat (multiple abiotic stresses sharing an oxidative stress
321 component) through ERF-VIIs. It has been proposed that, during salinity, ERF-VII proteins become
322 stabilized following a decline in nitrate reductase activity and subsequent decrease in NO levels
323 (Vicente et al., 2017).

324 NO is an elusive gaseous signal involved in a range of plant stress and developmental responses,
325 including hypoxia (Pucciariello and Perata, 2017). Reports regarding the influence of nitric oxide
326 on a plant's ability to cope with hypoxia are controversial (Perazzolli et al., 2004; Gupta and
327 Igamberdiev, 2016; Mira et al., 2016; Peng et al., 2016), making it hard to draw conclusions
328 regarding the impact of the described regulation under hypoxia. However, ERF-VII behaviour as
329 novel NO sensors has made it possible to connect them to the physiology of this gaseous signal. NO
330 levels have been manipulated in *prt6* and in combinatorial *prt6erfvii* mutants, in order to reveal the
331 ability of stabilized ERF-VII factors to mediate specific responses. It has been found that
332 germination, inhibited hypocotyl elongation in the dark and stomatal closure responses are
333 promoted by NO as a result of the degradation of the constitutively expressed ERF-VIIs (Gibbs et
334 al., 2014). Detailed examination of the NO-dependent release of seed dormancy has shown that a
335 repressor of germination, *ABI5*, is directly targeted by the ERF-VII (Gibbs et al., 2014). This further
336 qualifies ERF-VIIs as novel players in the antagonistic interplay between ABA and NO during
337 germination, which has already been found to converge on *ABI5* through S-nitrosylation of a
338 regulatory moiety that facilitates its proteasomal degradation (Albertos et al., 2015). Another
339 investigated process, prone to NO regulation, is the repression of the apical hook opening during
340 seedling skotomorphogenesis. In this case, all subfamily members have been found to be active
341 (Abbas et al., 2015), suggesting that the involvement of HRE-type factors in the control of other
342 physiological responses might be restrained by specific regulatory mechanisms.

343 **ERF-VII in plant-pathogen interactions**

344 Genetic approaches have recently highlighted the participation of group VII ERFs in responding to
345 biotrophic pathogens and to the necrotroph *B. cinerea*. The mechanisms enabling ERF-VII
346 stabilization and operation in both phenomena have not been revealed yet. In the case of the
347 tumorigenic pathogens *Plasmodiophora brassicae*, *Meloydogyne japonica* and *Agrobacterium*
348 *tumefaciens*, infection has been observed to upregulate fermentative genes, along with a significant
349 proportion of ERF-VII and Arg-Cys/NERP targets (Gravot et al., 2016). In addition, root gall
350 formation, caused by the protist *P. brassicae* in the secondary infection phase, is enhanced by ERF-
351 VII stabilization (Gravot et al., 2016). Switching on the hypoxic metabolism, downstream of the
352 ERF-VIIs, may benefit gall-forming pathogens (Gravot et al., 2016).

353 During *Arabidopsis* interaction with *B. cinerea*, instead, RAP2.2 participates in plant defense
354 downstream of ethylene signaling (Zhao et al., 2012), along with its partner Med25 (Ou et al., 2011;
355 Fig. 2A). Since the occurrence of hypoxia during such a pathogen attack has been ruled out (Zhao
356 et al., 2012), a few scenarios can be put forward to explain the postulated impairment of RAP2.2
357 degradation. In principle, factors affecting the activity of Arg-Cys/NERP components can modify
358 the stability of the ERF-VII proteins independently of oxygen. During infection, PCO enzymes may
359 be sensitive to different signals, such as the redox status, ROS and NO generation, and the
360 availability of micronutrients, as discussed previously. In such case, lower PCO activity under *B.*
361 *cinerea* attack could explain why *RAP2.2* over-expression was not sufficient to upregulate
362 pathogenic markers in the absence of fungal infection (Zhao et al., 2012). PRT6 activity might also
363 change in specific conditions; the synthetic R-GUS substrate could be used to visualize the PRT6
364 activity pattern *in vivo* during pathogen attack (Garzón et al., 2007).

365 Several ERF transcription factors promote the integration of intracellular stimuli (Müller and
366 Munné-Bosch, 2015). RAP2.2 involvement in pathogen responses downstream of ethylene suggests
367 that ERF-VIIs might have emerged as bridging elements of low oxygen- and immune responses
368 (Zhao et al., 2012). In fact, the setup of defense mechanisms is particularly appropriate in flooded
369 plants, in which infection can be facilitated by the extent of submergence and post-submergence
370 injury events. Submergence-triggered immunity has been observed in *Arabidopsis*, and ascribed to
371 one of the submergence-inducible WRKY TFs, *WRKY22* (Hsu et al., 2013). Interestingly, the
372 observed transcriptional responses caused by constitutive *WRKY22* expression are very similar to
373 the transcriptome-level changes triggered by AtRAP2.12 stabilization under fully aerated conditions
374 (Giuntoli et al., 2017). In this case, the removal of the oxygen-sensitive N-terminal domain and
375 over-expression of the resulting RAP2.12 protein leads to the activation of defense markers (*WRKY*
376 and *pathogenesis-related* genes), components of salicylic acid and ABA metabolism and ROS-

377 responsive genes, supporting the hypothesis of pathway convergence. A defense network involving
378 ERF-VII proteins might also include mitogen-activated kinases (MPKs) and the TF WRKY33.
379 MPK3/6 act in retrograde signaling following mitochondrial ROS stress during hypoxia (Chang et
380 al., 2012) and activate ERF6 (a hub of immunity, ROS and hormone responses; Huang et al., 2016)
381 upon *B. cinerea* attack or ROS treatment (Meng et al., 2013). WRKY33 contributes to Arabidopsis
382 resistance to *B. cinerea* (Liu et al., 2015) and submergence tolerance (Hwang et al., 2011).

383 **Novel protein interactions of the ERF-VII factors**

384 The previous examples indicate that, when subtracted from proteolytic degradation, the ERF-VII
385 transcription factors can promote the activation of specific responses (e.g. to hypoxia, oxidative
386 stresses, darkness, or pathogens). It would seem that specificity is achieved by the regulation of
387 particular, only partially overlapping, subsets of target genes. Selection of different protein partners
388 and recruitment in distinct multiprotein complexes could modulate ERF-VII activity. This has been
389 illustrated by a few recent studies.

390 AtRAP2.3 and AtRAP2.12 associate with DELLA proteins (Marín-de la Rosa et al., 2014).
391 DELLAs were known to prevent ethylene-induced gene expression by sequestering the
392 transcriptional activator EIN3 (An et al., 2012). In this case, the interplay between GA signaling
393 and ethylene is enriched by sequestration of RAP-type ERFs, shown to be downstream targets of
394 the EIN3/EIL TFs (Hinz et al., 2010; Zhao et al., 2012). This interaction helps prevent premature
395 apical hook opening in etiolated seedlings (Fig. 2B). Since association with the DELLA protein
396 GAI involves the N-terminal half of RAP2.3, including its AP2/ERF DNA binding domain, it has
397 been suggested that DELLAs regulate ERF-VII activity by hindering DNA binding, specifically to
398 GCC-box containing ethylene- and GA-target promoters (Marín-de la Rosa et al., 2014). DELLAs
399 may also mask the oxygen-sensitive ERF-VII domain, in such a way that the TFs would be exposed
400 to the N-end rule pathway only in the presence of GA. Whether or not the protected ERF-VIIs are
401 then available for association with other DNA motifs, i.e. not the GCC-box, requires further
402 experimentation. This example suggests that ERF-VII abundance and promoter preferences might
403 be reshaped in different physiological pathways, upon specific partner selection.

404 RAP2.2 has been revealed to be part of a PP2C-SNRK3 complex that promotes ABA insensitivity
405 (Lumba et al., 2014; Fig. 2C). This notable study demonstrates that ERF-VII functions can be tuned
406 by post-translational modifications (e.g. RAP2.2 phosphorylation by SNRK3) and partner selection.

407 Specifically, the interaction of RAP2.2 with the SNRK3.15/22 isoforms enables it to mediate
408 negative ABA responses, acquiring an opposite function to that observed by Gibbs et al. (2015).

409 Finally, specificity in promoter targeting can be achieved by the constitution of different
410 transcriptional complexes. RAP2.12 and RAP2.3 interact with BRAHMA (BRM; Vicente et al.,
411 2017), a SWI/SNF chromatin-remodeling ATPase that, among other functions, represses ABA
412 responses. BRM and RAP2.3 share a GCC-box binding site on the *ABI5* promoter. It has been
413 proposed that, during salinity, the interplay between BRM and the stress-stabilized ERF-VIIs
414 balances ABA-responsive gene expression through opposite functionalities (Fig. 2D).

415

416 **CONCLUDING REMARKS**

417 Knowledge of the role of ERF-VIIs has increased significantly over the last decade. A perspective
418 is emerging, in which a diversified set of mechanisms can influence ERF-VII expression,
419 availability and activity in order to specify their functions in a wider network of physiological
420 pathways activated by stress and hormones. However, important questions need to be addressed,
421 before a more detailed picture of ERF-VII regulation is gained (see Outstanding Questions Box).
422 The most recent observations suggest novel mechanisms enriching the role of ERF-VIIs in the
423 hypoxic response and connecting it to additional physiological, developmental and stress-related
424 processes.

425

426 **FIGURE LEGENDS**

427 **Figure 1.** Overview of the regulation of group-VII ERF factor stability in Arabidopsis. The stability of plant
428 ERF-VII proteins is controlled by intracellular O₂ and NO levels, by means of the Arg-Cys/N-end rule
429 pathway (NERP). The N-terminal cysteine (Cys), exposed upon methionine cleavage by MAP (methionine
430 aminopeptidase) enzymes, is susceptible to oxidation. Arginyl transferase (ATE) enzymes conjugate
431 oxidized cysteine (*Cys) to arginine (Arg), which in turn recruits the Arg-specific N-recognin PRT6 (Garzón
432 et al., 2007), an N-end rule pathway-specialized E3 ubiquitin ligase which labels the substrate for
433 degradation through the 26S proteasome (see Box 1 for additional details of the pathway). Cys oxidation can
434 be promoted by specific thiol oxygenases called plant cysteine oxidases (PCOs): in the presence of oxygen,
435 PCOs convert Cys into Cys-sulfinic acid, which acts as an ATE substrate (White et al., 2016). Therefore,
436 PCOs target ERF-VII proteins to the proteasome in an oxygen-dependent fashion. Besides oxygen, nitric

oxide (NO) also promotes ERF-VII turnover via the Arg-Cys/NERP, through a still-undetermined Cys-dependent mechanism (Vicente et al., 2017; Gibbs et al., 2014). Finally, although N-terminal Cys reactivity to hydrogen peroxide (H₂O₂) has not been assessed in ERF-VII proteins, *Cys forms generated in relation to H₂O₂ concentration (García-Santamarina et al., 2014) could in principle play a role in the pathway, by either working as an alternative ATE substrate or interfering with Cys-sulfinic acid catalysis. Plasma membrane localization has been observed for RAP2.3 (Abbas et al., 2015) and RAP2.12 (Giuntoli et al., 2017; Kosmacz et al., 2015). As the latter has been found to be associated with peripheral membrane proteins belonging to the ACBP (Acyl-CoA Binding Protein) family, it has been proposed that this interaction is useful to maintain an inactive pool of RAP2.12 factor at the plasma membrane (Licausi et al., 2011). ERF-VIIs have a primary role as master activators of the hypoxic metabolism. ERF-VII transcription factors (represented in this figure by the five subfamily members from *A. thaliana*, AtRAP2.2/2.3/2.12 and AtHRE1/2) exert direct control on the hypoxia-inducible expression of plant anaerobic genes by binding an HRPE (Hypoxia Response Promoter Element) motif present in their promoters (e.g. *ADH*, *PDC*, *LBD41*, *HRE1* and *HRE2*, and *HRA1*) (Gasch et al., 2016). The hypoxia-inducible factors HRE1 and HRE2 are further controlled at the post-transcriptional level through the Arg-Cys/NERP (Gibbs et al., 2011). During hypoxic regulation, HRA1 acts as a feed-back repressor of anaerobic gene expression, by interaction with RAP2.12 (Giuntoli et al., 2014). The SINAT pathway, which is an N-end rule pathway-independent proteolysis, is also shown. RAP2.12 can be ubiquitinated by the E3 ligases SINAT1/2 (Papdi et al., 2015). These proteins modulate the autophagy pathway and thereby enhance Arabidopsis tolerance to nutrient starvation (Qi et al., 2017). In fact, autophagy responses are also activated during hypoxia and contribute to plant submergence tolerance (Chen et al., 2015 and 2017). This evidence suggests that an additional tier of regulation might connect the ERF-VIIs to submergence responses, through the SINAT factors. Solid lines refer to experimentally established reactions or relationships, dashed lines to hypothetical relationships drawn from observed regulation, and dotted lines depict hypothetical reactions.

Figure 2. Additional roles of ERF-VIIs through interaction with distinct protein partners. A, resistance to necrotrophic fungi (Zhao et al., 2012). After *B. cinerea* infection, ethylene accumulation leads to *RAP2.2* gene induction downstream of the EIN2-EIN3/EIL ethylene signaling cascade. *RAP2.2* activates the resistance genes *PDF1.2* and *ChiB*, by interaction with its partner Med25 (Ou et al., 2011), and contributes positively to Arabidopsis resistance to fungal attack. B, *RAP2.3* is a positive regulator of apical hook development in Arabidopsis seedlings and its action is counteracted by interacting DELLA proteins (Marín-de la Rosa et al., 2014). In etiolated seedlings, *RAP2.3* gene expression is promoted by dark-induced ethylene production, while low levels of DELLA proteins prevent *RAP2.3* functional restriction. Therefore, *RAP2.3* participates in the interplay between ethylene and GA, which regulates apical hook formation (Abbas et al., 2013), by hindering premature hook opening under darkness. C, during germination, *RAP2.2* is as a negative regulator of ABA responses (Lumba et al., 2012). This function has been associated with *RAP2.2* phosphorylation, following its interaction with an SNRK3 kinase complex that mediates ABA

473 insensitivity. D, ERF-VII stabilization enhances plant tolerance to multiple abiotic stresses (Vicente et al.,
474 2017). During salinity, decreased NO biosynthesis due to NR enzyme impairment has been proposed to lead
475 to ERF-VII protein stabilization in the presence of oxygen. The beneficial effects of the ERF-VIIs on plant
476 tolerance to salinity is antagonized by its interacting partner BRM, possibly due to competition for the same
477 *cis*-element on the target gene promoters (Vicente et al., 2017). EIN2, Ethylene-insensitive 2; EIN3,
478 Ethylene-insensitive 2; EIL, EIN3-like; Med25, Mediator subunit 25; DELLA, GRAS-domain family
479 proteins (GAI, RGA, RGLs); PP2C, Protein phosphatase 2C; SnRK3, SNF1-related protein kinase 3; NR,
480 nitrate reductases; NO, nitric oxide; BRM, BRAHMA ATPase.

481

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ADVANCES

- N-terminal cysteine oxidation of ERF-VII proteins is enzymatically controlled by specific cysteinyl dioxygenases, the PCO family enzymes, as a prerequisite for substrate protein processing via the Arg-Cys/N-end rule pathway.
- ERF-VII bind anaerobic gene promoters through a novel cis-acting element, HRPE, which is different from the canonical GCC-box element recognized by other AP-2 domain-containing ethylene response factors.
- The first ERF-VII partner proteins have been identified and are involved in transcription (Med25, BRM), hormone signaling (GAI, PP2C), and proteolysis (SINAT2). The investigation of these interactions broadens the perspective of ERF-VII regulation beyond their direct dependence upon O² availability.

OUTSTANDING QUESTIONS

- Which signals and mechanisms (e.g. metal ion switching and ROS) regulate PCOs activity beyond intracellular oxygen tension?
- Can ROS and RNS impact on ERF-VII stability through the Arg/Cys-N-end rule pathway?
- Regarding the Arg-Cys/N-end rule pathway, is the development of an enzymatic control point for Cys2 oxidation a particular feature of plant evolution?
- Which mechanism shuttles AtRAP2.12 to the plasma membrane when cells are normally aerated and what mediates its release to the nucleus upon hypoxia?
- Do different protein-protein interactions determine ERF-VII specificity in stress and hormone response regulatory modules?
- What is the pattern of promoter occupancy by the ERF-VIIs at the genome-wide level?
- How is ERF-VII activity regulated by posttranslational modifications (e.g. phosphorylation, acylation, glycosylation and sumoylation) different from Cys2 oxidation?

BOX 1. ERF-VII Factors as N-end Rule Substrates

Group-VII ERFs were the first plant substrates of the Arg/N-end rule pathway (NERP) to be discovered. The NERP is a proteolytic system that promotes the turnover of proteins containing N-terminal sequences (N-degrons) that work as degradation signals (Bachmair et al., 1986). Substrate proteins are degraded through the proteasome, following polyubiquitination by specific N-degron-recognizing E3 ubiquitin ligases (N-recognins). Primary destabilizing residues are directly targeted by E3 ligases. They consist in basic or bulky hydrophobic residues (Arg/NERP; Varshavski, 2011), acetylated residues (Ac/NERP; Hwang et al., 2010), and proline (Pro/NERP; Chen et al., 2017). Secondary and tertiary destabilizing residues, instead, can be converted into primary ones upon enzymatic modifications, such as N-terminal deamidation (Gln, Asn), arginylation (Glu, Asp, *Cys), acetylation (Gly, Ala, Ser, Thr, Val, Cys), or oxidation (Cys). Therefore, the NERP assumes a hierarchical architecture, which is conserved across eukaryotes (Tasaki et al., 2012).

ERF-VII proteins enter the Arg/NERP upon co-translational Met cleavage, enabled by the small side chain of the neighboring Cys2, which matches the substrate specificity of methionine aminopeptidases (MAPs; Xiao et al., 2010). Exposed Cys behave as tertiary destabilizing residues, being converted into oxidized cysteine (*Cys, secondary destabilizing residue) in the presence of oxidizing agents, such as O₂, NO, and hypothetically, ROS (Fig. 1). Chemical similarity

between acidic residues and *Cys underlies its recognition by plant arginyl transferases (ATE1/2, in Arabidopsis; Graciet et al., 2009), triggering Arg conjugation and subsequent targeting by the Arg-specific E3 ligase PRT6 (Proteolysis 6; Garzón et al., 2007). Therefore, Cys2 oxidation provides a link between oxygen and NERP regulation, in plants as well as in animals (Hu et al., 2005).

Direct Cys-dependent ERF-VII regulation by the proteasome was first shown in heterologous rabbit reticulocyte lysate assays (Gibbs et al., 2011). In vivo, the amenability of ERF-VII proteins to Arg-Cys/NERP regulation has been mainly investigated by the expression of reporter substrates or HA-tagged ERF-VIIs. MC-ERF-VII-HA over-expressors have been used for immunological detection, to display protein dynamics (1) under hypoxia and post-stress re-oxygenation, (2) in the prt6 mutant (Gibbs et al., 2011), and (3) after NO manipulation by chemical treatments or genetic impairment of NO biosynthesis (Gibbs et al., 2014). Alternatively, the impact of these conditions on ERF-VII stability has been shown by means of MC-GUS and UBI-C-GUS histochemical reporters (Vincente et al., 2017; Gibbs et al., 2014). MC-GUS consists in a translational fusion between an ERF-VII-derived Cys-N-degron and the β -glucuronidase reporter, UBI-C-GUS in a ubiquitin-Cys reporter fusion, from which an N-terminal Cys-reporter is generated by ubiquitin-specific endoproteases (Garzón et al., 2007).

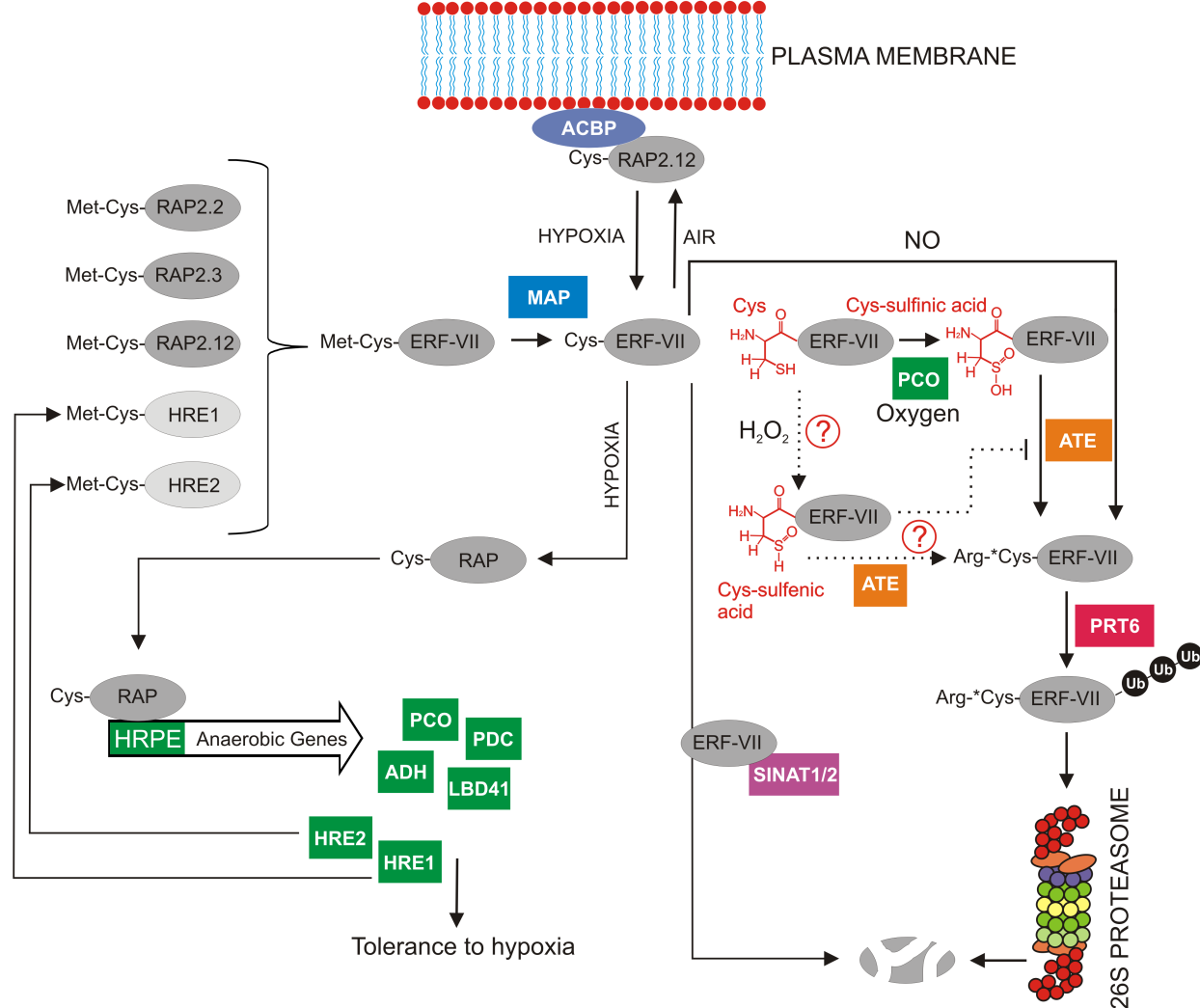


Figure 1. Overview of the regulation of group-VII ERF factor stability in Arabidopsis. The stability of plant ERF-VII proteins is controlled by intracellular O_2 and NO levels, by means of the Arg-Cys/N-end rule pathway (NERP). The N-terminal cysteine (Cys), exposed upon methionine cleavage by MAP (methionine aminopeptidase) enzymes, is susceptible to oxidation. Arginyl transferase (ATE) enzymes conjugate oxidized cysteine (*Cys) to arginine (Arg), which in turn recruits the Arg-specific N-recognin PRT6 (Garzón et al., 2007), an N-end rule pathway-specialized E3 ubiquitin ligase which labels the substrate for degradation through the 26S proteasome (see Box 1 for additional details of the pathway). Cys oxidation can be promoted by specific thiol oxygenases called plant cysteine oxidases (PCOs): in the presence of oxygen, PCOs convert Cys into Cys-sulfenic acid, which acts as an ATE substrate (White et al., 2016). Therefore, PCOs target ERF-VII proteins to the proteasome in an oxygen-dependent fashion. Besides oxygen, nitric oxide (NO) also promotes ERF-VII turnover via the Arg-Cys/NERP, through a still-undetermined Cys-dependent mechanism (Vicente et al., 2017; Gibbs et al., 2014). Finally, although N-terminal Cys reactivity to hydrogen peroxide (H_2O_2) has not been assessed in ERF-VII proteins, *Cys forms generated in relation to H_2O_2 concentration (García-Santamarina et al., 2014) could in principle play a role in the pathway, by either working as an alternative ATE substrate or interfering with Cys-sulfenic acid catalysis. Plasma membrane localization has been observed for RAP2.3 (Abbas et al., 2015) and RAP2.12 (Giuntoli et al., 2017; Kosmacz et al., 2015). As the latter has been found to be associated with peripheral membrane proteins belonging to the ACBP (Acyl-CoA Binding Protein) family, it has been proposed that this interaction is useful to maintain an inactive pool of RAP2.12 factor at the plasma membrane (Licausi et al., 2011). ERF-VIIs have a primary role as master activators of the hypoxic metabolism. ERF-VII transcription factors (represented in this figure by the five subfamily members from *A. thaliana*, AtRAP2.2/2.3/2.12 and AtHRE1/2) exert direct control on the hypoxia-inducible expression of plant anaerobic genes by binding an HRPE (Hypoxia Response Promoter Element) motif present in their promoters (e.g. *ADH*, *PDC*, *LBD41*, *HRE1* and *HRE2*, and *HRA1*) (Gasch et al., 2016). The hypoxia-inducible factors HRE1 and HRE2 are further controlled at the post-transcriptional level through the Arg-Cys/NERP (Gibbs et al., 2011). During hypoxic regulation, HRA1 acts as a feed-back repressor of anaerobic gene expression, by interaction with RAP2.12 (Giuntoli et al., 2014). The SINAT pathway, which is an N-end rule pathway-independent proteolysis, is also shown. RAP2.12 can be ubiquitinated by the E3 ligases SINAT1/2 (Papdi et al., 2015). These proteins modulate the autophagy pathway and thereby enhance Arabidopsis tolerance to nutrient starvation (Qi et al., 2017). In fact, autophagy responses are also activated during hypoxia and contribute to plant submergence tolerance (Chen et al., 2015 and 2017). This evidence suggests that an additional tier of regulation might connect the ERF-VIIs to submergence responses, through the SINAT factors. Solid lines refer to experimentally established relationships, and dotted lines depict hypothetical reactions.

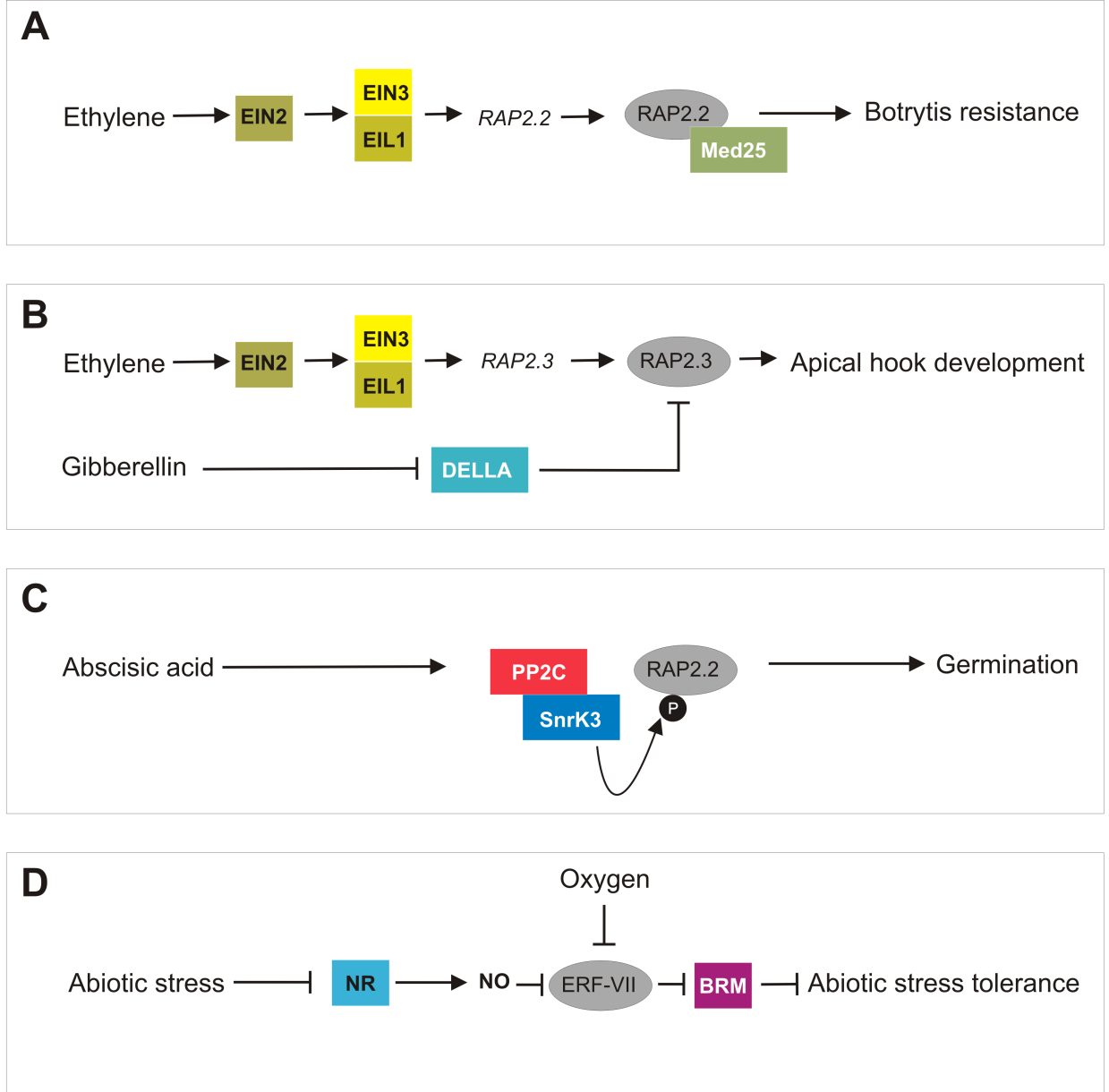


Figure 2. Additional roles of ERF-VII through interaction with distinct protein partners. A, resistance to necrotrophic fungi (Zhao et al., 2012). After *B. cinerea* infection, ethylene accumulation leads to *RAP2.2* gene induction downstream of the EIN2-EIN3/EIL ethylene signaling cascade. *RAP2.2* activates the resistance genes *PDF1.2* and *ChiB*, by interaction with its partner Med25 (Ou et al., 2011), and contributes positively to Arabidopsis resistance to fungal attack. B, *RAP2.3* is a positive regulator of apical hook development in Arabidopsis seedlings and its action is counteracted by interacting DELLA proteins (Marin-de la Rosa et al., 2014). In etiolated seedlings, *RAP2.3* gene expression is promoted by dark-induced ethylene production, while low levels of DELLA proteins prevent *RAP2.3* functional restriction. Therefore, *RAP2.3* participates in the interplay between ethylene and GA, which regulates apical hook formation (Abbas et al., 2013), by hindering premature hook opening under darkness. C, during germination, *RAP2.2* is as a negative regulator of ABA responses (Lumba et al., 2012). This function has been associated with *RAP2.2* phosphorylation, following its interaction with an SNRK3 kinase complex that mediates ABA insensitivity. D, ERF-VII stabilization enhances plant tolerance to multiple abiotic stresses (Vicente et al., 2017). During salinity, decreased NO biosynthesis due to NR enzyme impairment has been proposed to lead to ERF-VII protein stabilization in the presence of oxygen. The beneficial effects of the ERF-VIIs on plant tolerance to salinity is antagonized by its interacting partner BRM, possibly due to competition for the same *cis*-element on the target gene promoters (Vicente et al., 2017). EIN2, Ethylene-insensitive 2; EIN3, Ethylene-insensitive 2; EIL, EIN3-like; Med25, Mediator subunit 25; DELLA, GRAS-domain family proteins (GAI, RGA, RGLs); PP2C, Protein phosphatase 2C; NR, nitrate reductase; NO, nitric oxide; BRM, BRAHMAATPase.

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