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Malectin/Malectin-like domain-containing proteins: A repertoire of cell surface molecules with broad functional potential

He Yang [a,b], Dong Wang [a,b,c], Li Guo [b,d], Huairong Pan [b,e], Robert Yvon [a,b], Scott Garman [a,b], Hen-Ming Wu [a,b], Alice Y. Cheung [a,b,c,*]

[a] Department of Biochemistry and Molecular Biology, University of Massachusetts, USA
[b] Molecular and Cellular Biology Program, University of Massachusetts, USA
[c] Plant Biology Graduate Program, University of Massachusetts, Amherst, MA 01003, USA
[d] Faculty of Electronic and Information Engineering, Xi'an Jiaotong University, Xi'an 710049, China
[e] College of Biology, Hunan University, Changsha 410082, China

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ABSTRACT

Cell walls are at the front line of interactions between walled-organisms and their environment. They support cell expansion, ensure cell integrity and, for multicellular organisms such as plants, they provide cell adherence, support cell shape morphogenesis and mediate cell–cell communication. Wall-sensing, detecting perturbations in the wall and signaling the cell to respond accordingly, is crucial for growth and survival. In recent years, plant signaling research has suggested that a large family of receptor-like kinases (RLKs) could function as wall sensors partly because their extracellular domains show homology with malectin, a diglucose binding protein from the endoplasmic reticulum of animal cells. Studies of several malectin/malectin-like (M/ML) domain-containing RLKs (M/MLD-RLKs) from the model plant *Arabidopsis thaliana* have revealed an impressive array of biological roles, controlling growth, reproduction and stress responses, processes that in various ways rely on or affect the cell wall. Malectin homologous sequences are widespread across biological kingdoms, but plants have uniquely evolved a highly expanded family of proteins with ML domains embedded within various protein contexts. Here, we present an overview on proteins with malectin homologous sequences in different kingdoms, discuss the chromosomal organization of Arabidopsis M/MLD-RLKs and the phylogenetic relationship between these proteins from several model and crop species. We also discuss briefly the molecular networks that enable the diverse biological roles served by M/MLD-RLKs studied thus far.

Introduction

Malectins are conserved disaccharide-binding proteins of about 190 amino acid residues found in the lumen of the endoplasmic reticulum (ER) of animal cells (Schallus et al., 2008, Schallus et al., 2010). They associate with the oligosaccharyltransferase complex and bind to the diglucosylated intermediate of N-linked glycans early in the secretory pathway and target misfolded glycoproteins to degradation, thus playing an important role in protein quality control (Muller et al., 2010; Galli et al., 2011; Takeda et al., 2014; Tannous et al., 2014). *In vitro*, malectins bind diglucose, such as maltose (glucose- α-1,4 glucose) and nigerose (glucose-α-1,3 glucose), the latter its potential native ligand in the ER (Schallus et al., 2008). Plants have evolved exceptionally large families of receptor-like kinases (RLKs) and they have diversified into several distinct clades (Shiu and Bleecker, 2003; Shiu et al., 2004). The discovery of malectin revealed a group of plant RLKs as having malectin homologous regions in their extracellular domains (ECDs). As single-span transmembrane proteins, the ECDs of RLKs decorate the cell membrane-cell wall interface. The exterior of the cell is often considered topologically equivalent to the ER lumen in that membrane proteins facing the ER lumen are exposed to extracellular environment (Cooper and Hausman, 2004), which, in walled cells, are enriched in complex carbohydrates. These properties and the functions of the first two studied Malectin/Malectin-like (M/ML) domain RLKs (M/MLD-RLKs), THESEUS1 (THE1) and FERONIA (FER), from the model plant *Arabidopsis thaliana* (Hematy et al., 2007; Escobar-Restrepo et al., 2007),

* Corresponding author.
E-mail addresses: Yangheharold@163.com (H. Yang), Dongw@biochem.umass.edu (D. Wang), guo_li@xjtu.edu.cn (L. Guo), hrpan@hnu.edu.cn (H. Pan), Ryvon@umass.edu (R. Yvon), garman@biochem.umass.edu (S. Garman), hmwu@biochem.umass.edu (H.-M. Wu), acheung@biochem.umass.edu (A.Y. Cheung).

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provoked widespread speculations that the ML sequences might interact with cell wall polysaccharides and that these proteins might serve as wall sensors (Hematy and Hofte, 2008; Cheung and Wu, 2011; Boisson-Dernier et al., 2011). Studies since then have demonstrated that some M/MLD-RLKs are crucial for plant growth and survival and regulate diverse processes, including the capacity to mediate cell wall-related phenomena. Given the intense interest on M/MLD-RLKs in recent years, we undertake a discussion here regarding the distribution of malectin homologous sequences from bacteria to higher plants and explore how knowledge from carbohydrate binding modules (CBMs) in bacterial proteins and M/ML domain-containing proteins in other species might inform about the evolution of plant M/MLD-RLKs. We also examine the chromosomal organization of a subset of M/MLD-RLKs from Arabidopsis and the phylogeny of related protein families from several model and crop plant species. The functions of some of these M/MLD-RLKs and the molecular interactions that they engage in are discussed briefly to provide some biological contexts. We refer readers to recent reviews for deeper discussions (Galindo-Trigo et al., 2016; Frank et al., 2018; Doblas et al., 2018)

Widespread presence of malectin homologous sequences and their expansion in plants

The malectin globular core is structurally most similar to several non-catalytic CBMs present in bacterium-secreted glycolytic enzymes found in the plant cell wall (Schallus et al., 2008; Gilbert et al., 2013; Duan et al., 2016). CBMs interact with non-substrate carbohydrate moieties from glycan or short oligosaccharide chains in the cell wall. This might augment the proximity between the catalytic domain of the enzymes and their substrate carbohydrates and potentiate their glycolytic activity (Crouch et al., 2016). In animal cells the binding of malectin to diglucosylated glycans early in the secretory pathway might recruit other proteins for glycol-modification or protein quality control (Tannous et al., 2014). It is possible that the carbohydrate-binding propensity in malectins and ML sequences, whether acting alone or as part of a larger protein, could facilitate processes occurring in a context involving carbohydrates.

Malectin homologous sequences are widespread throughout biological kingdoms (Fig. 1A). The Pfam database for protein families (http://pfam.xfam.org) (Mistry et al., 2021) identifies numerous malectin homologous sequences and classifies them into malectin (PF11721) and ML (PF12819) subfamilies. Both families are grouped under the large Galactose-binding domain-like superfamily (CL0202) containing ~ 70 families of proteins with beta sandwich domains and a jelly roll topology [https://pfam.xfam.org/clan/CL0202]. To avoid confusion with animal malectins, we shall use "malectin domains" to designate the PF11721 domains from hereon. Relative to malectin domains, MLs are generally longer and more variable in lengths, some have

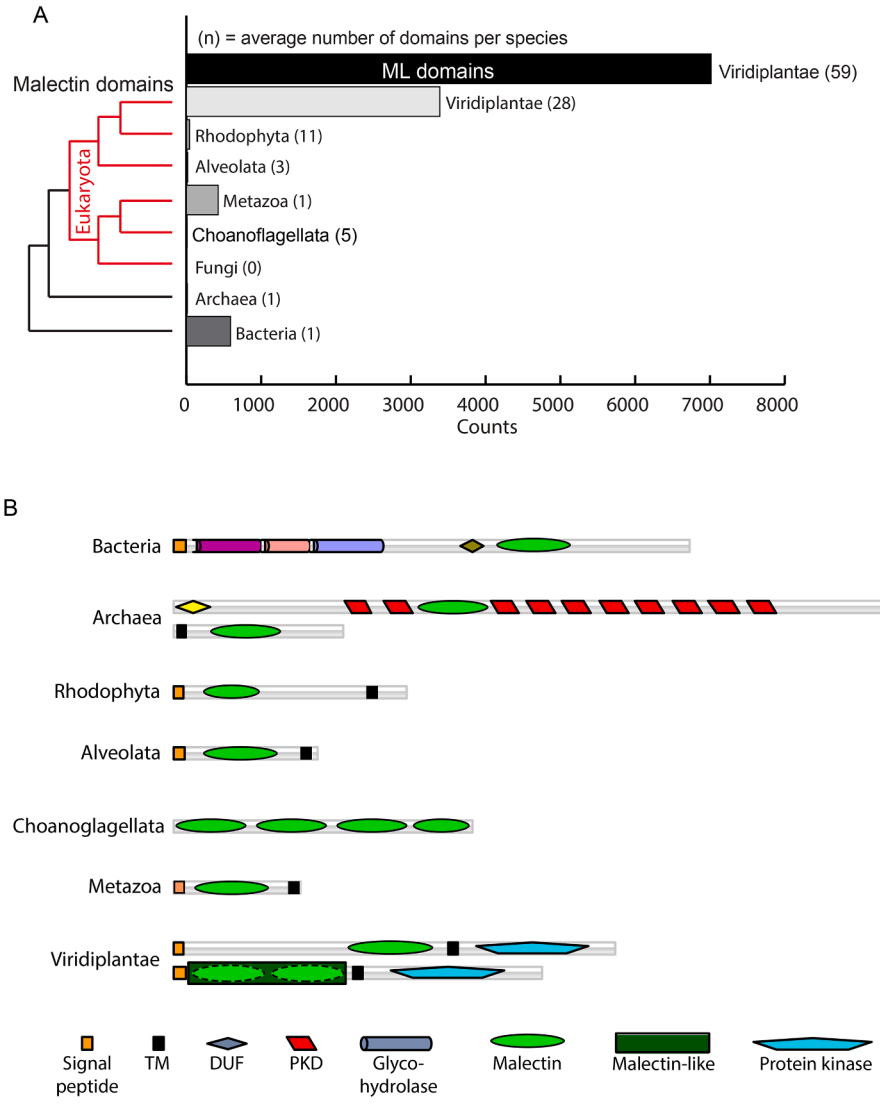

Fig. 1. Malectin domains across kingdoms. (A) Distribution of malectin domains across various kingdoms, including unicellular and multicellular protists (*Rhodophyta*, *Alveolata*, and *Choanoflagellata*, the closest living protist relatives of the animals [Lang et al., 2002; Carr et al., 2008]), but not in fungi. Tandem malectin domains (malectin-like, ML) are only identified in the plants. X-axis indicates total number of Malectin or ML domains identified by Pfam. Average number of domains per species (total domain identified/number of species within each kingdom) are shown in parentheses. (B) Most prevalent protein domain architecture in each of the kingdoms. TM, transmembrane; DUF, domain of unknown function; PKD, polycystic kidney disease domain.

two complete malectin homologous sequences (Fig. 1B). More than 5000 malectin domains have been identified (Fig. 1A) with almost 3400 from *Viridiplantae* (land plants), distributing across 121 species analyzed whereas on the average only one to eleven malectin domains are found in each of the other species examined. Fungi, evolutionarily close to animals, however lack malectin homologous sequences. The ML family has emerged uniquely in plants, became highly expanded, averaging ~ 60 per species (Fig. 1A), and diversified into several distinct clades (Fig. 2A). The expansion of malectin homologous sequences in plants is remarkable and, like the plant RLK superfamily (Shiu et al., 2004), could have evolved to generate expanded capacity to meet the functional needs of land plants, sessile but in an always-changing environment.

The malectin domains found in bacteria, animals and plants have distinct characteristics (Fig. 1B). An N-terminal signal peptide targets animal malectins to the secretory pathway, and a short C-terminal transmembrane helix tethers its carbohydrate-binding core to the ER membrane (Schallus et al., 2008). In bacteria, malectin domains are usually within glycosyl hydrolases. In prokaryotic Archaea and other eukaryotic taxonomic groups such as the *Rhodophyta*, *Alveolata* and *Choanoflagellate*, malectin domains are embedded in different protein contexts. Most plant malectin homologous sequences are in the ECDs of protein kinases. These differences suggest that organisms in these taxa had experienced lineage-specific divergence in malectin homologous sequence-containing proteins. Association of malectin homologous sequences with diverse protein contexts could be a result of different functional adaptations. Animal malectins function in a relatively simple carbohydrate environment and interact primarily with intermediates of glycoproteins undergoing modification and quality control checkpoints in the ER (Schallus et al., 2008; Tannous et al., 2014). The malectin domains in bacterial proteins might function as CBMs of cell wall hydrolases to potentiate their catalytic activities (Gilbert et al., 2013; Duan et al., 2016; Crouch et al., 2016). When linked with domains that mediate protein–protein interactions, such as Kelch motifs (Adams et al., 2000) (Fig. 1B) and leucine-rich repeats (LRR) (Wu et al., 2016) (Fig. 2B), the malectin homologous sequences, perhaps via interaction with the cell wall, might provide a scaffold function thereby stabilizing the LRR or Kelch motif-mediated interactions with other cell surface molecules. Tandem malectin domains in plant proteins might augment the affinity for a specific target or each might interact with distinct targets, improving specificity or extending their functional range.

With the widespread presence of malectin homologous sequences across the biological kingdoms, it is interesting to consider how they might have arisen and what drove their diversification. Given the various domain compositions, the most plausible scenario could be that a single domain malectin protein had existed as a common progenitor. This precursor protein might have taken up residence in the ER where the carbohydrate environment is simple, leading to proliferation of animal proteins with just a malectin core for carbohydrate-binding. On the other hand, the plant cell wall is made up of complex carbohydrates, and the microbiomes in the mammalian gut or in the rhizosphere are also highly complex. These could have driven the diversification of malectin homologous sequence-containing proteins in walled-organisms. Partnering malectin domains with glycolytic enzymes in bacteria could have provided an advantage to facilitate their cell wall degradation activities and beneficial to survival and propagation. The sheer number of RLKs with malectin homologous sequences in plants suggests the partnership between these extracellular domains and protein kinases was unlikely to be coincidental but had evolved for functional adaptations.

The Arabidopsis malectin and malectin-like protein family: Phylogeny and functions

A BLASTp search of the malectin/ML domain sequences against the *A. thaliana* proteome identified 90 family members. These proteins fall into two major monophyletic groups, distinguished by one having a single malectin domain and the other having tandem malectin domains (Fig. 2A,B). For easier referral, we shall refer to these single or tandem malectin domain proteins as Malectin and Malectin-like Domain (M/MLD) proteins, respectively. The MD proteins are all RLKs and include several Leucine-rich repeats (LRR)-containing BRASSINOSTEROID (BR)-SIGNALING KINASE (BSK) 3-INTERACTING RLKs (BSR) (Xu et al., 2013). The MLD proteins are further divided into three subclades. Based on the canonical protein domain architecture in each of these clades, we name them (i) the MLD–RECEPTOR-LIKE PROTEIN (Wang et al., 2008, 2010) (MLD–RLP) clade, (ii) a RLK-containing clade (MLD–RLK) clade with FERONIA (FER) and THESEUS1 (THE1) receptor kinases as its first functionally examined members (Escobar-Restrepo et al., 2007; Hematy et al., 2007), and (iii) a MLD–LRR–RLK clade with the MLD- and LRR domain-containing RLK IMPAIRED OOMYCETE SUSCEPTIBILITY 1 (IOS1) (Hok et al., 2011) as its first functionally studied member. Almost all M/MLD proteins are predicted to have a signal peptide (Fig. 2B) and therefore decorate the cell wall-cell membrane interface. Little is known about the MLD-RLPs, but lacking a substantial cytoplasmic domain (Fig. 2B), they might function in partnership with other RLKs to mediate downstream signaling (Jeong et al., 1999; Lee et al., 2012). Two proteins, the cytoplasmic Malectin Domain Kinesin1 and 2 [MDKIN1, 2] (Galindo-Trigo et al., 2020b), constitute an outgroup among M/MLD proteins. Why a protein domain that has largely evolved to be in the extracellular milieu or the ER lumen had become cytoplasmic and associated with a cytoskeleton protein is intriguing. MDKIN2 belongs to an angiosperm-specific clade while MDKIN1 is present in angiosperms, gymnosperms, *Selaginella selmo*, *Physcomitrella patens* and *Marchantia polymorpha*. MDKIN2 has been localized to the phragmoplast midzone during cell division where cell wall materials are being laid down while the adjacent cell membrane is not yet fully defined (Smertenko, 2018). How this characteristic might contribute to its function, characterized as non-essential but important for pollen and seed development (Galindo-Trigo et al., 2020b), will be interesting to explore.

The Arabidopsis M/MLD-RLKs

The M/MLD-RLKs refer collectively to the LRR–MD–RLKs, the FER/THE1 family of MLD–RLKs, and the MLD–LRR–RLKs (Fig. 2B).

The LRR–MD–RLK clade. The LRR–MD–RLKs have a LRR domain followed by a single malectin domain (Fig. 2B). These malectin domains share the highest identity with *Xenopus* malectin than those in the other clades. Several LRR–MD–RLK genes, some of which are *BSRs*, are transcriptionally responsive to BR (Xu et al., 2013) and could be involved in the signaling pathways regulated by this hormone. There are considerable cross-talks between BR and immunity signaling (Lozano-Diran and Zipfel, 2014). The expression of several *BSRs*, including *RECEPTOR-LIKE KINASE IN FLOWERS 1* (*RKF1*), *BSR430*, *BSR840/LIK1* and *At1G56120*, was triggered during immunity response (Qutob et al., 2006, Hok et al., 2011). Interestingly, BSR840/LIK1 interacts with the LysM motif-containing chitin receptor CERK1 and loss-of-LIK1 resulted in defective jasmonic acid and ethylene signaling; mutant plants were also more resistant to bacterial and fungal infections (Le et al., 2014). These M/MLD-RLKs might bridge BR and immunity signaling cross-talks.

The MLD–RLK clade. This comprises a family of 17 related RLKs (Fig. 2A) that is originally referred to as the CrRLK1-L RLKs (for *Catharanthus roseus* RLK1-like RLKs), after the founding member (Schulze-Muth et al., 1996), for which no further studies have been reported. To date, the biological roles of all but one (At5g24010) of these MLD-RLKs have been examined, some in detail. Together they regulate diverse processes throughout the plant life cycle, controlling growth and mediating survival (Galindo-Trigo et al., 2016; Doblas et al., 2018; Frank et al., 2018). The fact that achieving this level of functional revelation has taken just over a decade is quite remarkable. It also suggests that ML domains, with tandem malectin homologous regions, must have provided an important functional advantage, rendering phenotypic manifestation from their loss readily notable.

The first functionally studied members of this clade, FER and THE1,

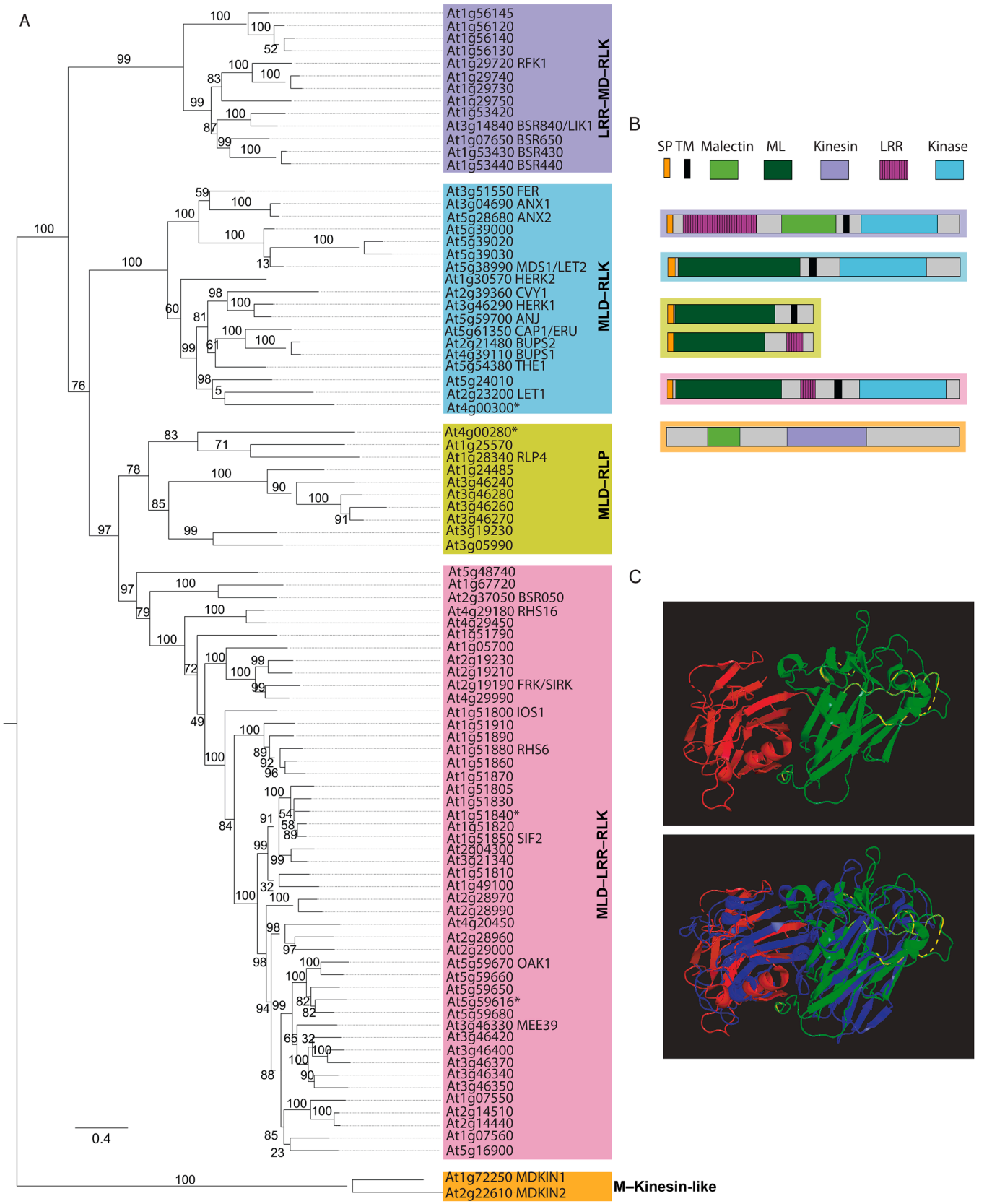

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Fig. 2. M/MLD proteins in Arabidopsis. (A) Mid-point rooted phylogenetic tree of M/MLD family proteins. These proteins were first identified by searching the Arabidopsis proteome with Pfam profile (PF11721 and PF12819) using HMMER (http://hmmer.org/). Retrieved proteins were used as blastp queries against the *A. thaliana* proteome (E value < 1e-5). Protein domain analysis was used to verify the presence of single Malectin domains (MD) and tandem Malectin domains (MLD). Four proteins, encoded by *At4g00300, At4g00280, At1g51840, At5g59616* and indicated by asterisks, either have low supporting values or have truncated ML sequences. They were not included in plant M/MLD-RLKs phylogenetic analysis. Domain organization of M/MLD family proteins. (B) The most prevalent organization for each clade seen in (A) is shown in corresponding color blocks here. MLD–RLPs lack a cytoplasmic domain and are further divided into two classes, some having a predicted transmembrane helix others LRR domains of various lengths. (C) Structural alignment of the MLD in FER with animal malectin. (Top) The FER ECD structure (pbd 6A5B, from Xiao et al., 2019) with the tandem malectin domains MalA and MalB are shown in red and green, respectively. (Bottom) The Xenopus Malectin structure [pdb 2JWP, from Schallus et al., 2008] is shown in blue and superimposed onto MalA and MalB. Comparable superimposition was shown with the structurally determined MLDs of ANXs (Moussu et al., 2018) and could be achieved in structures of other MLD–RLKs predicted by computational modeling (not shown). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

belong to two sub-clades (Fig. 2A). FER (named after the Etruscan goddess of fertility FERONIA) was identified as a key regulator of reproduction success (Escobar-Restrepo et al., 2007; Duan et al., 2014; 2020). The closely related ANXUR (ANX)1 and ANX2 (named after the consort of FERONIA), are expressed almost exclusively and to very high levels in the pollen (Boisson-Dernier et al., 2009; Miyazaki et al., 2009). Loss of FER severely hampers female fertility while loss of ANX1 and 2 together results in male sterility. However, the biological outcomes of their functions are diametrically different, FER induces pollen tube rupture during the temporally and spatially very restricted phase of pollen tube-female gametophyte encounter whereas ANXs prevent their rupture during pollen tube growth through the pistil. Fertilization in flowering plants relies on the pollen tube to transport two sperm cells from the pollen receptive surface in the pistil to the female gametophyte whereupon the pollen tube ruptures, freeing the sperm for fertilization (Johnson et al., 2019; Ge et al., 2019a, 2019b). Knock-out *fer* mutants are severely compromised in female fertility because their female gametophytes fail to induce pollen tube rupture and sperm release, precluding fertilization. ANX1 and 2, on the other hand, prevent pollen tube from bursting during the entire pollen tube growth process until reaching the female gametophyte. Pollen tubes in *anx1 anx2* double mutants are male sterile because pollen tubes burst precociously, never having a chance to reach their target female gametophytes. CpRLK1, is found in a heterothallic strain of the *Closterium peracerosum-strigosum-littorale* complex, a unicellular charophycean alga close to land plants, is phylogenetically related to MLD-RLKs. It is expressed in mating-type (+) cells and important for bursting the conjugal apparatus to release a naked gamete for fertilization (Hirano et al., 2015), reminiscent of the FER function in the female gametophyte, suggesting an ancient presence of ML sequences, perhaps even before the emergence of land plants.

Further studies of FER and ANXs showed that they are more broadly engaged than initially realized. FER is almost ubiquitously expressed, except in pollen, and has a remarkable functional range, controlling growth, development, biotic and abiotic stress responses (Li et al., 2016; Doblas et al., 2018; Frank et al., 2018), mediating processes regulated by various hormones such as auxin, BR, ethylene, abscisic acid and jasmonic acid, and peptide growth regulators (Guo et al., 2009, 2018; Deslauriers and Larsen, 2010; Duan et al., 2010; Yu et al., 2012; Haruta et al., 2014; Li et al., 2015; Stegmann et al., 2017; Liu et al., 2021). FER also mediates mechano-sensing (Shih et al., 2014), and is pivotal for survival under high salinity conditions (Feng et al., 2018) and immunity responses (Kessler et al., 2010; Stegmann et al., 2017) where ANX1 and 2 also play notable roles (Mang et al., 2017). Both FER and ANXs interact physically with well-established components of disease response pathways, providing a basis for their functional intersections.

The THE1 subfamily comprises ten MLD-RLKs (Fig. 2). THE1 was identified through a screen for suppressor of growth defects in cellulose deficient mutant *procuste1-1* (Hematy et al., 2007), referring to its short hypocotyl phenotype and after PROCUSTE, an iron smith and inn keeper in Greek mythology who had the habit of shortening people to fit them into small beds; THESEUS killed PROCUSTE. Mutations in THE1 resulted in mitigating the short hypocotyl defect in the cellulose deficient seedlings but without alleviating the cell wall defect. Overproduction of THE1 in *procustes1-1* exacerbated the phenotype. However, when expressed in the wild type background, *the1* mutations did not induce notable phenotypes. Together these observations suggest that THE1 functions as a surveyor of cell wall conditions, responding to perturbances in the wall to suppress growth and relieve load-bearing in seedlings with a compromised cell wall. A second pair of pollen-specific MLD-RLKs, BUDDHA'S PAPER SEAL1 (BUPS)1 and 2, also belongs to the THE1 subclade. Like the ANXs, BUPS1 and 2 are required to prevent pollen tube from precocious rupture (Ge et al., 2017). The closely linked MEDOS (MDS) 1–4 (Fig. 2A) were first found to mediate responses to metal ion stresses (Richter et al., 2018) but MDS1 is important in immunity regulation and was renamed LETUM (LET) 2 (Huang et al., 2020). LET2 associates with another MLD-RLK, LET1 (Liu et al., 2020). LETUM is the personification of death in Roman mythology; the name was adopted to reflect the autoimmunity-regulated cell death phenotype observed in *let1* and *let2* mutants.

Other THE1 clade RLKs also contribute to growth and development, albeit individually, their biological roles might be relatively subtle. For instance, loss of HERCULES RECEPTOR KINASES 1 (HERK1) induced negligible impact on seedling growth (Guo et al., 2009) whereas loss of CURVY1 (CVY1) appears to only impact epidermal cell morphogenesis producing abnormal trichomes and pavement cell interdigitation pattern (Gachomo et al., 2014). Interestingly, *cvy1* mutants are late-flowering and have significantly increased silique numbers and seed yields than wild type plants. The nearest relative to BUPS1 and 2, ERULUS (ERU) (son of the goddess FERONIA)/CAP1 (Bai et al., 2014), is expressed in seedlings and pollen. *eru* mutants are relatively normal displaying only root hair growth and pollen tube guidance defects (Kwon et al., 2018; Schoenaers et al., 2017, 2018). HERK1 or ANJEA (ANJ) (after the fertility goddess of Aboriginal mythology) are also expressed in the pistil. Loss of either of these receptor kinases does not noticeably impact reproductive yield but their combined loss induces pollen tube rupture, phenocopying loss of FER (Galindo-Trigo et al., 2020a). Nevertheless, ANJ and and FER function in a gating mechanism to facilitate productive pollination on the stigma surface but prevents unwanted invasion (Liu et al., 2021; Zhang et al., 2021).

The ECDs of some MLD-RLKs have apparently diverged from one another for functional specialization. In domain-swapping experiments, hybrid ANX ECD-FER kinase domain hybrid proteins expressed in where FER is normally located failed to rescue the female gametophyte defect in knockout *fer* mutants (Kessler et al., 2015). These results should not be too surprising given how FER and ANXs act and the environments where they act are considerably different. ANXs regulate pollen endogenous reactive oxygen species (ROS) homeostasis to sustain cell wall integrity during pollen tube growth (Boisson-Dernier et al., 2013; Feng et al., 2019). ANXs need to sense subtle changes in cell wall rigidity and malleability at the pollen tube tip and moderate their downstream signaling pathway to maintain the proper ROS output. FER controls the ROS environment at the entrance of the female gametophyte where a pollen tube penetrates (Duan et al., 2014). The high level of local ROS acts exogenously and maximally on the pollen tube, most likely weakening its wall and priming it for an explosive rupture upon entering the female gametophyte. Molecules that interact with the FER and ANX ECDs to regulate their activity would be different (Duan et al., 2014; Ge et al., 2017, 2019a, 2019b; Li et al., 2015).

The MLD-LRR-RLK clade. The ML domain in the MLD-LRR-RLKs are followed by a region of LRRs (Fig. 2B) and they represent a majority of the MLD-containing RLKs (Fig. 2A). Several are involved in immunity signaling, such as IOS1 (Hok et al., 2011; Yeh et al., 2016), STRESS-INDUCED FACTOR2 (SIF2) (Chan et al., 2020), FLG22-INDUCED RECEPTOR-LIKE1 (FRK1)/SENESCENCE-INDUCED RECEPTOR KINASE (SIRK1) (Yeh et al., 2015; Robatzek and Somssich, 2002), and OUTGROWTH-ASSOCIATED PROTEIN KINASE (OAK) (Smith et al. 2011). Some are associated with developmental processes, such as MATERNAL EFFECT EMBRYO ARREST39 (MEE39) and ROOT HAIR SPECIFIC (RHS) 6 and RHS16 for endosperm (Pagnussat et al., 2004) and root hairs (Won et al., 2009), respectively.

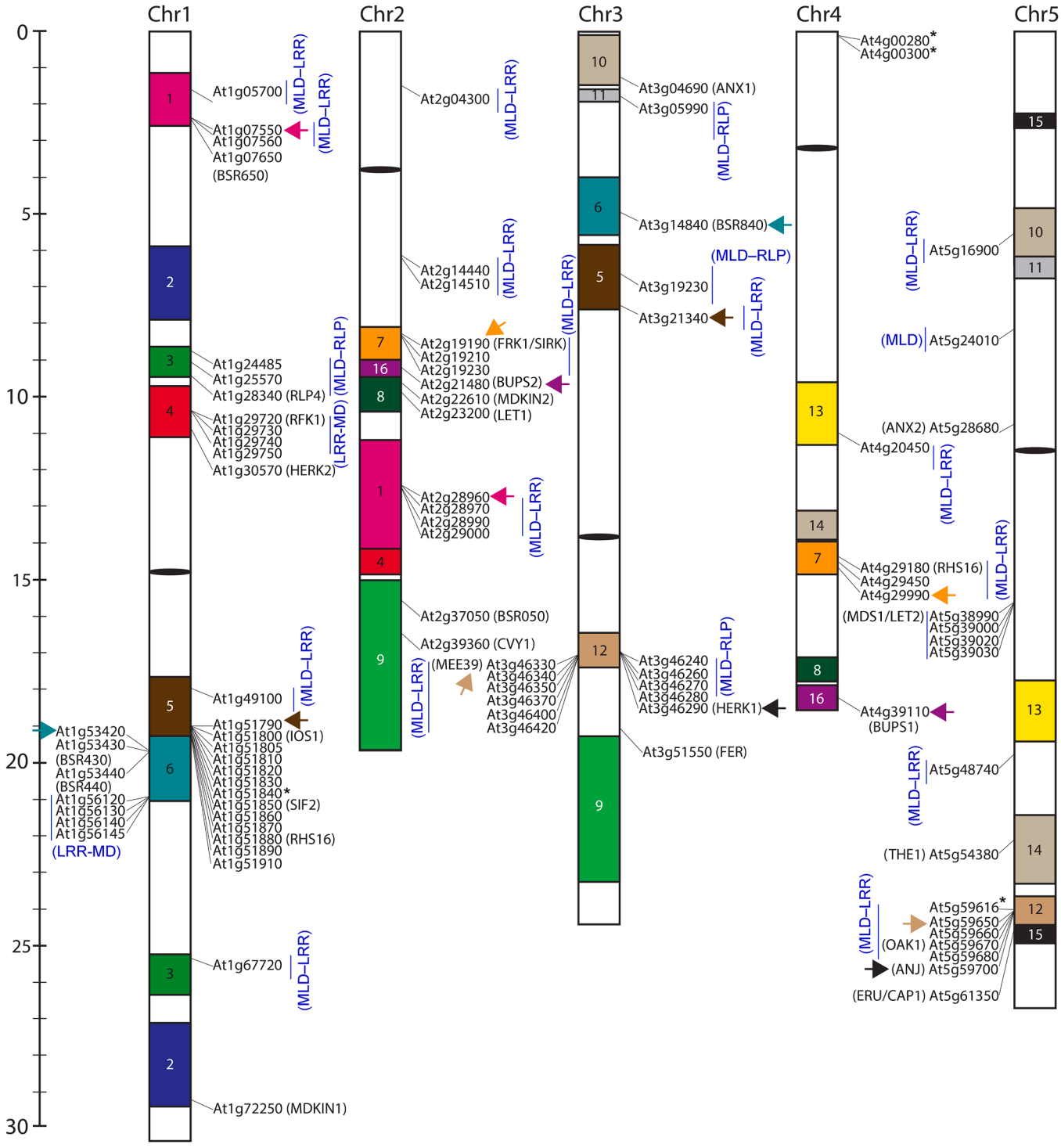

Fig. 3. Chromosomal and synteny map of ML proteins in *A. thaliana*. The Arabidopsis synteny information was obtained from The Samuel Robert Noble Foundation (http://plantgrn.noble.org/LegumeIPv2/download.jsp). The genetic features of M/MLD protein genes was downloaded from the Arabidopsis Information Resource (TAIR) (https://www.arabidopsis.org/portals/genAnnotation/gene_structural_annotation/agicomplete.jsp) on www.arabidopsis.org. The M/MLD genes were mapped to synteny regions. Only syntenic blocks with synteny scores higher than 1000 containing M/MLD family proteins are retained here. Pairs of syntenic regions are represented as the same color-coded blocks; syntenic gene pairs are indicated by the same color-coded arrows. Clade names are shown in blue. *, designated as indicated in Fig. 2A. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Analysis of transcriptomic data extracted from Genevestigator (Hruz et al., 2008) shows that the MLD-LRR-RLK clade stands out with many of its members showing higher than a two-fold increase in expression during pathogen or elicitor treatments (Group 1, S. Fig. 1A; Group 3, S. Fig. 1B). These include IOS1, FRK1/SIRKI, and SIF2, consistent with their already elucidated roles in plant defense, and several others in the same chromosomal cluster between *At1G51790* to *At1G51890* (Fig. 2A; Fig. 3). These data also show that biotic stresses down-regulate a group from all three MLD-RLK clades (Group 2, S. Fig. 1A; Group 4, Supple. Fig. 1B). To what extent these MLD-RLKs have expanded to provide functional redundancy to safeguard survival and how many of them have evolved to play specific roles under different conditions will be interesting functional and evolutionary questions to explore.

Chromosomal distribution of M/MLD protein genes in Arabidopsis

Chromosomal mapping and synteny analysis of genes encoding *A. thaliana* M/MLD proteins shows that many of them are tandemly arranged within segmentally duplicated regions of the genome (Fig. 3). Typically, a protein family arose from multiple duplications of an ancestral gene through whole genome duplication (WGD), gene duplication, exon duplication and shuffling (Cannon et al., 2004; França et al., 2012; Panchy et al., 2016). The *A. thaliana* genome has experienced WGD, gene loss, local gene duplication, transposition, and segmental duplication events, thus duplicated genes are shuffled throughout the genome (Arabidopsis Genome Initiative, 2000). The occurrence of syntenic blocks of M/MLD protein genes and local duplications is consistent with the notion that gene expansions that led to the Arabidopsis RLK superfamily had occurred via recent duplications.

Eight syntenic blocks containing M/MLD protein genes were identified (paired color-coded blocks, Fig. 3). Genes for the LRR–MD–RLK and MLD–LRR-RLK clades display considerable duplications and local expansions. 12 of the 13 LRR–MD–RLK genes are located on chromosome 1. *BSR840* is maintained as a single gene on chromosome 3 and paired with the homolog *At1g53420* in the BSR cluster on chromosome 1 (block 6). Duplication events at the *At1g53420* locus likely happened giving rise to the local cluster with *BSR430* and *BSR440*, and also dispersing *BSR650* to block 1 on the same chromosome (Fig. 3). This genomic arrangement suggests an initial duplication event had given rise to these BSR blocks, which was followed by more local gene expansions.

The MLD–LRR–RLK genes also occur in multiple clusters. Pairing of the MLD–LRR–RLK cluster on chromosome 1 with the single *At3g21340* on chromosome 3 (block 5) suggests an early duplication event could have generated the two loci, followed by extensive local duplications at the chromosome 1 locus to yield the large contiguous cluster. Similarly, a duplication followed by local expansion could have generated the tandem arrays of genes in the three other paired chromosomal IOS1 gene segments (blocks 1, 7, and 12). An analysis of the gene cluster between *At5g59650* and *At5g59680* in block 12 on chromosome 5 in more than three hundred accessions of *A. thaliana* and its close relative *A. lyrata* (Smith et al., 2011) suggests that the *A. thaliana* cluster had arisen through a duplication of the central RLK gene of an ancestral three-gene cluster with *At5g59650* and *At5g59680* flanking *At5g59670 (OAK1)*, giving rise to *At5g59660*, making up the 4-gene cluster (Fig. 3). It is interesting to note that the gene for the MLD-RLK ANJ is just adjacent to the *OAK1* MLD-LRR-RLK cluster but ANJ lacks the LRR-coding sequence. *ANJ* is paired with *HERK1* in block 12 on chromosome 3, where local expansion has given rise to the adjacent IOS1 cluster. An initial duplication may have happened in one form, either with or without LRR, followed by losing or gaining the LRR, respectively. A duplication of the MLD–LRR–RLK gene pair in block 1 on chromosome 1, *At1g07550* and *At1g07560*, could have generated the block 1 MLD–LRR–RLK cluster on chromosome 3.

In contrast, most of the MLD–RLK clade genes, in particular those associated with notable biological roles, are mapped in unique chromosomal locations. Even when existing as duplicated genes, e.g. the pollen-specific *ANX1* and *2* genes and *BUPS1* and *2* genes, they did not further expand locally. On the other hand, the functionally subtle *MDS1-4* (*At5g38990–At5g39030*) under normal growth conditions (Richter et al., 2018), are clearly a result of local expansion. Do the chromosomal organization of the MLD–RLK clade genes with crucial biological roles and the mostly clustered organization of the MLD–LRR–RLK, LRR–MD–RLK clade genes and *MDS1-4* reflect a correlation with the biological roles maintained for these genes? Perhaps local gene expansion could be a mean to dilute functional contribution from a single progenitor with an essential function so the biological burden is shared by gene redundancy. Alternatively, it could also be a mean to augment functional impacts via expansion of a progenitor gene in a chromosomal region of low expression activities. Stability at chromosomal locations for the MLD–RLK clade gene locations could allow these genes to be preserved for conserved functional roles whereas instability at the MLD–LRR–RLK clade gene locations could have facilitated their neo-functionalization to meet varying environmental demands (Duarte et al., 2006).

M/MLD–RLKs among diverse plant genomes

Moss (*Physcomitrela patens)*, Medicago (*Medicago truncatula*), tomato (*Solanum lycopersicum*) and rice (*Oryza sativa*) were selected as a representative non-vascular land plant, a model legume, a dicot and a monocot crop, respectively, for a broader phylogenetic analysis of M/MLD–RLKs. We identified 279 M/MLD-RLKs from these plants, with 87, 75, 65, 32 and 20 from Medicago, *A. thaliana*, rice, tomato and moss, respectively. Similar to the Arabidopsis proteins, these M/MLD–RLKs are classified into two major phylogenetic branches, the single malectin domain-containing LRR-MD–RLK clade and the tandem malectin domain-containing MLD clade that further divides into the MLD–RLK and MLD–LRR–RLK subclades (Fig. 4). Each of these three clades are further divided into two subclades (Fig. 4, inner circle).

The LRR–MD–RLK and MLD–RLK clades. These clades share evolutionary patterns with their counterparts from Arabidopsis with the LRR–MD–RLK clade displaying extensive lineage-specific local expansion while the MLD-RLK clade shows only limited expansion. Of the LRR-MD–RLK clade, Medicago and rice genes have evolved their own lineage, arisen from local expansion after segmental duplications. Most Arabidopsis LRR–MD–RLK clade genes do not have close relatives in these species, except for two of its members (blue arrowheads, Fig. 4). Many close homologs of the Arabidopsis MLD–RLK clade genes are found in all four species examined. For example, *HERK2* are in a group with two rice, one Medicago and one tomato genes, suggesting that they are descended from a common ancestor. Strikingly, a large family of Medicago *MLD–RLKs* and the Arabidopsis *FER* and *ANXs* evolved within two monophyletic clades, which are also occupied by several rice and tomato homologs. Together with the already recognized functional importance of FER- and THE1-related Arabidopsis MDL–RLKs and several FER-Like Receptors (FLRs) in rice, such as DWARF AND RUNTISH SPIKELET1, 2 (DRUS1/FLR2 and DRUS2) in reproduction and immunity (Pu et al., 2017; Yang et al., 2020; Huang et al., 2020), it appears that genes in the MLD-RLK clade had evolved under considerable constrain for functional conservation.

The MLD–LRR–RLK clade and Symbiosis Receptor Kinases (SymRKs). The MLD–LRR–RLK subclade 1 includes a large majority of its members and comprises five lineage-specific monophyletic groups (Fig. 4). Lineages I to IV include the majority of IOS1 clade genes from Arabidopsis and the other species examined, with no or few interruptions. Lineage V has a small number of Arabidopsis, Medicago, rice and tomato genes interrupting a large moss gene cluster. Like in Arabidopsis MLD-LRR-RLK clade, the subclade1 genes from these three species had also experienced duplications and local expansions.

The Sub-MLD-LRR-RLK clade 2, with only six members, comprises

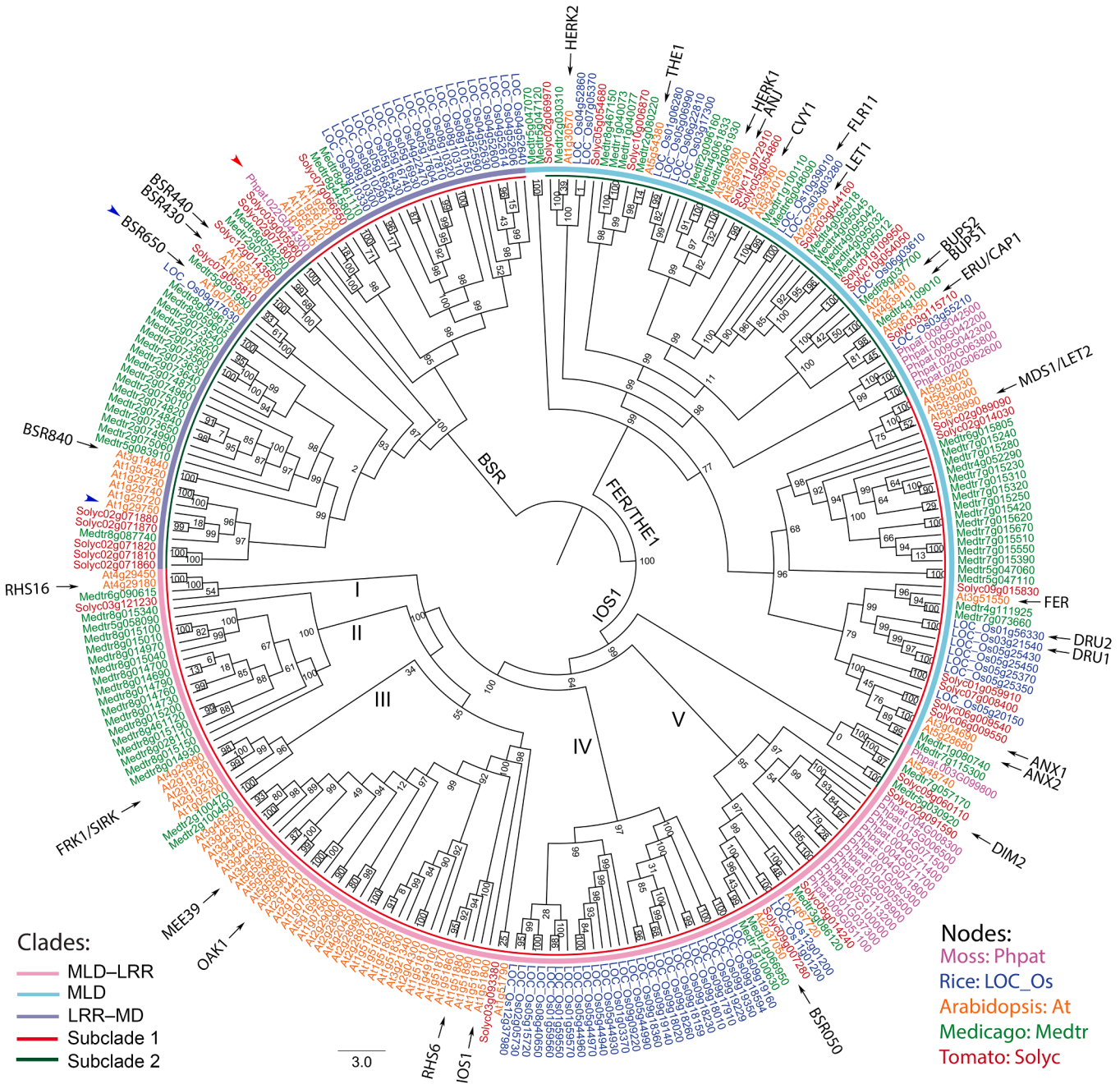

Fig. 4. Phylogenetic analysis of M/MLD-RLKs from Arabidopsis and four other plant species. A mid-point rooted approximately-maximum-likelihood phylogeny analysis of M/MLD-RLKs from *A. thaliana*, moss (*Phycomitrella paten*), rice (*Oryzae sativa* ssp *japonica*), tomato (*Solanum lycopercicum*) and *Medicago truncatula* was carried out by the Fasttree software (Price et al., 2010). Arabidopsis ML family proteins were used as queries against the proteomes from the other species (E value ≤ 1e-5). Retrieved proteins were confirmed by protein domain analysis. Clades (LRR–MD–RLK, MLD–RLK, MLD–LRR–RLK, outer circle) are color-coded as for the Arabidopsis phylogeny tree shown in Fig. 2A. Each of these clades are further divided into subclades 1 and 2, marked as red and green segments, respectively, in the inner circle. I-V indicate the five monophyletic groups within the MLD–LRR–RLK clade. Blue arrowheads, Arabidopsis BSR clade genes *At1G29750* with two closely related tomato genes and *BSR650,* are closely related to a Medicago and a rice gene. Red arrowhead, the only moss LRR–MD–RLK gene identified. Databases are from The Arabidopsis Information Resource (TAIR10; https://www.arabidopsis.org/), the *M. truncatula* Genome Project (Mt4.0; http://jcvi.org/medicago/) (Tang et al., 2014), the Rice Genome Annotation Project (Osativa_204_v7.0; http://phytozome.jgi.doe.gov/pz/#) (Ouyang et al., 2007), International Tomato Genome Sequencing Project (ITAG2.4; http://solgenomics.net/), moss from the Joint Genome Institute site for *P. patens* (http://phytozome.jgi.doe.gov/pz/portal.html#) (Lang et al., 2018). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the Symbiosis RKs (SymRKs) (Markmann et al., 2008) (Fig. 4), including the *DO NOT MAKE INFECTION2* (*DMI2*) from Medicago (Endre et al., 2002). In most land plants, SymRKs are known to play important roles in mediating symbiotic interactions with arbuscular mycorrhizal (AM) fungi and, in addition, nitrogen-fixing symbiosis with certain bacteria, mostly in legumes (Stracke et al., 2002; Markmann et al., 2008; Gherbi et al., 2008). Defects in SymRK abolish AM symbiosis and, where applicable, nitrogen-fixing symbiosis. Overexpressing full-length or just the kinase domain of SymRK leads to spontaneous nodule formation in the absence of nitrogen-fixing rhizobia (Markmann et al., 2008; Saha et al., 2014). A precise functional role for the ML domain in SymRK remains unclear. The rice SymRK is missing in the phylogeny map

(Fig. 4) because it lacks a ML domain (Markmann et al., 2008). Yet expressing rice SymRK and the ML domain-containing tomato SymRK in a *Lotus japonicus symrk* mutant resulted in each restoring AM symbiosis but not nitrogen-fixing symbiosis (Markmann et al., 2008). These results imply that the ML domain is dispensable for AM symbiosis as well as insufficient for supporting nitrogen-fixing symbiosis. It is possible that the ML domain modulates LRR-mediated interactions or impact SymRK stability (Antolin-Llovera et al., 2014; Pan et al., 2018).

Given the paucity of functional information, it is clear that the huge signaling potential harnessed by the MLD–LRR–RLKs remains to be recognized.

Outlook towards potentially shared mechanisms among MLD-RLKs

Functioning in different cellular contexts and so likely to have interactive components serving their individual signaling pathways (e.g. Boisson-Dernier et al., 2015; Du et al., 2016; Huang et al., 2020), the Arabidopsis MLD–RLKs studied thus far nevertheless display considerable conservation in their core signaling strategies. For example, they function as homo- and/or hetero-oligomers and interact with a glycosylphosphatidylinositol-anchored protein (GPI-AP) from the LORELEI and LLG1,2,3 protein family (Li et al., 2015; Ge et al., 2019a, 2019b; Feng et al., 2019; Galindo-Trigo et al., 2020a; Liu et al., 2021; Noble et al., 2021). Thus far, Rapid Alkalinization Factor (RALF) peptides (Blackburn et al., 2020) have been identified as ligands for FER, THE1, ANXs, BUPSs and ANJ (Haruta et al., 2014; Stegmann et al., 2017; Ge et al., 2017; Gonneau et al., 2018; Liu et al., 2021). The FER ECD–RALF23 (an N-terminal 1–17 amino acid fragment) and LLG2, which is specific to pollen where FER is not expressed, form a stable complex *in vitro* (Xiao et al., 2019), suggesting that functionally non-cognate components are structurally compatible. This is consistent with the LORELEI/LLG proteins can functionally substitute for each other (Noble et al., 2021). The LORELEI/LLG proteins also chaperone the partnered receptor kinases to their functional location on the cell membrane (Li et al., 2015; Feng et al., 2019). It would be interesting to examine whether similar strategies involving variants of the MLD–RLK and LORELEI/LLG coreceptor partners could be employed by a broader set of M/MLD-RLKs and that RALFs and other unrelated peptides (Liu et al., 2021) could act as ligands to regulate their activity.

On the transmembrane and inner cell membrane levels, FER and THE1 interact with guanine nucleotide exchange factors (GEFs) to activate RHO GTPases (Duan et al., 2010, 2014; Li et al., 2015; Huang et al., 2013; Qu et al., 2017; Lin et al., 2018), thus linking signals perceived to a hub capable of dispatching them to diverse intracellular processes (Nibau and Cheung, 2011). FER and ANX are functionally linked to the RHO-regulated NADPH oxidases (Duan et al., 2010; Boisson-Dernier et al., 2013; Li et al., 2015; Liu et al., 2021; Zhang et al., 2021; Song et al., 2021), which control ROS production. ROS are ubiquitous signaling molecules whose oxidative power also impacts cell wall quality. FER, ANX1 and THE1 also interact with several other cell surface receptors important for growth, immunity and other stress signaling pathways (Stegmann et al., 2017; Dressano et al., 2017; Mang et al., 2017; Van der Does et al., 2017). Interactions with cytoplasmic receptor-like kinases (Boisson-Dernier et al., 2015; Du et al., 2016; Shen et al., 2017) and various molecular conglomerates of intracellular signaling molecules along the cytoplasmic membrane surface (Mang et al., 2017; Liu et al., 2020; Huang et al., 2020) have also been demonstrated. Additional mechanisms will inevitably emerge to further elaborate the molecular interaction networks engaged by MLD-RLKs as more are being examined.

Interacting physically and/or functionally with the cell wall, the potential property that first brought intense attention to the MLD-RLKs, could also be a shared mechanistic theme. The identification of THE1 suggested that MLD-RLKs could serve as surveyors of cell wall quality to act on demand to signal the needed cellular responses (Hematy et al., 2007). FER physically interacts with homogalacturonan, the backbone of the cell wall polysaccharide pectin (Feng et al., 2018; Lin et al., 2018; Duan et al., 2020). Altered cell wall quality could contribute to growth and immunity related phenotypes in loss of function *fer* mutants (Doblas et al., 2018; Frank et al., 2018), in particular in root growth responses under high salinity (Feng et al., 2018) and FER-controlled process to suppress supernumerary pollen tube penetration of ovules (Duan et al., 2020). Moreover, *fer* mutants also lack the elaborate puzzle-like epidermal cell pattern in leaves (Li et al., 2015; Noble et al., 2021) where differential pectin deposition is believed to underlie the morphogenesis of the interdigitated pavement cells (Haas et al., 2020). ANXs or BUPSs are crucial for pollen tube wall quality that prevents precocious pollen tube rupture (Boisson-Dernier et al., 2009, 2013; Miyazaki et al., 2009; Ge et al., 2017, 2019a, 2019b). ERU affects pectin deposition in root hair cell walls and *eru* mutant root hairs are short and stocky (Schoenaers et al. 2018). However, although some structural homology exists (Fig. 2C), a sugar-binding pocket analogous to that in the diglucose binding animal malectin (Schallus et al., 2008) could not be assigned in the crystal structures elucidated for ANX1, ANX2 and FER (Moussu et al., 2018; Du et al., 2018; Xiao et al., 2019). At the cell membrane-wall interface, MLD-RLKs are in the vicinity of many components of the extracellular matrix in addition to peptide ligands, pectin and the LLG family proteins. These broader interactions can conceivably provide a signaling linkage to molecules that lack cytoplasmic signaling capacity, such as additional GPI-AP proteins (Hou et al., 2016) or as in the demonstrated interaction between FER and the tightly cell wall-associated Leucine-rich repeat extensins (LRXs) (Zhao et al., 2018; Dunser et al., 2019; Herger et al., 2020), linking extracellular sensing to intracellular processes.

The abundance of M/MLD -containing proteins in plants might represent a unique niche that has facilitated species diversification and survival. Well-characterized model and crop plant species are well suited to further decipher how the malectin homologus sequences in M/MLD-RLKs enable plants to respond to endogenous demands and environmental conditions in order to thrive and propagate. Understanding the functional involvement of M/MLD proteins across the broader plant kingdom should reveal interesting specialization strategies to meet the demands from diverse plant forms and unique environmental challenges faced by different species in their habitats.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tcsw.2021.100056.

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