

RALF–FERONIA Signaling: Linking Plant Immune Response with Cell Growth

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<https://doi.org/10.1016/j.xplc.2020.100084>

ABSTRACT

Plants perceive various external and internal signals to self-modulate biological processes through members of the receptor-like kinase (RLK) family, among which *Catharanthus roseus* receptor-like kinase 1-like (CrRLK1L) proteins with their ligands, rapid alkalization factor (RALF) peptides, have attracted considerable interest. FERONIA (FER), a CrRLK1L member, was initially reported to act as a major plant cell growth modulator in distinct tissues. Subsequently, the RALF–FER pathway was confirmed to function as an essential regulator of plant stress responses, including but not limited to immune responses. Furthermore, the RALF–FER pathway modulates immune responses and cell growth in a context-specific manner, and the vital roles of this pathway are beginning to be appreciated in crop species. The recent remarkable advances in understanding the functions and molecular mechanisms of the RALF–FER pathway have also raised many interesting questions that need to be answered in the future. This review mainly focuses on the roles of FER and other CrRLK1L members in modulating immune responses in the context of cell growth in response to their RALF peptide ligands and presents a brief outlook for future research.

Keywords: FER receptor kinase, RALF peptide, immune responses, cell expansion, cell wall

Zhang X., Yang Z., Wu D., and Yu F. (2020). RALF–FERONIA Signaling: Linking Plant Immune Response with Cell Growth. *Plant Comm.* **1**, 100084.

INTRODUCTION

Plants must survive and reproduce under different environmental conditions despite being immobile. Thus, sensing external environmental signals and being able to respond accordingly are extremely important for plant growth and survival. Receptor-like kinases (RLKs), the largest single-transmembrane receptor family in plants, are employed to handle external signals. More than 600 RLKs have been recognized in *Arabidopsis thaliana* (hereafter referred to as *Arabidopsis*), and different RLKs contribute to multiple aspects of plant life (Shiu and Bleecker, 2001; Lehti-Shiu et al., 2009; Dievart et al., 2020). *Catharanthus roseus* receptor-like kinase 1-like (CrRLK1L) proteins are a subfamily of RLKs, and they structurally contain two malectin-like domains (MLDs) in their extracellular domain (ECD), a transmembrane domain (TMD) and an intracellular kinase domain. The first CrRLK1L member, CrRLK1, was cloned in 1996 (Schulze-Muth et al., 1996), and the function of CrRLK1L has been comprehensively studied in *Arabidopsis* over the past decade. Among CrRLK1Ls in *Arabidopsis*, 15 of 17 have been studied in detail, revealing their functions (Table 1). Recently, the roles of CrRLK1L proteins in regulating agronomic traits have begun to be appreciated in crop species (Table 1). In general, CrRLK1L

proteins play versatile roles in plant growth and development, reproduction, hormone signaling, stress responses, immunity (Escobar-Restrepo et al., 2007; Guo et al., 2009, 2018; Duan et al., 2010, 2014; Yu et al., 2012, 2014; Haruta et al., 2014; Li et al., 2015, 2016a; Mao et al., 2015; Chen et al., 2016; Du et al., 2016; Ge et al., 2017, 2019; Mecchia et al., 2017; Stegmann et al., 2017; Chakravorty et al., 2018; Feng et al., 2018; Franck et al., 2018; Gonneau et al., 2018; Hansen et al., 2019; Wang et al., 2020a; Zhou and Zhang, 2020), energy production and RNA metabolism (Xu et al., 2019; Zhu et al., 2020a; Wang et al., 2020b).

Rapid alkalization factor (RALF) peptides, as ligands of CrRLK1L receptors, constitute an evolutionarily conserved peptide family, with at least 37 RALF members in *Arabidopsis*. Most of the reported RALF members induce rapid alkalization of the extracellular compartment of plant cells and regulate a series of developmental and physiological responses in plants. The functions of RALF peptides in different plant species have been

Published by the Plant Communications Shanghai Editorial Office in association with Cell Press, an imprint of Elsevier Inc., on behalf of CSPB and IPPE, CAS.

Name	Gene ID	Growth and development	Biotic stress and abiotic stress	Ligands
AtFER	AT3G51550	Vegetative growth (Guo et al., 2009); root growth and cell wall integrity (Haruta et al., 2014; Du et al., 2016; Stegmann et al., 2017); root hair development (Duan et al., 2010; Zhu et al., 2020a); leaf epidermis cell morphogenesis (Li et al., 2015); pollen tube growth and fertilization (Haruta et al., 2014; Stegmann et al., 2017); flowering time (Wang et al., 2020a); seed size and seed set (Yu et al., 2014; Li et al., 2016a); C/N balance (Xu et al., 2019); mRNA alternative splicing (Wang et al., 2020a, 2020b); nitric oxide accumulation (Duan et al., 2020); stomatal movement (Yu and Assmann, 2018)	Positively regulates plant resistance to bacteria and fungus (Keinath et al., 2010; Kessler et al., 2010; Stegmann et al., 2017; Guo et al., 2018; Xiao et al., 2019). Negatively regulates resistance to <i>Fusarium oxysporum</i> (Masachis et al., 2016). Hypersensitive to cold, heat, and salt stress; hyposensitive to osmotic stress (Yu et al., 2012; Chen et al., 2016; Feng et al., 2019)	RALF1, RALF17, RALF23, RALF32, RALF33; F-RALF
AtANX1	AT3G04690	Pollen tube growth and integrity (Boisson-Dernier et al., 2009; Miyazaki et al., 2009; Ge et al., 2017; Gonneau et al., 2018; Feng et al., 2019); cell wall integrity in tip-growing cells (Boisson-Dernier et al., 2013; Franck et al., 2018)	Negatively regulate PTI and ETI (Mang et al., 2017)	RALF4, RALF19, RALF34
AtANX2	AT5G28680			
AtBUPS1	AT4G39110			
AtBUPS2	AT2G21480	Pollen tube growth and integrity (Feng et al., 2019; Ge et al., 2019).		
AtTHE1	AT5G54380	Cell wall synthesis and cell expansion (Hématy et al., 2007; Merz et al., 2017; Van der Does et al., 2017); cell wall integrity (Gonneau et al., 2018)	Positively regulates plant resistance to fungus <i>Botrytis cinerea</i> (Qu et al., 2017)	RALF34
AtHERK1	AT3G46290	Plant growth and cell elongation (Guo et al., 2009)		
AtHERK2	AT1G30570			
AtERU/CAP1	AT5G61350	Pollen tube growth; root development (Schoenaers et al., 2018)		
AtCVY1	AT2G39360	Cell elongation and morphogenesis (Gachomo et al., 2014)		
AtANJ	AT5G59700	Pollen tube reception (Galindo-Trigo et al., 2020)		
AtMDS1	AT5G38990		Metal ion stress response (Richter et al., 2018)	
AtMDS2	AT5G39000			
AtMDS3	AT5G39020			
AtMDS4	AT5G39030			
OsFLR1(DRUS1)	Os03g21540	FLR1 (DRUS1) and FLR2 (DRUS2) regulate rice growth, development, and reproduction (Li et al., 2016a; Pu et al., 2017)	Rice immunity (Yang et al., 2020)	
OsFLR2(DRUS2)	Os01g56330			
OsFLR9(RUPO)	Os06g03610	Pollen tube growth and integrity; K ⁺ homeostasis (Liu et al., 2016a)		
OsFLR11	Os10g39010		Rice immunity (Yang et al., 2020)	
OsFLR13	Os03g17300	Rice reproduction (Yang et al., 2020)	Rice immunity (Yang et al., 2020)	
CpRLK1	AB920609	Reproduction (Hirano et al., 2015)		

Table 1. Overview of CrRLK1L Family Members from Plants.

(Continued on next page)

Name	Gene ID	Growth and development	Biotic stress and abiotic stress	Ligands
<i>Mp</i> THE	KU758861	Cell wall integrity (Honkanen et al., 2016)		
<i>Mp</i> FER	BAF79940	Cell wall integrity; tip growth (Westermann et al., 2019)		
<i>Fa</i> MRLK47	13 568.1	Fruit ripening and quality formation (Jia et al., 2017a)		
<i>Pbr</i> CrRLK1L3	Pbr004347.1	Pollen tube rupture (Kou et al., 2017)		
<i>Pbr</i> CrRLK1L26	Pbr028472.1	Pollen tube growth (Kou et al., 2017)		
<i>Md</i> FERL1	MDP0000445374	Fruit ripening (Jia et al., 2017b)		
<i>Md</i> FERL6	MDP0000465341			

Table 1. Continued

comprehensively reviewed recently (Blackburn et al., 2020). Based on the currently available genomic data, the oldest *CrRLK1L* genes are found in charophytes, and the gene family gradually expanded before monocots diverged from dicots. The average numbers of *CrRLK1L* proteins per species are 22 and 30 in monocots and dicots, respectively, indicating the *CrRLK1L* gene family has not expanded since monocots diverged (Dievart et al., 2020). Although the oldest *RALF* genes are found in *Physcomitrella patens*, a non-flowering plant, the evolutionary history of *RALF* peptides is more complicated than that of the *CrRLK1L* gene family, as *RALF* genes are also found outside of the plant kingdom (Campbell and Turner, 2017). This review focuses on the roles of the *RALF*–*FER* pathway in immune responses in the context of cell growth in plants. We briefly provide an overview of the functions and components of the *RALF*–*FER* pathway, introduce *RALF* signals and their receptors outside of cells, and lastly discuss the factors involved in the roles of the *RALF*–*FER* pathway in immunity and their crosstalk in the cytoplasm.

An Overview of the Functions and Components of the *RALF*–*FER* Pathway

Arabidopsis *FER* is the best characterized *CrRLK1L* member (Haruta et al., 2014; Li et al., 2016b; Liao et al., 2017; Stegmann et al., 2017; Xiao et al., 2019; Duan et al., 2020). *FER* was first cloned by the Grossniklaus research group during a screen of double-fertilization regulators (i.e., pollen tube reception genes) (Escobar-Restrepo et al., 2007). *FER* has recently emerged as a potential target for crop improvement and protection because of its versatile, fundamental, and tissue-specific roles in plant growth, immune responses, crop yield control, and abiotic responses. *FER* modulates growth and stress responses, H⁺-ATPase activity, calcium accumulation, reactive oxygen species (ROS) burst, and cell wall integrity (CWI) in a variety of cell types in response to its *RALF* ligands (Table 1). *LORELEI* (*LRE*) is mainly expressed in synergid cells of the ovule, *lre* and *fer* mutants, and the *lre fer* double mutants that display the same defects in pollen tube reception, namely pollen tube overgrowth and sperm release defects, indicating that *LRE* requires *FER* for pollen tube reception (Capron et al., 2008; Liu et al., 2016b). *LORELEI*-like-GPI-anchored protein 1 (*LLG1*) is the closest homolog of *LRE* based on amino acid sequences. It is mainly expressed in vegetative tissues, with no deficiency in pollen tube reception observed in *LLG1* mutants (Li et al., 2015). Li et al. (2015),

showing that *LLG1* interacts with the *RALF1* peptide and the ECD of *FER* to regulate cell growth in vegetative tissues and acts as the co-receptor of the *RALF1* peptide. Recently, *RALF4/1*–*LLG2/3* has been shown to participate in pollen tube growth via *ANXUR1/2* (*ANX1/2*) and *BUDDHAPAPER SEAL1/2* (*BUPS1/2*) *CrRLK1L* members (Feng et al., 2019; Ge et al., 2019). Additionally, *RALF34* has been identified as a ligand of *THESEUS1* (*THE1*), which is a homolog of *FER* and a modulator of CWI (Gonneau et al., 2018). The leucine-rich repeat (LRR) extensin (*LRXs*) family of proteins functions to survey CWI. High-throughput screens of proteins interacting with *LRXs* indicated that *RALF* peptides interact with *LRXs*, suggesting that *LRXs* have roles in *RALF*-regulated pollen tube growth (Covey et al., 2010). Mecchia et al. (2017) further confirmed this finding and showed that *RALF4/19* interacts with *LRXs* to regulate pollen tube integrity and growth (Moussu et al., 2020).

Several interesting studies have reported the structural basis of *RALF* binding to its *LLG/LRX*–*CrRLK1L* receptor complex. Using mass spectrometry-based footprinting methods and covalent crosslinking experiments *in vitro*, Liu et al. (2018) revealed the ECD and juxtamembrane regions of *FER* linked to the highly conserved C terminus of *AtRALF1*. Furthermore, Xiao et al. (2019), using X-ray crystallography, showed that *LLG2* directly binds the N terminus of *RALF23* to nucleate the assembly of *RALF23*–*LLG2*–*FER* heterocomplexes. Detailed structural data show that the conserved *YISY* motif of *RALF23* forms extensive interactions with the loops of *LLG2* through a combination of hydrophobic and polar contacts. However, the X-ray structural data do not provide detailed information on how the C terminus of *RALF23* interacts with the *FER* ECD. Additionally, the crystal structures of the *LRX2*–*RALF4* and *LRX8*–*RALF4* complexes reveal that disulfide-bond-stabilized loops in folded *AtRALF4* peptides are a major factor in binding the LRR domain of *LRX* proteins, which is required to control pollen tube growth (Moussu et al., 2020). After recognizing the *RALF1* peptide, *FER* recruits and interacts with *RPM1*-induced protein kinase (*RIPK*), a receptor-like cytoplasmic kinase (*RLCK*), to inhibit cell growth (Du et al., 2016). In the cytoplasm, the *RALF1*–*FER* complex also uses the small G-protein pathway to regulate auxin responses and root hair growth (Duan et al., 2010) as well as abscisic acid (*ABA*) responses (Yu et al., 2012; Chen et al., 2016). *FER* also monitors the carbon/nitrogen (*C/N*) balance by interacting with *ATL6* (Xu et al., 2019), regulates mRNA alternative splicing by phosphorylating the RNA-binding protein

glycine-rich protein 7 (GRP7) to modulate plant fitness and flowering time (Wang et al., 2020a, 2020b) and promotes protein synthesis and polar cell growth by phosphorylating eIF4E1 (Zhu et al., 2020a). The RALF1–FER complex uses a “shortcut” mechanism to directly regulate gene expression by phosphorylating a DNA-binding protein, namely ErbB3-binding protein 1 (EBP1) (Li et al., 2018). The RALF–FER complex also interferes with jasmonic acid (JA) signaling and flg22-induced complex formation between the immune receptor kinase FLAGELLIN-SENSING 2 (FLS2) and its co-receptor BRASSINOSTEROID INSENSITIVE 1-ASSOCIATED RECEPTOR KINASE 1 (BAK1) (Shen et al., 2017; Stegmann et al., 2017; Guo et al., 2018; Xiao et al., 2019).

Ligands and Co-receptors/Receptors Involved in RALF–CrRLK1L Signaling

The initial function of the RALF peptide was derived from the rapid alkalinization of tobacco (*Nicotiana tabacum*) extracellular media and the activation of mitogen-activated protein kinase (MAPK) kinase (Pearce et al., 2001). In plants, most mature RALF peptides share conserved domains, namely the YISY motif in the N terminus and four cysteine residues near the C terminus (referred to as the RGC(5N)C motif) (Campbell and Turner, 2017). As mentioned above, the C and N terminus of RALF interact with the FER–LLGs receptor complex and LRXs. The history and functions of RALF peptides in plants have been comprehensively reviewed elsewhere (Blackburn et al., 2020). Here, we mainly review the roles of RALF and its co-/receptors, including FER and other CrRLK1L receptor kinases, in immune responses.

The Grossniklaus and Panstruga research groups reported the role of FER in fungal and bacterial triggered immune responses, first linking FER with immune responses (Keinath et al., 2010; Kessler et al., 2010). In search of the ligand of FER, Haruta et al. (2014) first reported that AtRALF1 peptides bind to the FER ECD and initiate FER kinase activation, which inhibits H⁺-ATPase activity and proton transport, thus suppressing root elongation. RALF peptides are expressed as precursors that need to be cleaved by proteases in order to produce a mature RALF peptide that can execute its function. Besides the AtRALF1 precursors, nine other related AtRALF precursors, including AtRALF22 and AtRALF23, are predicted to be cleaved by site-1 protease (AtS1P), a plant subtilisin-like serine protease (Srivastava et al., 2009; Stegmann et al., 2017). During a screening of the modifiers of bak1–5 immunity response mutants, Stegmann et al. (2017) found that AtS1P cleaves endogenous AtRALF precursors, such as RALF23, to inhibit plant immunity. The RALF23–FER complex suppresses flg22-induced ROS burst, as well as immune responses, by destabilizing the complex formation of EFR and FLS2 with their co-receptor BAK1 (Stegmann et al., 2017). The authors proposed that FER acts as a RALF-regulated scaffold that modulates the assembly of the receptor kinase complex. Notably, this study also suggests that there is an opposite role in the immune response between S1P cleaved and non-S1P cleaved RALF peptides. Thus, the roles of the predicted S1P cleaved RALF peptides in plant growth and development merit further investigation. In the future, additional studies are needed to identify new proteases that produce mature RALF peptides. The RALF co-receptor, LLG1, also regu-

lates innate immunity via its association with and modulation of FLS2 receptor kinase (Shen et al., 2017; Xiao et al., 2019).

Accumulating evidence suggests that RALF peptides are conserved across the plant kingdom as well as outside of it. Potential RALF peptides have been isolated from fungal and bacterial genomes (Masachis et al., 2016; Thynne et al., 2017). For example, F-RALF from *Fusarium oxysporum* was determined to be a functional peptide that induces the alkalinization and inhibition of root growth as well as AtRALF1 (Masachis et al., 2016). Additionally, it promotes fungal virulence and suppresses plant immune responses through the FER receptor kinase (Masachis et al., 2016). Moreover, *F. oxysporum* infection was found to involve JA signaling (Thatcher et al., 2009), and AtRALF23, the closest homolog of F-RALF (Masachis et al., 2016), has been shown to stabilize the basic helix-loop-helix transcription factor MYC2 and promote JA signaling via FER (Guo et al., 2018). Thus, it will be interesting to determine whether F-RALF from *F. oxysporum* modulates JA signaling via FER. Plant and non-plant RALFs possess similar sequences in both their C- and N-terminal regions, but both have numerous sequence polymorphisms in their middle domains, which has been reported to contribute to RALF–LRXs affinity, as Moussu et al. (2020) found that pH and disulfide-bond-stabilized RALFs and LRXs are important for RALF–LRXs affinity. As plant immune responses are always coupled with pH (Kesten et al., 2019) and ROS changes, there is the potential for microorganisms to trigger pH and ROS changes to modulate RALF–LRXs and RALF–FER affinity and further regulate plant immune responses. The evolutionary history of RALFs and whether plant FER receptor complexes can differentiate plant RALFs from non-plant RALFs still requires further investigation.

RALF-Mediated pH Changes Regulate Plant Growth and Immunity

The cell wall maintains plant cell morphology and is the first barrier between plant cells and their environment. Thus, the cell wall acts as a dynamic barrier against the invasion of pathogens. Therefore, the maintenance of CWI is necessary for plant survival and cell growth and development. To promote plant cell growth, the cell wall must be remodeled to allow cell expansion. Cell wall acidification triggers cell wall loosening, thus allowing plant cell expansion, as cell wall-loosening enzymes are activated by low pH conditions (Cosgrove, 2015). As mentioned above, the RALF1–FER pathway phosphorylates the proton pump (e.g., AHA2), leading to transient alkalinization of the extracellular matrix and inhibiting primary root cell elongation (Haruta et al., 2014). Except for pollen-specific RALF4, all RALF peptides tested so far have the ability to promote extracellular alkalinization (Morato do Canto et al., 2014). Alkalinization is proposed to be the mechanism through which RALF peptides regulate cell growth. However, RALF peptides have different roles in cell growth in different tissues and cell types, and additional studies are needed to understand the roles of RALF in modulating cell growth via extracellular alkalinization.

Extracellular pH is a key factor controlling the virulence of pathogens. Several studies have reported that the dynamic phosphorylation of AHAs can rapidly regulate proton pump activity and cause apoplastic pH changes, which are involved in the response

to invasion by pathogenic microorganisms (Masachis et al., 2016; Yu et al., 2019). RALF-induced pH alterations may also regulate pathogenicity. Specifically, *F. oxysporum* secretes RALF-like (F-RALF) peptides that mimic plant RALFs, activate FER kinase, and inhibit AHA activity, thus inducing the alkalization of apoplasts, which activates the orthologous MAPK FMK1 kinase and promotes virulence in fungi (Masachis et al., 2016). Conversely, the rhizosphere-associated bacterium *Pseudomonas* decreases the environmental pH to suppress plant immune responses (Yu et al., 2019). Stegmann et al. (2017) has reported that RALF-induced extracellular alkalization is not required for the inhibition of the plant immune response by RALFs. Thus, RALF triggers extracellular alkalization in context-specific manners, which involve both cell growth and immunity. One possible explanation is that different microorganisms have different apoplastic pH preferences, which have diverse roles in processes such as parasitism and/or infection. Accordingly, how the RALF-FER pathway modulates immune responses and cell growth by triggering pH changes in a context-dependent manner requires further investigation.

Cell Walls Act as Dynamic Barriers, Affecting Plant Growth and Pathogen Invasion

The cell wall is actively remodeled and reinforced around sites of pathogen invasion. Most plant microorganisms seek to break through cell walls to access intracellular nutrients. Thus, most pathogenic microorganisms interact with cell walls (Underwood, 2012; Franck et al., 2018). Studies have demonstrated that plants treated with cell wall biosynthesis inhibitors or cell wall mutants show a series of immune responses such as defense-related gene expression, ROS production, and defense-related hormone accumulation (Hamann, 2015). Not surprisingly, the RALF-CrRLK1L complex also participates in the invasion of pathogens. The ECD of CrRLK1L, which contains two MLDs, is homologous to a carbohydrate-binding domain. Plant cell walls are rich in hemicellulose, pectin, and other complex carbohydrates. Thus, CrRLK1L was hypothesized to bind and survey cell wall perturbations. However, CrRLK1L MLDs lack residues important for carbohydrate-rich ligand binding (Du et al., 2018). This characteristic pattern of the CrRLK1L domain was established early in plant evolution. Studies in both seed and non-seed plants suggest that there is functional conservation in the role of CrRLK1L as a cell wall sensor (Franck et al., 2018). THE1 was the first CrRLK1L member identified to monitor cell wall status and repress growth by inhibiting cellulose synthesis in the context of cell wall perturbations (Hématy et al., 2007; Merz et al., 2017; Van der Does et al., 2017). THE1 negatively regulates cell growth in the presence of cell wall perturbations. Furthermore, THE1 acts upstream of the plasma membrane-localized mechanosensitive Ca²⁺ channel MCA1 and the RLK FEI2 to perceive cell wall damage. THE1, FEI2, and MCA1 regulate CWI, further inducing the expression of host defense peptides that promote pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) (Engelsdorf et al., 2018). Additionally, THE1 recognizes cell wall modifications caused by fungal-induced necrosis and plays positive regulatory roles in the resistance of plants to the necrotrophic fungus *Botrytis cinerea* via the GEF4 pathway (Qu et al., 2017). RALF34 acts as a ligand of THE1, and the RALF34-THE1 pathway has been

reported to participate in the regulation of CWI, which is coordinated by RALF-FER signaling (Gonneau et al., 2018). Furthermore, RALF4, RALF19, and RALF34, as ligands of ANXBUPS, also play essential roles in maintaining CWI in tip-growing cells (Ge et al., 2017). Moreover, LLG2 and LLG3 have been identified to act as co-receptors of RALF4/19 and to maintain pollen tube CWI in cooperation with ANX1/2 and BUPS1/2 (Feng et al., 2019; Ge et al., 2019).

Cell wall-anchored LRXs, as RALF-binding proteins, consist of an N-terminal LRR domain and a C-terminal extension domain attached to the cell wall (Ringli, 2010; Draeger et al., 2015; Doblás et al., 2018). A recent crystallography study revealed that disulfide-bond-stabilized loops in AtRALF4_{folded} are a major determinant of LRX binding affinity, which is required to control pollen tube growth (Moussu et al., 2020). A previous study has reported that pH alterations modulate the interaction of RALF4_{folded} with LRX8 and LLGs, with LRX proteins consistently recognizing RALF4_{folded} with higher affinity (Moussu et al., 2020). No simultaneous interactions were observed among RALF4_{folded}, LRX proteins, and LLGs or CrRLK1Ls, suggesting that RALF peptides trigger two parallel, converging, but mechanistically distinct signaling pathways to modulate CWI (Moussu et al., 2020). Moreover, ANX1 and ANX2 negatively regulate PTI and effector-triggered immunity (ETI) by associating with the bacterial flg22 receptors FLS2/BAK1 and nucleotide-binding domain leucine-rich repeat (NLR) protein RPS2, respectively (Mang et al., 2017). Bacterial recognition by ANX1/2 regulates plant physiological processes, such as CWI and apoplastic pH changes, but this requires further investigation. Finally, the ECD of FER associates with pectin, which is a component of the cell wall, to protect cell walls from damage induced by salinity (Feng et al., 2018). Therefore, FER senses cell wall pectin polymers to monitor CWI and regulates the formation of the leaf epidermis cell shape (Li et al., 2015; Lin et al., 2018). As previously discussed, CWI influences pathogen recognition by plants, and pectin may be an immune signal that is sensed by FER. Furthermore, RALF-FER signaling coordinates immune receptor complex assembly and dynamics to respond to cell wall changes. However, whether FER or other CrRLK1L members connect the plasma membrane to the cell wall to coordinate receptor complex assembly and dynamics merits further investigation.

FER has been described to be a molecular component shared between pollen tube reception and powdery mildew infection, which involves communication between tip-growing hyphae and plant cell walls (Kessler et al., 2010). The RALF23-LLG2-FER complex has been reported to be involved in immune responses (Xiao et al., 2019), as has been demonstrated for the F-RALF-FER complex (Masachis et al., 2016). FER positively regulates CWI and polar growth. However, THE1, despite its functional homology with FER, appears to negatively regulate cell growth in the presence of cell wall perturbations. This also coincides with the roles of FER and THE1 in immune responses.

Compared with FER, the immune-related functions of ANX1/2 have been studied more intensely, revealing that ANX1/2 negatively regulates PTI and ETI by blocking the formation of receptor FLS2/BAK1 and destabilizing RPS2, respectively. By contrast, as reported by Stegmann et al. (2017), FER has positive roles in the

formation of PRR complexes that FER promotes the formation of FLS2 and BAK1 to respond to bacterial pathogens until sensing RALFs (e.g., RALF23). RALF23–FER also influences the phosphorylation of MYC2, which directly controls JA signaling. Additionally, apoplastic pH changes induced by FER seem to be involved in *F. oxysporum* parasitism. However, almost all plant RALFs can trigger such pH changes. The S1P protease may be a key factor regulating RALF–FER signaling in immune responses, such that mature RALF23 cleaved by S1P suppresses the PTI response, whereas non-S1P-cleaved RALFs promote the PTI response. Thus, the relationship among RALF23–FER, apoplastic pH, and S1P proteases needs to be further studied with the aim of developing a context-dependent view. FER also regulates immune responses in a developmental stage-dependent manner. For example, FER mutant seedlings were resistant to *Pseudomonas syringae* pv. tomato DC3000 (*Pst* DC3000) growth (Keinath et al., 2010), whereas 4- to 5-week-old FER mutants were hypersensitive to this pathogen (Stegmann et al., 2017; Guo et al., 2018). Complicating matters, RALF peptides have different or even opposite roles toward FER in a context-dependent manner. For example, RALF1 and RALF23 activate FER signaling during root growth, whereas RALF23 represses FER signaling during PTI responses. Thus, the mechanisms of CrRLK1Ls' malectin-like domain and LRXs' cell wall fusion domain in sensing different RALFs and/or cell wall perturbations to modulate various signaling endpoints remain mostly enigmatic.

ROS, Ca²⁺, NO, and mRNA Local Translation Modulate Polar Cell Growth by the RALF–FER Network

Once plant pathogens approach the host plant, cell wall-sensing mechanisms are activated and PTI or ETI responses are triggered. PTI responses are usually accompanied by MAPK signaling, ROS bursts, transcriptional activation of defense-related genes, and accumulation of callose (Nünberger et al., 2004), whereas the ETI response is a more rapid and robust form of the PTI response that is typically associated with a localized cell death reaction known as the hypersensitive response (Jones and Dangl, 2006). During these processes, plant cells tightly control the cell wall composition and modifications. They also modulate their signaling components with spatial and temporal specificity. The RALF–FER pathway is involved in the manipulation of its signaling components in terms of this context specificity to regulate polar cell growth and immune responses. FER plays an essential role in ROS production. FER regulates root hair polar growth by positively regulating auxin-triggered ROS production. FER also positively regulates flg22-induced ROS production during immune responses, whereas FER negatively regulates ROS levels in guard cells in relation to ABA (Yu et al., 2012). ROS are ubiquitous and can be divided into two types based on their location, namely apoplastic ROS and intracellular ROS (Qi et al., 2017). Apoplastic ROS have more important roles in plant interactions with pathogens, which are primarily regulated by NADPH oxidases, cell wall peroxidases, or amine oxidases (Kadota et al., 2015). NADPH oxidases, also known as respiratory burst oxidase homologs (RBOHs), consist of ten members from RBOHA to RBOHJ (Baxter et al., 2014). Among these, RBOHC, RBOHD, RBOHF, RBOHH, and RBOHJ have been found to be regulated by FER and related proteins (Franck et al., 2018). The FER–LLG1–Rop-guanine nucleotide exchange factor

(RopGEF)–RAC/ROP complex recruits and positively regulates RBOHC-dependent ROS production (Duan et al., 2010, 2014; Li et al., 2015). THE1 acts upstream of RBOHD and RBOHF in response to cell wall damage, triggering ROS production and immune responses (Sagi and Fluhr, 2006; Ogasawara et al., 2008; Denness et al., 2011). ANX1 and ANX2 modulate RBOHH and RBOHJ, maintain ROS production, and regulate CWI during pollen tube growth (Boisson-Dernier et al., 2013). Thus, the RALF–CrRLK1L complex uses ROS as important signaling molecules, affecting polar cell growth and stress responses. Unfortunately, how the RALF–CrRLK1L complex regulates ROS production remains unknown. RAC and Rho guanosine triphosphatases of plants (ROPs) may act as potential links during this process. RAC/ROP (referred to collectively as ROP) activates cellular responses by switching the inactive guanosine diphosphate-bound state to the active GRP-bound state. ROP is a conserved molecule that regulates cell polarity (Fu et al., 2001; Molendijk et al., 2001). ROP functions as an essential downstream factor during FER-regulated auxin and ABA signaling by regulating ROS levels in plants (see [RALF–FER Regulates Hormone Signaling Crosstalk](#) for more details). ROP2 has been reported to interact with the ECD of RBOHD, which is likely to regulate ROS levels (Li et al., 2015). Recently, PBL13 (a homolog of RIPK) has been reported to interact with RBOHD to regulate NADPH oxidase-induced ROS production (Lee et al., 2020). Thus, further studies are needed to determine whether CrRLK1L/FER uses the ROP (e.g., ROP2) pathway to directly modulate ROS production, thus affecting cell polar growth and immune responses.

The Ca²⁺ signature is also critical for RALF–CrRLK1L-mediated polar cell growth, and it always works with the ROS synergism. For example, synergid-derived ROS mediates pollen tube rupture in a Ca²⁺-dependent manner (Duan et al., 2014) in a process that involves FER, LER, and NORTIA (NTA). NTA is a member of the MLO family and contains a calmodulin domain for binding Ca²⁺. However, the gene or genes encoding Ca²⁺ channels that are involved in RALF–CrRLK1L signaling have not yet been identified.

Recently, Zhu et al. (2020a) found that polar-localized RALF1–FER interacts with eIF4E1 (an early translation factor) and forms a complex with the translation machinery in the tips of growing root hairs. RALF1, FER and eIF4E1 show polar localization in root hairs, providing spatial control of localized protein synthesis and the determination of polarized cell growth (Zhu et al., 2020a). Phosphorylated eIF4E1 increases mRNA affinity, and thus, regulates the translation of mRNAs to affect the synthesis of several polar cell growth-related proteins, such as ROP2, RIPK, and RSL4, in a spatiotemporal manner. Both ROPs and ROS generated by ROPs are known to regulate myriad biological processes, such as polarized cell growth (Zhu et al., 2020b). In animals, plants, and fungi, there are distinct examples of cells that exhibit polarized growth, including growth of neuronal axons, pollen tubes, root hairs, and fungal hyphae (Drubin and Nelson, 1996; Hepler et al., 2001). During the rapid uniaxial extension of cells, rapid protein synthesis (and cell wall components for plants) and accumulation with spatial precision in the tip growth region are indispensable.

Recently, FER was reported to modulate nitric oxide (NO) levels, which resulted in the nitrosation of cysteines in the

chemoattractant LURE1 and XIUQIU peptides, thereby blocking their secretion and interaction with their RLK receptors, respectively, and in turn suppressing pollen tube attraction (Duan et al., 2020). Thus, ROS, Ca²⁺, NO, and mRNA local translation are all involved in the regulation of polarized cell growth by RALF-FER. However, it is not clear whether these processes are also involved in the invasion of pathogens (e.g., the polarized growth of fungal hyphae cells into plant cell walls). We assume that the RALF-FER pathway spatiotemporally controls ROS, Ca²⁺, and NO levels and mRNA local translation, which leads to the rapid production and accumulation of defense-associated components near the region of pathogen invasion. Additionally, this process is indispensable for activating appropriate immune responses, such as changes in cell wall composition and modifications. Indeed, during pollen tube reception, polar localization of FER is necessary for NTA to have polarized accumulation and be redistributed at the filiform apparatus, enabling pollen tubes to penetrate synergid cells.

RALF-FER Regulates Hormone Signaling Crosstalk

RALF-FER signaling has multiple roles in crosstalk with several hormone pathways, regulating key processes such as plant growth and immunity. FER mediates RALF signaling interfaced with auxin (Duan et al., 2010; Li et al., 2015; Barbez et al., 2017), brassinosteroid (BR) (Guo et al., 2009; Deslauriers and Larsen, 2010), ethylene (Mao et al., 2015), ABA (Yu et al., 2012; Chen et al., 2016), and JA signaling (Guo et al., 2018). Liao et al. (2017) have reviewed how FER mediates crosstalk with different hormones to regulate cell growth and stress responses. Here, we concentrate on the latest advances in FER-mediated plant immune responses. Pathogens secrete a large number of effectors and phytotoxins during infection, and among these, coronatine (COR) originates from *Pst* DC3000 and mimics JA-isoleucine, thus promoting JA signaling and leading to host disease susceptibility (Xin and He, 2013). FER offsets excessive JA signaling by phosphorylating and destabilizing MYC2, which plays a key role in JA signaling. However, RALF23 mediates JA signaling by stabilizing MYC2 via FER, which negatively contributes to plant immune responses to bacterial pathogens (Guo et al., 2018). Unfortunately, it is still unknown how membrane-localized FER interacts with and phosphorylates MYC2 in the nucleus and how RALF23 inhibits the phosphorylation of MYC2 by FER.

FER is a key modulator of ethylene responsiveness in *Arabidopsis* (Deslauriers and Larsen, 2010) and negatively modulates the production of S-adenosylmethionine (SAM) via SAM1 and SAM2, which partially block the ethylene biosynthesis pathway (Mao et al., 2015). Besides regulating plant growth, ethylene signaling also modulates plant innate immunity, which is regulated by PAMP signaling, Ca²⁺ signaling, ROS production, NO signaling and MAPK signaling (Vidhyasekaran, 2015). In particular, ethylene signaling was found to contribute to ROS production triggered by flg22 in *Arabidopsis*, as the accumulation of the FLS2 receptor relies on ethylene signaling (Mersmann et al., 2010), suggesting that RALF-FER signaling participates in ROS production and ethylene signaling to affect immune responses.

Stomata offer entry points into plant tissues for plant pathogens (Mersmann et al., 2010). Coincidentally, ABA signaling is a key

modulator of stomatal closure. The accumulation of ABA in guard cells induces stomatal closure under biotic or abiotic stresses (Assmann, 2003), which reduces entry for plant pathogens (Melotto et al., 2008). The crosstalk of the RALF-FER pathway with ABA signaling, whereby FER mediates RALF1 and interacts with the downstream partners of GEF1/4/10-ROP11-ABI2, further inhibits ABA signaling, whereas ABI2 interacts with FER and dephosphorylates FER to provide negative feedback on the FER-GEF1/4/10-ROP11 cascade (Yu et al., 2012; Chen et al., 2016). Additionally, FER regulates salt stress responses via directly interacting with AGB1, the β subunit of a G-protein that positively regulates ABA-mediated regulation of stomatal movements. *At*RALF1 inhibits stomatal opening and promotes stomatal closure (Yu and Assmann, 2018). Taken together, the RALF-FER pathway may interact with ABA signaling to modulate abiotic stress responses and plant growth and may further regulate immune responses via stomatal closure.

Hormone signaling crosstalk also occurs in other plant species. *Md*FERL6 and *Md*FERL1, two FER-like receptors in apple, interact with *Md*SAMS. In apples, SAMs suppress ethylene production, which delays apple fruit ripening (Jia et al., 2017b). *S*FERL1, a FER-like receptor in tomato, also modulates ripening via ethylene signaling (Jia et al., 2017b). Meanwhile, *Fa*MRLK47, a FER-like receptor in strawberry, interacts with *Fa*ABI1, a negative regulator of ABA signaling, thus modulating strawberry ripening and fruit quality (Jia et al., 2017a).

Downstream Immunity-Related Factors in the RALF-FER Pathway

FER mediates RALF signaling from membrane to nucleus, recruiting a series of downstream partner proteins. RIPK, a plasma membrane-associated RLCK involved in *P. syringae* invasion (Liu et al., 2011), can directly interact with FER. FER phosphorylates RIPK in a RALF1-dependent manner, leading to apoplastic alkalization, which cooperatively suppresses primary root growth (Du et al., 2016). Additionally, RIPK has been shown to phosphorylate RPM1-INTERACTING PROTEIN 4 (RIN4), which perceives *P. syringae* effectors AvrB and AvrRpm1. Furthermore, phosphorylated RIN4 is sensed by the NLR protein RPM1 (Mackey et al., 2002), and the degraded RIN4 perceives AvrRpt2, which is sensed by another NLR protein, RPS2, thus triggering immune responses (Axtell and Staskawicz, 2003; Mackey et al., 2003). It may be productive to determine whether the RALF-FER-RIPK pathway regulates plant immunity via RIN4 and RPM1/RPS2. Notably, ANX1 interacts with RPM1 and RPS2, thus negatively regulating immunity (Mang et al., 2017).

Increasing evidence suggests that RALF1-FER signaling plays dual roles in energy metabolism and immunity by recruiting different functional proteins. Cytosolic glyceraldehyde-3-phosphate dehydrogenase (GAPDH, GAPC1, and GAPC2) was identified to be involved in FER signaling by modulating energy metabolism (Yang et al., 2015). Additionally, ATL6, an E3 ubiquitin ligase, directly interacts with FER, destabilizing 14-3-3 proteins, which modulate the C/N balance and signaling (Xu et al., 2019). FER-like receptors 1 and 2 (FLR1 and FLR2) from rice are also involved in plant height, branching and tillering as

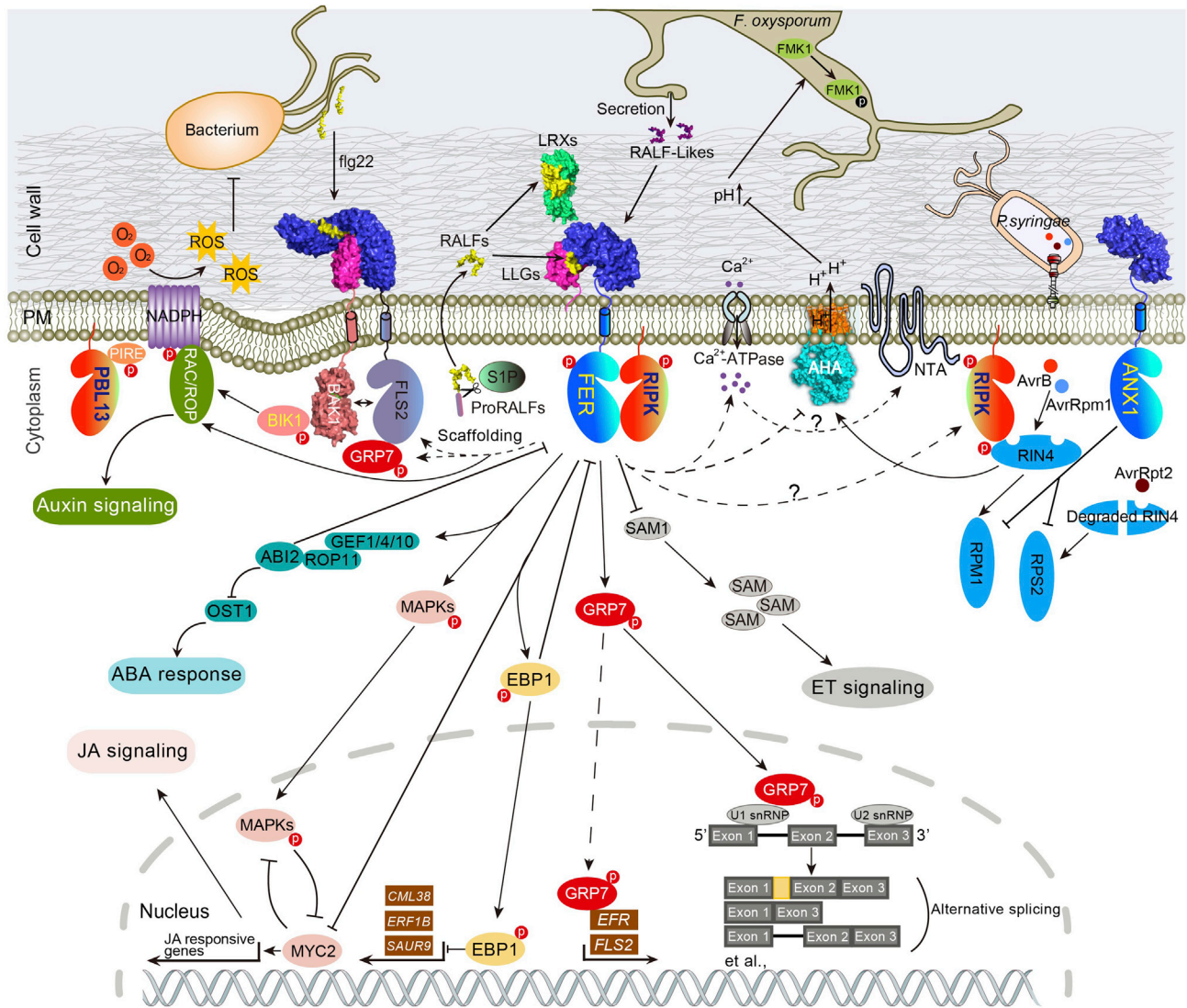


Figure 1. Network of RALF-FER Signaling in Plant Immunity.

FER and LLGs respond to RALF23, which is cleaved by S1P, and modulate plant immunity, whereas LRXs mediate RALF signaling to maintain cell growth. RALF23-FER-LLGs destabilize the formation of the FLS2-BAK1 complex. *Fusarium oxysporum* secretes F-RALF peptides that hijack the RALF-FER pathway, leading to the phosphorylation of *F. oxysporum* MAPK FMK1 and potentially facilitating host infection, together with the suppression of *PDF1.2* expression. FER modulates auxin, abscisic acid (ABA), ethylene (ET), Ca²⁺, reactive oxygen species (ROS), MAPK phosphorylation, and pH to affect cell growth and immunity. FER interacts with and phosphorylates RIPK, modulating AHA2 activity. RIPK phosphorylates RIN4, which is detected by RPM1 and RPS2, triggering immune responses. ANX1 also inhibits ETI responses by inhibiting RPM1 and RPS2. PBL13, a homolog of RIPK, interacts with RBOHD to regulate NADPH oxidase-induced ROS production. FER mediates RALF1-induced mRNA alternative splicing via GRP7, which also interacts with FLS2, EFR, and their transcripts. Positive regulatory actions are indicated by arrows, negative regulatory actions are indicated by bars, physical interactions between different proteins are indicated by solid lines and potential physical interactions are indicated by dashedotted lines. Question marks denote mechanisms that remain to be empirically demonstrated.

well as male gametophyte development (Li et al., 2016a) and negatively regulate immunity against rice blast. FLR2 negatively modulates fungus-triggered ROS associated with rice blast. The mutation of *FLR2* and *FLR11* increases disease resistance against rice blast without reducing the growth of rice plants (Yang et al., 2020).

The mechanisms by which RALF1-FER signaling controls gene expression are being revealed. Li et al. (2018) found that RALF1-FER signaling uses a “shortcut” mechanism to directly regulate gene expression. RALF-FER signaling promotes the

mRNA translation of *EBP1*. FER directly phosphorylates the cytoplasmic nuclear shuttle protein EBP1, leading to the accumulation of EBP1 in the nucleus and the expression of binding genes (Li et al., 2018). Conversely, EBP1 has feedback along the RALF1-FER pathway via transcription-translation feedback loops to regulate cell growth. Interestingly, EBP1 is also involved in the regulation of plant immunity, as demonstrated by RALF1 more severely impairing flg22-triggered ROS burst in *ebp1* mutant plants compared with wild-type plants. As discussed above, FER interacts with the transcription factor MYC2 to modulate JA signaling. At the RNA level, besides its role in

the RALF1–FER–eIF4E module, which is involved in mRNA translation, FER also directly interacts with and phosphorylates GRP7, thus enhancing its mRNA-binding ability in a RALF1-dependent manner and regulating mRNA alternative splicing to affect plant stress responses (Wang et al., 2020b). FER regulates flowering time via the mRNA alternative splicing of key flowering genes, such as FLOWERING LOCUS C (FLC) and its homolog MADS AFFECTING FLOWERING (MAF) (Wang et al., 2020a). Notably, GRP7 is an essential component of the FLS2-EFR complex. *P. syringae* type III-secreted effector HopU1 hijacks GRP7, decreasing the expression of FLS2 and EFR, thereby suppressing ROS burst (Nicaise et al., 2013). It is reasonable to assume that the RALF1–FER complex modulates both cell growth and immune responses partly via GRP7. Meanwhile, there are many other downstream signaling partners of the RALF–FER pathway that need to be explored, which might benefit from the elucidation of the RALF–FER cascade.

Prospects of RALF–FER Signaling

Taken together, these findings indicate that CrRLK1L originated in early non-seed plants, where it was probably involved in monitoring CWI and modulating plant cell growth and stress responses under environmental changes. Following the discovery of FER receptor kinase, FER has become the most widely studied member of the CrRLK1L family. FER has recently emerged as a potential target for crop improvement and protection because of its versatile, fundamental, and tissue-specific roles in plant growth and development, crop yield control, multiple biotic stress and abiotic stress responses, energy production, and RNA metabolism (Figure 1). Despite recent advances in understanding the functions and molecular mechanisms of the RALF–CrRLK1L network, many questions remain unanswered.

The number of non-plant genomes that encode RALF-like peptides is largely unknown, and the evolutionary history of RALF peptides is also unclear. It is likely that non-plant species acquired RALF peptide-encoding genes through horizontal gene transfer from host plants during their long-term coevolution. The detailed mechanisms through which CrRLK1Ls, LLGs, and LRXs combine and sense different RALF peptides to respond to distinct environmental changes (e.g., pH, ROS and pathogen invasion) are unknown. More importantly, how different RALF peptides activate (e.g., RALF1 or RALF23 for FER in cell growth regulation) and suppress (e.g., RALF23 for FER in immunity) CrRLK1L signaling in a cell type-specific manner remains enigmatic. Furthermore, RALF–FER signaling can have opposite effects in different cell types. For example, RALF1–FER inhibits primary root cell growth but promotes root hair cell growth. Further studies of this mechanism may provide fruitful means to maximize yields and minimize agricultural losses. RALF–FER signaling contributes to root elongation, flowering and reproduction, which is an appropriate entry point to increase crop yields. Furthermore, RALF–FER signaling seems to be a common strategy for the invasion of microorganisms. Therefore, understanding the features of RALF–FER/CrRLK1L signaling is an effective and meaningful way to improve agronomically important crop traits.

FUNDING

Research on this subject in the authors' laboratory is supported by grants from the National Natural Science Foundation of China (NSFC-31871396,

31571444, 31400232) and the Young Elite Scientist Sponsorship Program by CAST (YESS20160001).

ACKNOWLEDGMENTS

We thank the past and present members of the Yu Laboratory for their contributions in establishing the RALF–FER network. We also apologize to colleagues whose work could not be cited due to the limited space of this review. No conflicts of interest are declared.

Received: April 20, 2020

Revised: June 8, 2020

Accepted: June 9, 2020

Published: June 11, 2020

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