Rice

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Lesion Mimic Mutant: An Ideal Genetic Material for Deciphering the Balance Between Plant Immunity and Growth

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Abstract

Lesion mimic mutants (LMMs) form hypersensitive response (HR)-like lesions, a form of programmed cell death (PCD), in the absence of pathogens, that often confer durable and broad-spectrum disease resistance, representing a potential source for breeding resistance. However, most LMM plants have significant growth retardation including cell death, leaf senescence, damaged chloroplast structure, decreased chlorophyll contents, and undesirable agronomic traits. Therefore, LMMs represent ideal genetic materials to decipher interactions between defense signaling and programmed cell death, and growth. Many LMMs have been identified in rice, and at least 61 genes have been cloned and functionally confirmed. LMM genes are reported to participate in various regulation pathways, including gene transcription and protein translation, ubiquitin–proteasome pathway, protein phosphorylation, vesicle trafficking, metabolic pathways, and phytohormone signaling, highlighting the complexity of regulatory mechanisms. This review discusses recent progress on characteristics of rice LMM and mechanisms of LMM gene regulation, and suggests directions for future theoretical research and the potential use of LMMs in rice breeding.

Keywords Cell death, Immunity, Lesion mimic mutant, Regulation mechanism, Rice

Introduction

Rice (*Oryza sativa*) is one of the most important food crops globally, in that is a staple in the diets of more than half of the world's population. Approximately 40% more rice must be produced by 2030 to cope with demands from an increasing population (Khush 2005; Miah et al. 2013). Stable rice production is constrained by various diseases caused by pathogens, which can cause average yield losses exceeding 30% (Liu et al. 2021; Shasmita et al. 2023). In nature, plants have evolved sophisticated immune mechanisms to protect themselves from pathogen attack. Hypersensitive response, a specialized form of programmed cell death, is one of the most efficient and immediate resistance reactions for plants to fight pathogens (Dangol et al. 2019; Pitsili et al. 2020). Upon perception of pathogen infection, the HR can be rapidly initiated in and around the infection site, and the plant kills its own cells to inhibit continued pathogen invasion or proliferation (Lam et al. 2001; Singh et al. 2018).

Rice lesion mimic mutants are a class of mutants that spontaneously form necrotic lesions that resemble

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symptoms of plant HR in vivo; these lesions occur on leaves, leaf sheathes, or panicles in the absence of pathogen infection (Zhang et al. 2022). Numerous studies have demonstrated that most rice LMMs can confer durable and broad-spectrum disease resistance with cell death, reactive oxygen species (ROS) accumulation, and the activation of defense genes, and that they represent a potential source for breeding resistant varieties (Sha et al. 2023). However, most LMMs have undesirable agronomic traits such as decreased tiller number, plant height, seed-setting rate, grain number per panicle, 1000-grain weight, and yield. Therefore, these mutants represent ideal genetic materials with which to study PCD, plant defense mechanisms, and the balance between plant immunity and growth.

The *sekiguchi lesion* (*sl*) is a naturally occurring mutant, and the first LMM reported by Sekiguchi (1965) in rice (Rao et al. 2021). Thereafter, similar LMMs have been characterized by artificial mutagenesis, with corresponding genes characterized and cloned via forward and reverse genetic methods. Yamanouchi et al. (2002) first cloned the LMM gene *Spl7* in rice using map-based cloning, which encodes a heat stress transcription factor. Fujiwara et al. (2010) cloned the sekiguchi lesion gene *SL*, which encodes a cytochrome P450 monooxygenase catalyzing conversion of tryptamine to serotonin. To date, at least 61 LMMs and their corresponding genes have been characterized and cloned in rice. We summarize identifications, characteristics, and functions of these rice LMMs and their corresponding genes, and describe molecular regulation pathways of cloned LMM genes, to identify new directions for theoretical research and for the application of LMMs to develop elite rice varieties with both high yield and disease resistance.

Characteristics and Functions of Rice LMMs

Mutants are usually designated based on their phenotype including lesion mimic mutant, spotted leaf, and accelerated cell death, among which the LMM is most prevalent (Zhu et al. 2020). Many rice LMMs have been characterized. We summarize characteristics of at least 61 of them for which causal genes have been cloned and characterized (Table 1). Among them, the appearance of lesions is mostly accompanied by ROS accumulation, leaf senescence, damaged chloroplasts, and decreased chlorophyll contents. The LM can occur throughout the entire rice-growth period (from seedling stages to maturity); 42 and 10 mutants exhibit lesions at the seedling and tillering stages, respectively, and 2 mutants exhibit lesions in each of the heading, booting, and flowering stages (Table 1). For some LMMs, abiotic factors such as ultraviolet radiation, temperature, and light can affect LM appearance. LM phenotypes in *lmm8*, *lil1*, *rlin1*, *lmp1/lmm22*, *sl*, *sdr7*-6, *spl88*, *scyl2*-1, *spl36*, *spl29*, *spl33*, *lmm24*, and *spl35* mutants, and *SGR*- and *NPR1*-overespression lines are induced by light (Table 1). Mutants have the LM phenotype when exposed to light, but no LM when not. In *lmpa* and *spl42* mutants, LM phenotypes are temperature-dependent. At 30 °C, the reddish-brown lesions of *lmpa* and *spl42* are serious, but no obvious lesions occur when plants are grown at 20 °C (Hu et al. 2022; Liu et al. 2023b). In *els1*, *lm212-1*, *osnsun2*, and *lml1* mutants the LM phenotypes are significantly affected by both light and temperature. In the *glp1* mutant, ultraviolet B radiation triggers lesion development (He et al. 2021). In the *spl7* mutant, high temperature or ultraviolet radiation causes lesion development (Yamanouchi et al. 2002).

Analysis of LMMs reveals many mutants to show typical recessive inheritance, mostly following Mendel's inheritance law (Table 1); only *lil1* and *Spl18* mutants manifest semi-dominant or dominant inheritance, respectively (Mori et al. 2007; Zhou et al. 2017). In rice, most LMMs improve resistance to rice blast and bacterial blight. Among the 61 LMMs, 27 mutants display enhanced resistance to both blast and bacterial blight, 10 show enhanced resistance to blast, and 11 show enhanced resistance to bacterial blight (Table 1). However, the response of both *sdr7-6* and *edr1* mutants to blast and bacterial blight differs; the resistance response to bacterial blight is increased, but resistance to rice blast disease is reduced (Zheng et al. 2022). All these 50 LMMs involved in immunity exhibit severe cell death, which is mainly caused by ROS accumulation that includes H_2O_2 and O^{2-}. Among the 50 LMMs, except for *spl7*, *lms*, *spl11* mutants and *OsRac1*-overexpression line, 46 mutants exhibit significant upregulation in the expression of one to eleven pathogenesis-related (PR) genes. These results confirm that the defense response is activated in these LMMs. The LM phenotype and enhanced disease resistance in 26 LMMs are caused by single base substitution in the genes; three mutants including *lm212-1*, *lmp1-1*, and *spl3*/*edr1* are caused by single base insertion or deletion; the *oscul3a* mutant is caused by 11-bp substitution and an 8-bp deletion; the *lmm24* mutant is caused by two base mutations and a 54-bp insertion; the *scyl2-1* and *rbl1* mutants are caused by 12- and 29-bp deletion, respectively; seven mutants including *NPR1*-, *OsPUB15*-, *OsWAK25*-, *OsRac1*-, *OsJAZ13*-overexpression lines and *Spl18*-, *OsGRDP1*-T-DNA insertion lines are caused by gene expression upregulation; eight mutants including *OsLSD1*-, *OsUbc13*-, *CslF6*-, *GF14e*-, *OsSEC3A*-RNAi lines and *OsNBL3*-, *SPL35*-, *OsMLD1*-T-DNA insertion lines are caused by gene expression downregulation (Table 1). While most LMMs confer broad-spectrum

Table 1 The characteristics of cloned rice lesion mimic genes

Gene name	Accession number	Induction	Inheritance	Gene function	Time	Protein category	Subcellular localization	Resistance	Reference
SPL7	*LOC_Os04g46580*	T/UV	recessive	MBC	tillering stage	heat stress transcription factor	nucleus	+ +	Yamanouchi et al. 2002
OsLSD1	*LOC_Os08g06280*	unknown	unknown	RNAi	6 W seeding	zinc finger protein	nucleus	+	Wang et al. 2005
OsNPR1	*LOC_Os01g09800*	L	unknown	OE	booting stage	NONEXPRESSOR OF PR1	cytoplasm	+	Chern et al. 2005
OsLMS	*LOC_Os02g42600*	unknown	recessive	MBC	30–40 DAS	double stranded RNA binding domain	unknown	+	Undan et al. 2012
SPL33	*LOC_Os01g02720*	L	recessive	MBC	three leaf stage	eEF1A-like protein	ER	+ +	Wang et al. 2017
LML1	*LOC_Os04g56480*	L/T	recessive	MBC	seedling stage	eukaryotic release factor 1 protein	ER	+ +	Qin et al. 2018
OsNBL3	*LOC_Os03g06370*	unknown	unknown	T-DNA	30 DAG	pentatricopeptide repeat protein	mitochondria	+ +	Qiu et al. 2021
OsMED16/SPL38	*LOC_Os10g35560*	unknown	recessive	MBC	tillering stage	MEDIATOR SUBUNIT	nucleus	+ +	Zhang et al. 2023a
SPL42	*LOC_Os02g07230*	T	recessive	MBC	third leaf stage	porphobilinogen deaminases	chloroplast	unknown	Liu et al. 2023b
SPL11	*LOC_Os12g38210*	unknown	recessive	MBC	seeding stage	E3 ubiquitin ligase	unknown	+ +	Zeng et al. 2004
OsPUB15	*LOC_Os08g01900*	unknown	unknown	OE	seedlings stage	E3 ubiquitin ligase	cytoplasm	+	Wang et al. 2015a
EBR1	*LOC_Os05g19970*	unknown	recessive	MBC	unknown	E3 ubiquitin ligase	unknown	+ +	You et al. 2016
OsCUL3a/SPL88	*LOC_Os02g51180*	L	recessive	MBC	45 DAS	Cullin3 protein	cytoplasm / nucleus	+ +	Liu et al. 2017
SPL35	*LOC_Os03g10750*	L	unknown	T-DNA	20 DAS	CUE domain-containing protein	cytoplasm	+ +	Ma et al. 2019
OsUbc13	*LOC_Os01g48280*	unknown	unknown	RNAi	30 DAS	ubiquitin-conjugating enzyme	unknown	+ +	Liu et al. 2023a, b
OsRPT5A	*LOC_Os02g56000*	unknown	recessive	MBC	seedling stage	26S protease regulatory subunit	cytoplasm	+	Wang et al. 2024
OsWAK25	*LOC_Os03g12470*	unknown	unknown	OE	seeding stage	wall-associated kinase	unknown	+ +	Harkenrider et al. 2016
ALS1/LIL1	*LOC_Os07g30510*	L	semi-dominant	MBC	three leaf stage	cysteine-rich receptor-like kinase	PM	+	Zhou et al. 2017
SLES	*LOC_Os07g25680*	unknown	recessive	MBC	two leaf stage	Raf MAPKKK	unknown	+	Lee et al. 2018
LMM24	*LOC_Os03g24930*	L	recessive	MBC	seedling stage	receptor-like cytoplasmic kinase	nucleus	+	Zhang et al. 2019
SPL36	*LOC_Os12g08180*	L	recessive	MBC	tillering stage	receptor-like protein kinase	cytoplasm/ PM	+	Rao et al. 2021
OsMKK6	*LOC_Os01g32660*	unknown	recessive	MBC	heading stage	MAP Kinase Kinase	nucleus	+ +	Jiang et al. 2023
OsRac1	*LOC_Os01g12900*	unknown	unknown	OE	young stage	GTPase	PM	+	Kawasaki et al. 1999
SPL28	*LOC_Os01g50770*	unknown	recessive	MBC	tillering stage	AP1M1	Golgi	+ +	Qiao et al. 2010
LMR/SPL4/LRD6-6	*LOC_Os06g03940*	unknown	recessive	MBC	five leaf stage	ATPase	chloroplast	+ +	Fekih et al. 2015

Table 1 (continued)

OsDRP1E	*LOC_Os09g39960*	unknown	recessive	MBC	30–45 DAG	dynamin-related protein	mitochondria	+ +	Li et al. 2017
OsSEC3A	*LOC_Os03g42750*	unknown	unknown	RNAi	tillering stage	exocyst subunit	PM	+	Ma et al. 2018
OsSCYL2	*LOC_Os01g42950*	L	recessive	MBC	tillering stage	SCYL protein family	Golgi/trans-Golgi/prevacuolar	+	Yao et al. 2022
LMPA	LOC_Os04g56160	T	recessive	MBC	seedling stage	ATPase	PM	unknown	Hu et al. 2022
Spl18	*LOC_Os10g11980*	unknown	dominant	T-DNA	juvenile stage	acyltransferase	unknown	+ +	Mori et al. 2007
SL/ELL1/CYP71P1	*LOC_Os12g16720*	L	recessive	MBC	seedling stage	cytochrome P450 monooxygenase	ER	+ +	Fujiwara et al. 2010
RLIN1/LLM1	*LOC_Os04g52130*	L	recessive	MBC	seedling stage	coproporphyrinogen III oxidase	unknown	+	Sun et al. 2011
SGR	*LOC_Os09g36200*	L	unknown	OE	two leaf stage	chlorophyll-degrading Mg + -dechelatase	thylakoid membrane	unknown	Jiang et al. 2011
OsRCCR1	*LOC_Os10g25030*	unknown	unknown	RNAi	three leaf stage	red chlorophyll catabolite reductase	unknown	unknown	Tang et al. 2011
CslF6	*LOC_Os08g0638*	unknown	unknown	RNAi	flowering stage	cellulose synthase-like F protein	unknown	+	Vega-Sánchez et al. 2012
OsAPX2	*LOC_Os07g49400*	unknown	recessive	T-DNA	tillering stage	scorbate peroxidase	chloroplast	unknown	Zhang et al. 2013
SPL29/UAP1	*LOC_Os08g10600*	L	recessive	MBC	seedling stage	UDP-N-acetylglucosamine pyrophosphorylase 1	cytoplasm	+	Wang et al. 2021
SPL32	*LOC_Os07g46460*	unknown	recessive	MBC	five leaf stage	ferredoxin-dependent glutamate synthase	chloroplast	+	Sun et al. 2017
OsPSL	*LOC_Os12g42420*	unknown	recessive	MBC	flowering stage	beta-1,6-N-acetylglucosaminyl transferase	unknown	unknown	Ke et al. 2019
OsACL-A2/SPL30	*LOC_Os12g37870*	unknown	recessive	MBC	three leaf stage	ATP-citrate lyase	nucleus/cytoplasm	+	Ruan et al. 2019
OsHPL3/MIL1	*LOC_Os02g02000*	unknown	recessive	MBC	two leaf stage	hydroperoxide lyase	chloroplast/cytoplasm	+	Tu et al. 2020
OsNSUN2	*LOC_Os09g29630*	L/T	unknown	KO	seedling stage	RNA 5-methylcytosine (m5C) methyltransferase	nucleus	unknown	Tang et al. 2020
WLL1	*LOC_Os04g42000*	unknown	recessive	MBC	seedling stage	lumazine synthase	chloroplast	unknown	Hu et al. 2021
OsCATC	*LOC_Os03g03910*	unknown	recessive	MBC	seedling stage	catalase	peroxisome	+	Liao et al. 2022
RBL1	*LOC_Os01g55360*	unknown	recessive	MBC	unknown	cytidine diphosphate diacylglycerol synthase	endoplasmic reticulum	+ +	Sha et al. 2023
LMM8/OsPPO1	*LOC_Os01g18320*	L	recessive	MBC	two leaf stage	protoporphyrinogen IX oxidase	chloroplast	+ +	Zhao et al. 2023

Table 1 (continued)

RBB1	*LOC_Os02g48650*	unknown	recessive	MBC	seedling stage	glucosamine-6-phosphate acetyltransferase	ER	+ +	Zhang et al. 2024
ELS1	*LOC_Os03g15780*	L/T	recessive	MBC	third leaf stage	anthranilate synthase α-subunit	chloroplast	unknown	Li et al. 2024
OsEDR1/OsACDR1/SPL3	*LOC_Os03g06410*	unknown	recessive	MBC	tillering stage	Raf-like kinase	nucleus	-+	Kim et al., 2009 Ma et al. 2021 Wang et al. 2015b
OsABA2	*LOC_Os03g59610*	unknown	recessive	MBC	3 WAS	xanthoxin dehydrogenase	unknown	+ +	Liao et al. 2018
OsJAZ13	*LOC_Os10g25230*	unknown	unknown	OE	30–45 DAS	jasmonate ZIM-domain (JAZ) proteins	nucleus/cytoplasm	+ +	Feng et al. 2020
SDR7-6	*LOC_Os07g46860*	L	recessive	MBC	six leaf stage	short-chain alcohol dehydrogenase	ER	-+	Zheng et al. 2022
OsPHD1	*LOC_Os01g26920*	L/T	recessive	MBC	seedling stage	UDP-glucose epimerase	chloroplast	+	Gao et al. 2022
OsLMP1/OsUBP2/LMM22	*LOC_Os09g32740*	L	recessive	MBC	tillering stage	deubiquitinase	nucleus	+ +	Sun et al. 2022
GF14e	*LOC_Os02g36974*	unknown	unknown	RNAi	3 WAS	phosphopeptide-binding proteins	nucleus	+ +	Manosalva et al. 2011
OsGRDP1	*LOC_Os11g40590*	unknown	unknown	T-DNA	heading stage	glycine-rich domain protein	cytoplasm/PM	+ +	Zhao et al. 2021
OsGLP1	*LOC_Os08g35760*	UV	unknown	RNAi	seedling stage	Germin-like protein	cytoplasm	unknown	He et al. 2021
OsRLR1	*LOC_Os10g07978*	unknown	recessive	MBC	seedling stage	NB-LRR protein	nucleus	+ +	Du et al. 2021
OsAAP3	*LOC_Os06g36180*	unknown	unknown	OE	unknown	amino acid transporter	unknown	unknown	Wei et al. 2021
OsMLD1	*LOC_Os03g03290*	unknown	unknown	T-DNA	booting stage	malectin protein	ER/Golgi	+ +	Feng et al. 2022
SPL50	*LOC_Os10g05370*	unknown	recessive	MBC	tillering stage	ARM repeat protein	cytoplasm	+	Ruan et al. 2024

The blue genes are involved in transcription and protein translation; the red genes are involved in ubiquitin-proteasome pathway; the black genes are involved in protein phosphorylation; the orange genes are involved in vesicle trafficking; the green genes are involved in metabolic pathway; the purple genes are involved in other regulation pathway, the pink genes involved in phytohormone signaling. The blue plus and red plus represent the resistance to blast and bacterial blight, respectively. The blue minus represent the susceptibility to blast. OE, overexpression; KO, knockout; MBC, map-based cloning; L, light; T, temperature; WAS, weeks after sowing; DAS, days after sowing; DAG, days after germination; ER, endoplasmic reticulum; PM, plasma membrane.

disease resistance, they have stunted agronomic traits. One mutant (*lmm9150*) with heightened resistance to blast and bacterial blight does not differ significantly from wild type (WT) rice in yield-related agronomic traits such as tiller number, seed-setting rate, grain weight per plant, and 1000-grain weight (Liao et al. 2018). This suggests that a type of LMM could be engineered with increased disease resistance but no yield loss.

Identification, Cloning, and Functional Analysis of LMM Genes

At least 61 LMM genes have been characterized and functionally confirmed, among which, 40 have been identified by map-based cloning, 6 have been cloned using T-DNA insertion mutants, and 15 have been identified through reverse genetics including RNA interference (RNAi), ectopic expression, and knockout (Table 1). These 61 genes occur widely on all 12 rice chromosomes:7, 6, 4, and 2 have been mapped to chromosomes 2, 10, 9, and 6, respectively; 10 to each of chromosomes 1

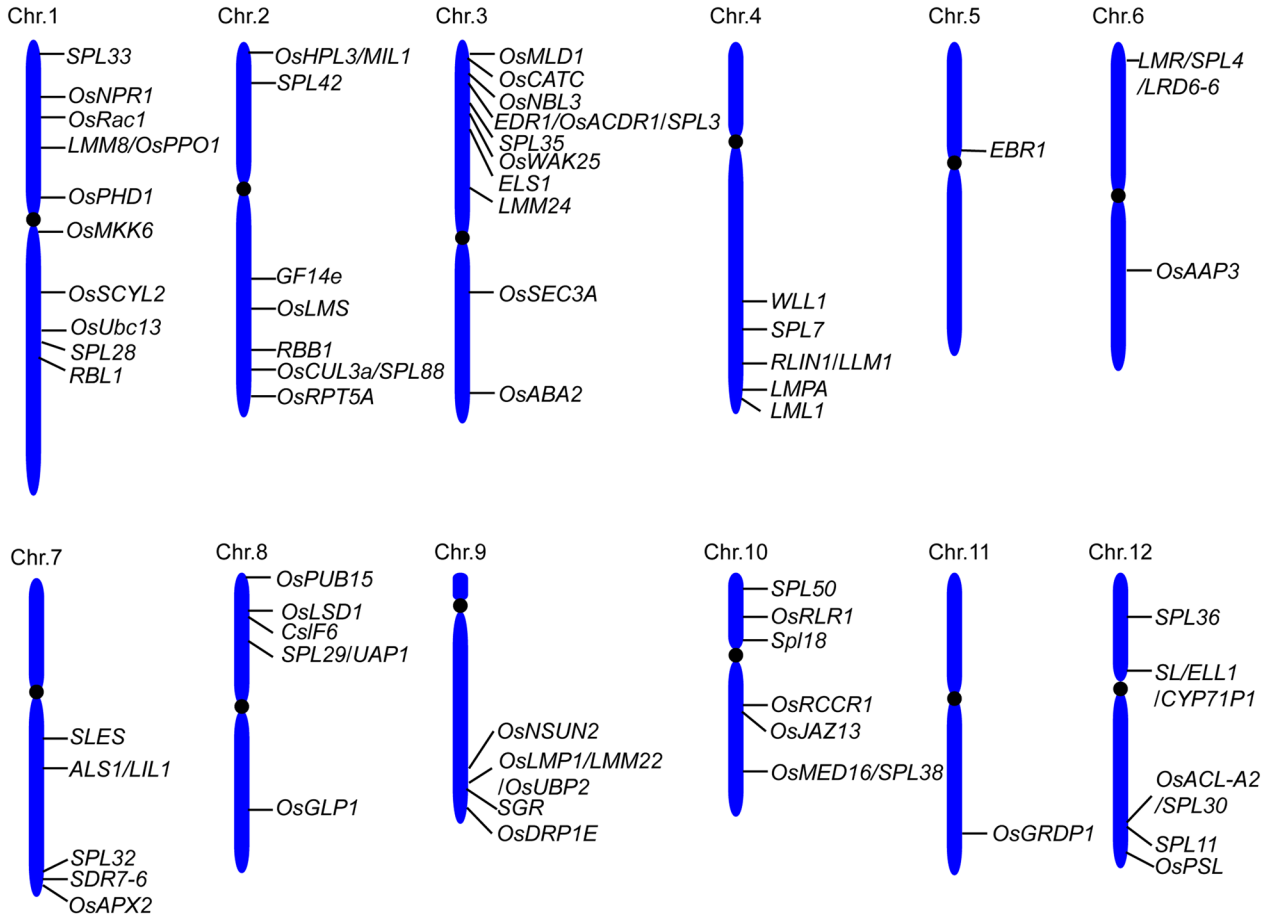

Fig. 1 Distribution of the cloned LMM genes on rice chromosomes

and 3; 5 to each of chromosomes 4, 7, 8, and 12; and one each to chromosomes 5 and 11 (Fig. 1).

Subcellular localization reveals that 40 LMM proteins harbor one localization. Among them, 10 proteins are located to the nucleus, 9 to the chloroplast, 7 to the cytoplasm, 6 to the endoplasmic reticulum (ER), 4 to the plasma membrane, 2 to mitochondria, and 1 each to the peroxisome and Golgi apparatus. Seven LMM proteins have two locations: OsHPL3/MIL1 is localized to the chloroplast and cytoplasm; OsMLD1 to the ER and Golgi; OsACL-A2, OsCUL3a/SPL88, and OsJAZ13 to the nucleus and cytoplasm; and OsGRDP1 and SPL36 to the cytoplasm and plasma membrane. Furthermore, OsSCYL2 is localized to three organelles (Golgi, trans-Golgi network, and prevacuolar compartment) (Table 1; Fig. 2). Functional analysis of cloned LMM genes indicates them to be mainly involved in gene transcription and protein translation, ubiquitin–proteasome pathway, protein phosphorylation, vesicle trafficking, metabolic pathways, phytohormone signaling, and others (Fig. 2).

Regulation Pathway of Rice LMM Genes

4.1 LMM Genes Involved in Gene Transcription and Protein Translation

Transcriptional factors (TFs) play essential roles in the growth and developmental responses of various plants. TFs, including transcriptional activators and repressors, determine initiation of transcription and often regulate spatiotemporal expression levels of target genes (Zhu et al. 2020; Ren et al. 2023). Several families of transcriptional regulators control LMM phenotypes in rice. *SPL7* encodes a heat stress TF, which has transcriptional activity. Both overexpression and knockout of *SPL7* result in LM and enhance resistance to blast and bacterial blight, accompanied by growth retardation, whereas moderate expression of *SPL7* increases resistance without LM and severe growth defects (Yamanouchi et al. 2002; Hoang et al. 2019). Expression of *OsLSD1*, which encodes zinc finger proteins and regulates rice PCD, is light-induced and dark-suppressed. Antisense transgenic *OsLSD1* rice manifests the LM phenotype and has enhanced resistance to blast (Wang et al. 2005).

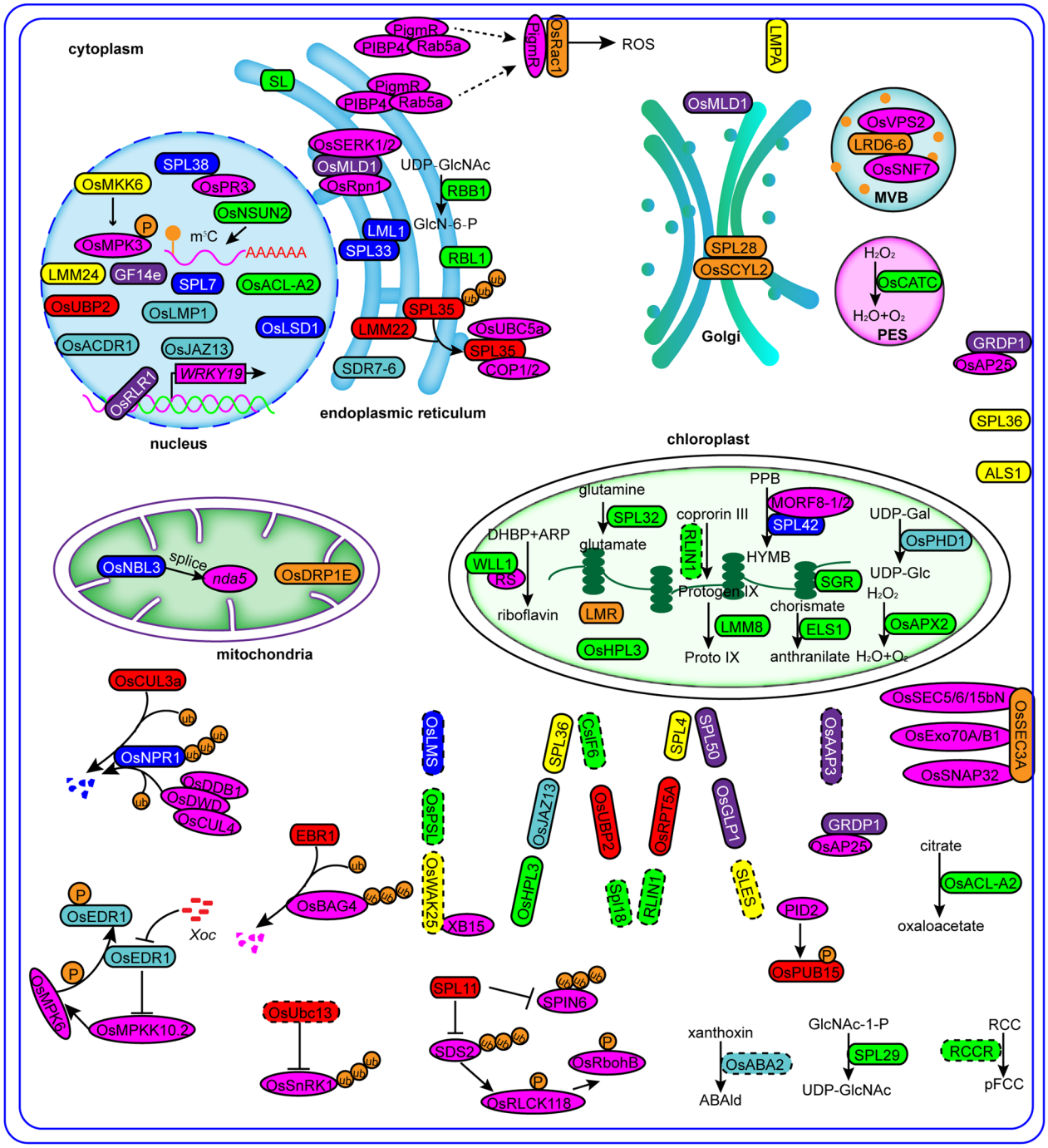

Fig. 2 The regulation mechanisms of LMM proteins in rice. The proteins in blue are involved in transcription and protein translation; the proteins in red are involved in ubiquitin–proteasome pathway; the proteins in yellow are involved in protein phosphorylation; the proteins in orange are involved in vesicle trafficking; the proteins in green are involved in metabolic pathway; the proteins in purple are involved in other regulation pathway; the proteins in indigo blue are involved in phytohormone signaling; the proteins in pink represent the interaction factors of the LMM proteins. Proteins represented by dashed lines indicate those with unclear subcellular localization, whereas proteins represented by solid lines indicate those with clear subcellular localization. The dashed arrows indicate that the regulatory pathway is unclear. PES, Peroxisomes; MVB, multivesicular bodies; PPB, porphobilinogen; HYMB, hydroxymethylbilane; ABAld, abscisyl aldehyde; RCC, red chlorophyll catabolite; pFCC, primary fluorescent chlorophyll catabolite; *Xoc*, *X. oryzae* pv. *Oryzicola*

OsNPR1 is a key regulator of systemic acquired resistance, conferring rice lasting broad-spectrum resistance. *OsNPR1*-overexpression plants develop LM spots on leaves in greenhouse, and acquire high levels of resistance to bacterial blight (Chern et al. 2005). OsNPR1 is a substrate of the OsCUL4-OsDDB1-OsDWD1 E3 ligase complex, in which OsNPR1 interacts with OsDWD1. Enhanced resistance in *OsDWD1* knockout lines depends on accumulation of OsNPR1 (Choi et al. 2022). Chern et al. (2016) screened a rice mutant (*snim1*) that suppresses *OsNPR1*-mediated immunity, and demonstrated deletion of two cysteine-rich-receptor-like kinase genes (*CRK6* and *CRK10*) to cause the *snim1* mutant phenotype. Mediator (MED) is an evolutionarily conserved multisubunit complex that controls gene expression by acting as a bridge between transcription factors and RNA polymerase II during transcription initiation. *SPL38* encodes MEDIATOR SUBUNIT 16 (OsMED16), which interacts with and inhibits chitinase precursor protein OsPR3, a positive regulator of rice innate immunity. The *spl38* mutant exhibits LM and enhanced resistance to rice blast and bacterial blight, whereas overexpression of *OsMED16* results in increased rice susceptibility to blast. The *ospr3 osmed16* double mutants exhibit no LM phenotype, suggesting that OsMED16 negatively regulates cell death in an *OsPR3*-dependent manner (Zhang et al. 2023a).

All RNA transcripts can undergo some form of post-transcriptional processing. Transcription of eukaryotic genes yields RNA precursors containing introns that must be spliced out and the flanking exons ligated together. RNA editing is an important post-transcriptional mechanism that alters the primary RNA sequence through the insertion/deletion or modification of specific nucleotides (Piazzi et al. 2023). In rice, several genes involved in RNA splicing and editing also regulate LM development. OsNBL3, a P-type pentatricopeptide repeat protein, is essential for mitochondrial development; it participates in the splicing of mitochondrial gene *nad5* intron 4. Functional loss of *OsNBL3* causes spontaneous cell death and enhances disease resistance (Qiu et al. 2021). *OsLMS* encodes a double-stranded RNA binding domain containing protein. A single-base G-A substitution in the splicing junction of *OsLMS* results in a splicing error that causes the LM phenotype and enhanced resistance to rice blast (Undan et al. 2012). *SPL42* encodes a porphobilinogen deaminase involved in chlorophyll and heme biosynthesis. SPL42 interacts with the multiple organelle RNA editing factors (MORFs) OsMORF8-1 and OsMORF8-2 to affect RNA editing. A single-base C-T substitution in the second exon of *SPL42* reduces porphobilinogen deaminase enzyme activity, and leads to the reddish-brown spotted leaf phenotype (Liu et al. 2023b).

Translation is divided into initiation, elongation, and termination phases. Translation elongation is controlled by eukaryotic translation elongation factor 1 alpha (eEF1A), which delivers aminoacylated tRNAs to the ribosome to lengthen nascent polypeptides (McLachlan et al. 2019). Translation termination is regulated by eukaryotic release factors eRF1 and eRF3, which form a ternary complex with a GTP molecule to enter the A-site of the ribosome. *SPL33* encodes an eEF1A-like protein, the functional loss of which causes cell death, early leaf senescence, and enhanced resistance to blast and bacterial blight. Both pathogen-associated molecular pattern-triggered immunity and effector-triggered immunity are activated in the *spl33* mutant (Wang et al. 2017). *LML1* encodes an eRF1 protein and is conserved in yeast, animals, and plants. The *lml1* mutant exhibits LM and phenotypic growth delay. Protein interaction assays indicate that LML1 forms a complex with SPL33, which is conserved between rice and yeast (Qin et al. 2018).

4.2 LMM Genes Involved in the Ubiquitin-Proteasome Pathway

Modification of target proteins by ubiquitin chains is an important regulatory process in eukaryotes. Protein ubiquitination is regulated by the ubiquitin-activating enzyme (E1), the ubiquitin-conjugating enzyme (E2), and the ubiquitin ligase (E3), which target ubiquitin to its substrate and tag the substrate for degradation by the 26S proteasome (Ren et al. 2023). The role of the ubiquitination proteasome pathway in regulating the LM phenotype in rice has been extensively researched. OsCUL3a/SPL88, a component of RING E3 ubiquitin ligases, is important for regulating cell death and immunity. OsCUL3a interacts with and degrades the cell-death positive regulator OsNPR1. The LM in the *oscul3a* mutant is caused by OsNPR1 accumulation, in which knockout of *OsNPR1* significantly inhibits cell death. Therefore, OsCUL3a negatively regulates cell death and immunity by degrading OsNPR1 in rice (Liu et al. 2017). *EBR1* encodes an E3 ubiquitin ligase and is a negative regulator of rice PCD and immunity. EBR1 interacts with OsBAG4, belongs to the BAG (Bcl-2-associated athanogene) family, and targets OsBAG4 for ubiquitination degradation. In the *ebr1* mutant, the accumulation of OsBAG4 triggers PCD and autoimmunity and decreasing *OsBAG4* expression inhibits cell death and disease resistance (You et al. 2016). SPL11 has E3 ubiquitin ligase activity and is a negative regulator of plant cell death and the defense response. *SDS2* encodes an S-domain receptor-like kinase and interacts with and phosphorylates SPL11, which then

ubiquitinates SDS2 to regulate its stability. In the *spl11* mutant, the mutation of *SDS2* partially suppresses LM and disease resistance. Furthermore, SDS2 interacts with OsRLCK118 and OsRLCK176 (two positive regulators of rice immunity). OsRLCK118 phosphorylates the NADPH oxidase OsRbohB to induce ROS burst during pathogen infection (Fan et al. 2018). *SPIN6* encodes a Rho GTPase-activating protein that is ubiquitinated and degraded by SPL11. Knockout of *SPIN6* leads to PCD and increased resistance to rice blast and bacterial blight (Liu et al. 2015).

OsPUB15 encodes a cytosolic U-box protein, which interacts with the kinase domain of PID2 (PID2K). PID2K has kinase activity and is able to phosphorylate OsPUB15 and phosphorylated form of OsPUB15 has E3 ligase activity. Overexpressing *OsPUB15* displays cell death lesions spontaneously and a constitutive activation of plant basal defense responses (Wang et al. 2015a). *OsUbc13* negatively regulates immunity against pathogens, and *OsUbc13*-RNAi lines exhibit HR-like lesions and enhanced resistance to blast and bacterial blight. OsUbc13 belongs to an E2 protein, which interacts with OsSnRK1. Silencing *OsUbc13* inhibits K63-linked polyubiquitination on OsSnRK1a, leading to enhanced SnRK activity. In the *OsUbc13*-RNAi line, knockdown of *OsSnRK1a* decreases disease resistance to blast to a level between those of the *OsUbc13*-RNAi line and WT, suggesting that regulation of rice blast resistance by *OsUbc13* is partially dependent on *OsSnRK1a* (Liu et al. 2023a). OsRPT5A belongs to 26S protease regulatory subunit 6A, and a point mutation (T-A) in the eighth exon of *OsRPT5A* leads to extensive leaf necrosis characterized by persistent reddish-brown leaf spots (Wang et al. 2024). *SPL35* encodes a CUE domain-containing protein, which interacts with the E2 protein OsUBC5a; knockdown of *OsUBC5a* causes LM resembling those in the *spl35* mutant, suggesting that *SPL35* may be involved in ubiquitination (Ma et al. 2019).

4.3 LMM Genes Involved in Protein Phosphorylation

Protein phosphorylation, a kind of post-translational modification, plays a critical role in signaling transduction during plant development and environmental adaptation. By precisely phosphorylating key components in signaling cascades, plants can switch on or off the specific signaling pathways needed for growth or defense (Zhang et al. 2023b). Protein phosphorylation is dynamically and reversibly catalyzed by protein kinases and protein phosphatases, respectively (Li and Liu 2021).

In rice, at least six genes associated with protein phosphorylation can regulate LM formation. *OsMKK6* encodes a MAP Kinase Kinase, the mutation of which in the *rsr25* mutant causes reddish-brown spots. OsMKK6 interacts with and phosphorylates OsMPK4 to form a MAPK cascade that negatively regulates immune responses (Jiang et al. 2023). SLES contains a kinase domain and is a member of the Raf MAPKKK family. A single nucleotide substitution in the sixth exon of *SLES* causes a mutant phenotype with LM restricted to the leaf sheath (rather than leaf blade), decreased chlorophyll content, ROS burst, and improved resistance to pathogen infection (Lee et al. 2018). *SPL36* encodes a receptor-like protein kinase containing leucine-rich domains. A single base replacement (T-C) at position 1462 in the coding region of *SPL36* causes a cysteine-to-arginine substitution that leads to cell death, growth and development retardation, and enhanced resistance to rice bacterial pathogens (Rao et al. 2021).

LIL1/ALS1 encodes a cysteine-rich receptor-like kinase. A missense G-A mutation in the fourth exon of *LIL1* creates a semi-dominant allele, which causes significantly elevated expression levels of *LIL1* that lead to the LM phenotype (Zhou et al. 2017; Du et al. 2019). *LMM24* encodes a receptor-like cytoplasmic kinase, two nucleotide substitutions and a 54 bp insertion in the fourth exon in the *lmm24* mutant displays dark brown lesions, enhanced resistance to blast, and early leaf senescence (Zhang et al. 2019). *OsWAK25* encodes a wall-associated kinase belonging to a sub-family of receptor-like kinases, that is induced by benzothiadiazole and wounding. Overexpressing *OsWAK25* lines have small necrotic spots, upregulation of PR genes (*NH1*, *OsPAL2*, *PBZ1*, and *PR10*), enhanced resistance to blast and bacterial blight, and increased susceptibility to *Rhizoctonia solani* and *Cochliobolus miyabeanus.* OsWAK25 interacts with XB15, a Type 2C protein phosphatase, overexpression of which compromises resistance to bacterial blight conferred by *OsWAK25* (Harkenrider et al. 2016).

LMM Genes Involved in Intracellular Vesicle Trafficking

Intracellular vesicle trafficking is a process that maintains intracellular material exchange and signal transmission. Vesicle trafficking transports cargo from the donor membrane to the target membrane, and plays an important role in plant immune responses (Robatzek et al. 2007; Cui et al. 2022). *SPL28* encodes a clathrin-associated adaptor protein complex 1, medium subunit micro 1 (AP1M1) involved in the post-Golgi trafficking pathway. *SPL28* participates in regulation of vesicular trafficking, expression of which in *apm1-1* Delta yeast mutants rescues the membrane trafficking defect (Qiao et al. 2010). OsSCYL2 belongs to a SCYL protein family and is a component of clathrin-mediated vesicle trafficking. OsSCYL2 interacts with SPL28 and the

interaction between them depends on clathrin protein OsCHC1, which provides an anchoring point for the interaction. Functional loss of *OsSCYL2* results in the LM phenotype and enhanced resistance to bacterial pathogens (Yao et al. 2022). Rice exocyst subunit OsSEC3A, involved in exocytosis, interacts with other exocyst subunits (OsExo70A1, OsExo70B1, OsSEC5, OsSEC6, and OsSEC15bN), indicating OsSEC3A is a member of the exocyst complex. OsSEC3A can bind phospholipids, which participate in plant disease resistance. The *ossec3a* mutant exhibits an LM phenotype and enhanced defense responses. OsSEC3A also interacts with OsSNAP32, a SNAP25-type SNARE protein involved in blast resistance, confirming the role of OsSEC3A in the defense response (Ma et al. 2018). *LRD6-6*/*LMR*/*SPL4* encodes a AAA ATPase, and possesses ATPase activity that is required for full function of LRD6-6. *LRD6-6* is essential for MVBs-mediated vesicular trafficking and prevents the biosynthesis of antimicrobial metabolites for immune responses in rice. LRD6-6 interacts with ESCRT-III components OsSNF7 and OsVPS2. The *lrd6-6* mutant manifests dysregulated MVBs-mediated vesicular trafficking, enhanced basal defense, and spontaneous cell death (Zhu et al. 2016). *LMPA* encodes a proton pump ATPase protein and is localized in the plasma membrane. A 433-bp fragment insertion in *LMPA* promoter results in the decreased promoter activity causing the reddish-brown lesions on leaf surface. The LM phenotype is sensitive to high temperatures and no obvious lesions are observed on in *lmpa* under low temperatures (Hu et al. 2022).

GTPases, the molecular switch toggling between an inactive GDP-bound state and an active GTP-bound state, play important roles in vesicle trafficking (Teng 2022). OsDRP1E, a group of large GTPases, can form a higher-order complex through self-interaction and negatively regulate cytochrome c release and PCD. Functional loss of *OsDRP1E* results in LM and enhanced disease resistance. The E409V substitution in OsDRP1E decreases the GTPase, impedes formation of higher-order complexes by disturbing its self-interaction, abolishes the mitochondrial localization of OsDRP1E that affects mitochondrial morphology, and increases the concentration of cytoplasmic cytochrome c (Li et al. 2017). *OsRac1* encodes a GTPase with both GTP-binding and GTPase activities and regulates ROS production and cell death in rice. Overexpression of a constitutively active form of *OsRac1*, in which a glycine at position 19 is substituted by valine, induces ROS production and necrotic lesions in leaf tissues. Overexpression of the dominant negative form of *OsRac1*, in which a threonine at position 24 is changed into asparagine, blocks ROS production, cell death, and LM formation in the *sl* mutant (Kawasaki et al. 1999). OsRac1 associates with PigmR, a broad-spectrum rice blast resistance gene, in which PigmR activates OsRac1 to stimulate ROS generation and trigger immune responses (Liang et al. 2024).

LMM Genes Involved in Metabolic Pathways

Enzymes are the proteins responsible for the catalysis of life. Plant growth and metabolism are jointly regulated by a variety of enzymes, the disruption of which causes plant metabolic disorder. At least 19 key enzymes involved in different metabolic pathways have been identified to regulate LM development, conferring autoimmunity and cell death in rice. *OsPPO1*/*LMM8* and *RLIN1*/*LLM1* encode protoporphyrinogen IX oxidase and coproporphyrinogen III oxidase, respectively, both of which are involved in tetrapyrrole metabolism. Protoporphyrinogen IX oxidase catalyzes the oxidation of Protogen IX to Proto IX. Mutation of *OsPPO1* causes spotted and rolled leaf; its overexpression enhances resistance to the herbicides oxyfluorfen and acifluorfen under field conditions (Liu et al. 2022; Zhao et al. 2023). A missense mutation in the second or last exon of *RLIN1* (*LLM1*) results in lesion spots in *rlin1* mutant leaves (Sun et al. 2011).

RBB1, Spl18, OsPSL, and OsNSUN2 are transferases. *RBB1* encodes a glucosamine-6-phosphate acetyltransferase, involved in D-glucosamine 6-phosphate acetylation. The *rbb1* mutant shows reduced enzyme activity, UDP-GlcNAc content, and enhanced broad-spectrum disease resistance. Proteome analysis reveals alterations in the N-glycosylation of several disease-resistant-related proteins, with a significant reduction in N-glycosylation modifications of two peroxidases (Prx4 and Prx13) in *rbb1-1*. Knockout of *Prx4* or *Prx13* enhances the immune response (Zhang et al. 2024). *Spl18* encodes an acyltransferase, and a T-DNA insertion downstream of *Spl18* results in the LM phenotype (Mori et al. 2007). *OsPSL* encodes a putative core 2/I branching beta-1,6-N-acetylglucosaminyl transferase involved in protein glycosylation modification. In the *psl* mutant, ethylene-related metabolic enzymes including S-adenosyl methionine synthetase are significantly increased, resulting in higher ethylene concentrations than in WT plants. Treatment with ethylene biosynthesis inhibitor partially rescues the mutant phenotype (Ke et al. 2019). *OsNSUN2* encodes an RNA 5-methylcytosine (m^5C) methyltransferase. In *osnsun2* the relative density of m^5C/C is approximately 30% lower compared with WT. The *osnsun2* mutant exhibits chloroplast dysfunction, disturbed photosynthesis gene expression, and a severe temperature- and light-dependent LM phenotype (Tang et al. 2020).

OsCATC and *OsAPX2* participate in ROS metabolism. *OsCATC* encodes a catalase. A single base mutation (C–T) of nucleotide 752 in the third exon of *OsCATC* causes abnormal chloroplast development and starch metabolism resulting in the LM and enhanced blast disease resistance (Liao et al. 2022). *OsAPX2* encodes a ascorbate peroxidase (APX), converting H_2O_2 into H_2O and O_2. Expression of *OsAPX2* is developmentally and spatially regulated, and induced by drought, salt, and cold stresses. In the *osapx2* mutant, APX activity is significantly reduced, and results in semi-dwarf seedlings, yellow-green leaves, LM, and seed sterility (Zhang et al. 2013). OsHPL3/MIL1 and ACL-A2/SPL30 are lyases. *OsHPL3/MIL1* encodes a hydroperoxide lyase (HPL) and possesses intrinsic HPL activity, catalyzing hydroperoxylinolenic acid to produce green leaf volatiles. *OsHPL3* positively regulates resistance to the brown planthopper on rice, but negatively modulates resistance to the striped stem borer (Tong et al. 2012; Tu et al. 2020; Yan et al. 2022). *ACL-A2*/*SPL30* encodes an ATP-citrate lyase catalyzing citrate to generate oxaloacetate and acetyl-CoA. A single base transversion (A–T) converts the Asn to Tyr, leading to significant degradation of SPL30 and attenuates ACL enzymatic activity resulting in ROS accumulation and the LM phenotype. Furthermore, suppressor screen, expression analysis, and allelism analysis reveal *SPL30* to be epistatic to *SL*, which acts as a downstream regulator in *spl30*-mediated defense responses in the serotonin metabolic pathway (Ruan et al. 2019).

RBL1, *WLL1*, *ELS1*, *CslF6*, and *SPL32* encode a series of synthases. RBL1 belongs a cytidine diphosphate diacylglycerol synthase, which is essential for phospholipid biosynthesis. Mutation of *RBL1* results in decreased levels of phosphatidylinositol and its derivative phosphatidylinositol 4, 5-bisphosphate (PtdIns(4,5)P_2). The exogenous supplementation of the medium with phosphatidylinositol postponed lesion formation in *rbl1* mutant (Sha et al. 2023). *WLL1* encodes a lumazine synthase, which interacts with riboflavin synthase to control riboflavin biosynthesis. The *wll1* mutant manifests a white and lesion-mimic phenotype with decreased riboflavin levels. Application of the riboflavin derivative flavin adenine dinucleotide rescues the *wll1* phenotype (Hu et al. 2021). *ELS1* encodes an anthranilate synthase α-subunit participating in anthranilate biosynthesis, an intermediate metabolite in the tryptophan synthesis pathway. In the *els1* mutant, the levels of most tryptophan intermediate metabolites are significantly increased. Mutation of *ELS1* induces expression of *ASA1*, a homolog of *ELS1*, through a genetic compensation response, causing ROS accumulation and PCD. In the *els1* mutant the knockdown of *ASA1* rescues leaf lesion (Li et al. 2024). The cellulose synthase-like F gene *CslF6* regulates biosynthesis of mixed-linkage glucan, a cell wall polysaccharide involved in regulation of cell-wall expansion. Knockout of *CslF6* drastically reduces mixed-linkage glucan content, weakens cell walls in mature stems, causes LM formation, and enhances disease resistance (Vega-Sanchez et al. 2012). *SPL32* encodes a ferredoxin-dependent glutamate synthase (Fd-GOGAT), in *spl32* mutant the enzyme activity of GOGAT is significantly decreased compared with WT, which significantly inhibits the reassimilating of ammonia and causes the necrotic spots and defense response (Sun et al. 2017).

SGR and *OsRCCR1* regulate chlorophyll metabolism. *SGR* encodes a chlorophyll-degrading Mg^+-dechelatase, overexpression of which leads to singlet oxygen release and Chl-dependent regional lesion-mimic cell death in leaves. Furthermore, promoter variations of *SGR* trigger higher and earlier induction of *SGR* in *indica*, accelerating *indica* senescence (Jiang et al. 2011). Knockdown of the red chlorophyll catabolite reductase gene *OsRCCR1* also causes lesion-mimic spots in older leaves (Tang et al. 2011). *SL*/*ELL1*/*CYP71P1* encodes a cytochrome P450 monooxygenase, which exhibits tryptamine 5-hydroxylase enzyme activity and converts tryptamine to serotonin. Exogenously applied serotonin induces defense-gene expression and cell death in rice suspension cultures, and increases rice blast resistance (Fujiwara et al. 2010; Cui et al. 2021; Zheng et al. 2021). *SPL29* encodes a UDP-N-acetylglucosamine pyrophosphorylase 1 (UAP1) using N-acetylglucosamine-1-phosphate as a substrate to generate UDP-N-acetylglucosamine. Mutation of *SPL29* eliminates UAP enzymatic activities, resulting in the LM. Exogenous application of UDPG can aggravate lesion initiation and development in the *spl29* mutant (Wang et al. 2015c). UAP2, a homolog of UAP1 (SPL29), shares high sequence identities, 3D structures and UAP enzymatic activity with UAP1. Overexpression of *UAP2* can completely rescue the mutant phenotype, providing direct evidence for a similar function between UAP1 and UAP2 (Wang et al. 2021).

LMM Genes Involved in Phytohormone Signaling

Plant hormones are a group of small signaling molecules produced by plants at very low concentrations that have the ability to move and function at distal sites, which have pivotal roles in the regulation of immune responses. In rice at least six LMM genes are reported to be involved in plant hormones signaling including salicylic acid (SA), jasmonic acid (JA), abscisic acid (ABA), and ethylene (ET). OsJAZ13 belongs to a subgroup of TIFY family, the expression of which is transiently responded to JA and ET. *OsJAZ13* has three splice variants: *OsJAZ13a*, *OsJAZ13b*, and *OsJAZ13c*. OsJAZ13a interacts with JA signaling pathway regulators OsMYC and OsNINJA.

After MeJA treatment, the nucleus localization signaling of OsJAZ13a disappeared. Overexpression of *OsJAZ13a* develops LM in the sheath (Feng et al. 2020). *OsLMP1*/*OsUBP2*/*LMM22* encodes a ubiquitin-specific protease. *OsLMP1* can cleave ubiquitination precursors and epigenetically modify SA synthetic pathway genes by deubiquitinating H2B to regulate the immune response. In the *lmp1-1* mutant the phenylalanine ammonia lyase pathway is activated, causing the accumulation of SA (Sun et al. 2021). *SDR7-6* encodes a short-chain alcohol dehydrogenase that forms homomultimers. In the *sdr7–6* mutant the relative expression levels of marker genes in the SA and JA pathways are significantly increased and total JA content is also significantly elevated, resulting in cell death, adverse agricultural characters, and increased resistance to bacterial blight, but decreased resistance to blast disease (Zheng et al. 2022). OsABA2, a xanthoxin dehydrogenase, involved in ABA biosynthesis, converts xanthoxin to abscisyl aldehyde. Mutation of *OsABA2* results in significantly decreased ABA levels leading to pre-harvest sprouting, enhanced growth, spontaneous cell death, and enhanced resistance. Exogenous application of ABA rescues the LM phenotype in the *lmm9150* mutant (Liao et al. 2018).

OsPHD1, a UDP-glucose epimerase, is localized in the chloroplast. In the *lm212-1* mutant JA and MeJA contents are significantly increased and the JA signaling pathways appear to be disordered that result in the enhanced resistance to bacterial blight (Gao et al. 2022). *SPL3*/*OsEDR1*/*OsACDR1* encodes a putative MAPKKK that promotes ethylene synthesis, and suppresses SA- and JA-associated defense signaling. Functional loss of *OsEDR1* results in spontaneous lesions and enhanced resistance to bacterial blight, but increased susceptibility to blast, related to increased accumulation of SA and JA and suppressed accumulation of 1-aminocyclopropane-1-carboxylic acid (ACC). ACC treatment inhibits SA and JA biosynthesis, rescues the lesion phenotype and increases susceptibility to bacterial blight (Shen et al. 2011; Wang et al. 2015b). Furthermore, OsEDR1 interacts with OsMPKK10.2 to inhibit its phosphorylation and kinase activity. In the *osedr1* mutant, knockout of *OsMPKK10.2* results in disease patterns similar to WT and displays fewer LM upon *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*) infection, OsMPKK10.2 is phosphorylated at S304 to activate OsMPK6, which phosphorylates and destabilizes OsECDR1, releasing inhibition of OsMPKK10.2; that result in enhanced resistance to *Xoc*. In the *osedr1* mutant, *OsMPK6*-knockout plants do not manifest the LM phenotype (Ma et al. 2021).

LMM Genes Involved in Other Regulation Pathways

OsAAP3 encodes amino acid transporter, overexpression of which causes abnormal gene expression in secondary metabolism and photosynthesis pathways, and leads to LM and leaf senescence in rice (Wei et al. 2021). *SPL50* encodes an ARM repeat protein that is essential to regulate ROS metabolism and boost resistance to blast disease (Ruan et al. 2024). OsMLD1, a malectin, physically interacts with ribophorin I (OsRpn1) to participate in ER quality control for glycoproteins. Furthermore, OsMLD1 interacts with OsSERK1 and OsSERK2 and suppresses OsSERK1- or OsSERK2-induced cell death. Disruption of *OsMLD1* results in spontaneous LM, enhanced disease resistance, and prolonged ER stress (Feng et al. 2022). *GF14e* encodes a 14–3–3 protein that is induced during effector-triggered immunity. *GF14e*-RNAi plants exhibit the LM phenotype and enhanced resistance to bacterial and sheath blight diseases after development of the LM phenotype, regardless of the presence of visible lesions (Manosalva et al. 2011).

Both RNAi and overexpression of *OsGRDP1*, encoding a glycine-rich domain protein, lead to the LM phenotype. OsGRDP1 interacts with the aspartic proteinase OsAP25. OsAP25 activity increases significantly in both *spl-D* mutant and overexpression lines compared with WT, and application of aspartic proteinase inhibitor pepstatin A partially suppresses lesion formation (Zhao et al. 2021). OsGLP1 is a germin-like protein, knockout of which results in UV-B-dependent LM in leaves. The *glp1* mutant manifests decreased plant height, increased leaf angle, and brown spots on leaf blades under solar radiation (including UV-B), however, there are no significant differences in phenotypes between the *glp1* mutant and WT under artificial light without UV-B (He et al. 2021). Mutation of *OsRLR1*, a NB-LRR protein, leads to HR-like lesions and broad-range resistance to blast and bacterial blight. OsRLR1 directly interacts with transcription factor OsWRKY19. Inhibition of OsWRKY19 in the *rlr1* mutant compromises the HR-like phenotype and resistance response. Furthermore, OsWRKY19 directly binds to the promoter of *OsPR10* to activate the defense response (Du et al. 2021).

Discussion and Perspective

So far, a large number of LMMs have been identified in rice, with most mutants exhibiting enhanced resistance to rice blast or bacterial blight. In addition to rice, numerous LMMs have been characterized in other crops such as wheat and maize, and some mutants are associated with disease resistance. In maize, *lls1* and *Rp1* mutants confer resistance against *Cochliobolus*

heterostrophus and *Puccinia sorghi* infections, respectively (Hu et al. 1996; Simmons et al. 1998; Smith et al. 2010; Adak et al. 2023). Both *Les4* and *Les8* mutants display enhanced resistance to *Curvularia* leaf spot (Mu et al. 2021; Li et al. 2023). In wheat, the LM line Ning7840 and *lm3* enhance resistance to leaf rust and powdery mildew, respectively (Li and Bai 2009; Wang et al. 2016). *Lm5* enhances stripe rust and powdery mildew resistance in bread wheat (Li et al. 2022). In conclusion, focusing on LMM research will facilitate the elucidation of molecular mechanisms underlying plant defense responses, thereby contributing to breeding elite varieties with improved disease resistance.

At least 61 genes that control LM have been isolated in rice. Proteins encoded by these genes fall into various functional groups (transcription and protein translation, ubiquitin–proteasome pathway, protein phosphorylation, vesicle trafficking, metabolic pathways, phytohormone signaling and others), highlighting the complexity of regulatory mechanisms. Several interactions exist between identified LMM proteins (LMM22 and SPL35, LML1 and SPL33, OsCUL3a and OsNPR1, OsSCYL2 and SPL28). It is unknown if other LMM proteins are similarly associated with each other. Furthermore, although some LMM proteins can interact with other regulators such as OsRLR1, SPL38, OsNBL3, EBR1, OsUbc13, OsEDR1, and OsRac1, most LMM proteins function independently, without interactions with other proteins. Consequently, it is necessary to identify the interaction factors of LMM proteins using transcriptome analysis, yeast library screening, and immunoprecipitation-mass spectrometry to decipher how they regulate cell death, LM development, and disease resistance. It is noteworthy that *sdr7–6* and *edr1* mutants display a unique disease resistance profile distinct from other LMMs. While other LMMs typically exhibit significantly enhanced resistance to rice blast or bacterial blight, the *sdr7–6* and *edr1* mutant specifically enhances resistance to bacterial blight while simultaneously reducing resistance to rice blast. In future researches, further identification of mutants with phenotypes similar to *sdr7–6* and *edr1* can help elucidate the distinctive disease resistance mechanisms specific to this class of mutants.

At present, the most effective and least harmful way to prevent diseases is to cultivate rice varieties with excellent resistance. Because most LMMs confer durable and broad-spectrum disease resistance to blast and bacterial blight, they represent valuable gene resources to breed resistance. However, LMMs often lead to undesirable agronomic traits, blocking gene application in rice breeding. Further research is required that focuses on trade-offs between plant growth and immunity in rice LMM. Sha et al. (2023) identified a LMM *rbl1* with broad-spectrum disease resistance, but an approximate 20-fold yield loss. *RBL1*$^{\triangle 12}$, an allele of *RBL1*, is obtained through a multiplexing genome-editing strategy to target multiple sites in *RBL1*, which has a four-amino-acid truncation and a reduced gene expression; this allele results in tiny HR-like lesions that start at the booting stage and confers robust broad-spectrum disease resistance without yield penalties. *SPL7* encodes a heat stress TF, and its overexpression and knockout results in LM accompanied by growth retardation; however, moderate expression of *SPL7* increases resistance without LM and severe growth defects (Hoang et al. 2019). Analysis of 50 LMMs with increased disease resistance reveals that 33 LMMs are caused by base substitution, insertion or deletion. Seven and eight mutants are caused by gene expression upregulation and downregulation, respectively. This provides crucial implications: we can edit the coding sequences of the LMM genes at multiple target sites to generate their alleles using genome-editing technologies such as CRISPR/Cas9, which show only tiny hypersensitive response-like lesions and confer broad-spectrum disease resistance with no obvious trade-off in yield. Furthermore, we can also edit the promoter sequences or utilize inducible promoters to precisely regulate the expressions (upregulation or suppression) of the LMM genes, thereby generating LMMs with either the number or size of lesions significantly reduced. Importantly, these mutants exhibit broad-spectrum disease resistance while maintaining unaffected yield.

Among identified LMMs, lesion formation in some of them is light- and temperature-dependent. In *spl35*, *lmm8*, *rsr1*, and *lmm22* mutants, areas of leaf that are not exposed to light develop no lesions, whereas those that are develop numerous lesions. At 30 °C, the reddish-brown lesions of *lmpa* and *spl42* mutants are serious, but no lesions are apparent when grown at 20 °C. We speculate that LM phenotype variation in the same genetic background with no sequence variation may be caused by disturbances in gene expression, protein synthesis or substance metabolism. Therefore, the molecular mechanisms of lesion formation should be further explored using transcriptomics, proteomics, and metabolomics.

Abbreviations

LMM	Lesion mimic mutant
HR	Hypersensitive response
PCD	Programmed cell death
sl	*Sekiguchi lesion*
LM	Lesion mimic
ROS	Reactive oxygen species

PR	Pathogenesis-related
WT	Wild type
ER	Endoplasmic reticulum
TFs	Transcriptional factors
APX	Ascorbate peroxidase
HPL	Hydroperoxide lyase
Fd-GOGAT	Ferredoxin-dependent glutamate synthase
SA	Salicylic acid
JA	Jasmonic acid
ABA	Abscisic acid
ET	Ethylene
Xoc	*Xanthomonas oryzae* Pv. *Oryzicola*

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics Approval and Consent to Participate
Not applicable.

Consent for Publication
The manuscript has been approved by all authors.

Competing interests
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