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# Cross kingdom immunity: the role of immune receptors and downstream signaling in animal and plant cell death

Thibault Roudaire<sup>1,2</sup>, Marie-Claire Héloir<sup>1,2</sup>, David Wendehenne<sup>1,2</sup>, Aymeric Zadoroznyj<sup>1,3</sup>, Laurence Dubrez<sup>1,3\*</sup>, Benoit Poinssot<sup>1,2\*</sup>

<sup>1</sup>Université de Bourgogne, France, <sup>2</sup>Agroécologie, Agrosup Dijon, CNRS, INRAE, Univ. Bourgogne, Univ. Bourgogne Franche-Comté, France, <sup>3</sup>INSERM U1231 Lipides, Nutrition, Cancer (LNC), France

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Review

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TR, MCH, DW, AZ, LD and BP contributed equally to the writing of this review.

### *Keywords*

Pattern recognition receptors (PRRs), Toll-like receptors (TLRs), NOD-like receptors (NLRs), Pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), Hypersensitive response (HR), programmed cell death (PCD)

### *Abstract*

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Both plants and animals use sophisticated innate immune systems to combat microbial pathogens. In these multicellular eukaryotes, innate immunity involves cell surface receptors and intracellular receptors to detect invasion patterns. Membrane-associated pattern recognition receptors (PRRs) such as Toll-Like receptors (TLRs), C-type lectin receptors (CLRs), receptor-like kinases (RLKs) and receptor like proteins (RLPs), are employed by these organisms for sensing different pathogen- or damage-associated molecular patterns (PAMPs/DAMPs) before triggering antimicrobial defenses that can be associated with a form of regulated cell death. Intracellularly, both plants and animals use nucleotide-binding domain leucine rich repeats (NLRs) immune receptors to detect effectors injected into the host cell by the pathogen to hijack the immune signaling cascade. Interestingly during the co-evolution between eukaryotes and their invaders, key cross-kingdom cell death-signaling macromolecular NLR-complexes have been selected, such as the inflammasome in mammals and the recently discovered resistosome in plants. In both cases, a programmed cell death located at the site of infection often remains the most effective mean for blocking the pathogen spread and protecting the whole organism from invasion. This review aims to compare the different immune mechanisms of animals and plants, mainly focusing on cell deaths, in order to highlight recent advances that could be used on one side or the other to link the missing signaling elements between the perception of the invasion pattern by immune receptors, the induction of defenses or the transmission of danger signals to other cells. Although knowledge of plant immunity is less advanced, these organisms have certain advantages allowing easier identification of the actors and regulators of cell death, which could then be exploited directly for crop protection purposes or by analogy for medical research.

### *Contribution to the field*

Dear Editor, please find our review about the role of immune receptors during animal and plant cell death. This review aims to compare the different immune mechanisms of animals and plants, mainly focusing on cell deaths, in order to highlight recent advances that could be used on one side or the other to link the missing signaling elements between the perception of the invasion pattern by immune receptors, the induction of defenses or the transmission of danger signals to other cells. Although knowledge of plant immunity is less advanced, these organisms have certain advantages allowing easier identification of the actors and regulators of cell death, which could then be exploited directly for crop protection purposes or by analogy for medical research.

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# Cross kingdom immunity: the role of immune receptors and downstream signaling in animal and plant cell death

1 Thibault Roudaire<sup>1</sup>, Marie-Claire Héloir<sup>1</sup>, David Wendehenne<sup>1</sup>, Aymeric Zadoroznyj<sup>2,3</sup>,

2 Laurence Dubrez<sup>2,3\*</sup>, Benoit Poinssot<sup>1\*</sup>

3

4 <sup>1</sup>Agroécologie, Agrosup Dijon, CNRS, INRAE, Univ. Bourgogne, Univ. Bourgogne Franche-Comté,  
5 F-21000 Dijon, France.

6 <sup>2</sup> Institut National de la Santé et de la Recherche Médicale (Inserm), LNC UMR1231, 21000 Dijon,  
7 France

8 <sup>3</sup> Université de Bourgogne Franche-Comté, F- 21000 Dijon, France

9 \* **Correspondence:**

10 Corresponding Authors

11 [benoit.poinssot@inrae.fr](mailto:benoit.poinssot@inrae.fr)

12 [ldubrez@u-bourgogne.fr](mailto:ldubrez@u-bourgogne.fr)

13 **Keywords:** pattern recognition receptors (PRRs), Toll-like receptors (TLRs), NOD-like  
14 receptors (NLRs), pathogen-associated molecular patterns (PAMPs), damage-associated  
15 molecular patterns (DAMPs), programmed cell death (PCD), hypersensitive response (HR).

16

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### 23 ABSTRACT

24 Both plants and animals use sophisticated innate immune systems to combat microbial  
25 pathogens. In these multicellular eukaryotes, innate immunity involves cell surface receptors and  
26 intracellular receptors to detect invasion patterns. Membrane-associated pattern recognition receptors  
27 (PRRs) such as Toll-Like receptors (TLRs), C-type lectin receptors (CLRs), receptor-like kinases  
28 (RLKs) and receptor like proteins (RLPs), are employed by these organisms for sensing different  
29 pathogen- or damage-associated molecular patterns (PAMPs/DAMPs) before triggering antimicrobial  
30 defenses that can be associated with a form of regulated cell death. Intracellularly, both plants and  
31 animals use nucleotide-binding domain leucine rich repeats (NLRs) immune receptors to detect  
32 effectors injected into the host cell by the pathogen to hijack the immune signaling cascade.  
33 Interestingly during the co-evolution between eukaryotes and their invaders, key cross-kingdom cell  
34 death-signaling macromolecular NLR-complexes have been selected, such as the inflammasome in  
35 mammals and the recently discovered resistosome in plants. In both cases, a programmed cell death  
36 located at the site of infection often remains the most effective mean for blocking the pathogen spread  
37 and protecting the whole organism from invasion. This review aims to compare the different immune  
38 mechanisms of animals and plants, mainly focusing on cell deaths, in order to highlight recent advances  
39 that could be used on one side or the other to link the missing signaling elements between the perception  
40 of the invasion pattern by immune receptors, the induction of defenses or the transmission of danger  
41 signals to other cells. Although knowledge of plant immunity is less advanced, these organisms have  
42 certain advantages allowing easier identification of the **actors** and regulators of cell death, which could  
43 then be exploited directly for crop protection purposes or by analogy for medical research.

44

45

### 46 INTRODUCTION

47 Eukaryotic cells have evolved complex defense mechanisms in order to combat microbial  
48 challenges and preserve organism integrity. Both plants and animals are endowed with a conserved  
49 innate immune system able to neutralize pathogens and contain the infection. It uses specialized  
50 receptors to detect microbial patterns, pathogen-derived compounds and danger signals and elicits an  
51 adapted specific response. The immune response includes a transcriptional reprogramming, the  
52 production of microbicidal molecules, the activation of a regulated cell death program in infected cells  
53 and the release of soluble factors such as cytokines and phyto-hormones able to signal away from the  
54 original infection site and alert the host organism to the danger. In many organisms, an immunological  
55 memory, called systemic acquired resistance (SAR) in plants (1), is also established to prevent  
56 forthcoming microbial assault. In addition, vertebrates have evolved an adaptive immune system  
57 involving specialized cells able to produce a stronger, specific immune response and ensure long-term  
58 protection.

59 The activation of cell death processes at the site of pathogen attack constitutes an efficient  
60 strategy shared by plants and animals to protect organism from pathogen invasion by directly  
61 destroying the pathogen niche. Cell death can also produce alert signals for neighboring cells through  
62 the release of intracellular components that can elicit or amplify the anti-microbial response. During a  
63 microbial infection, three types of regulated cell death are classically described in animals for confining  
64 pathogen progression: apoptosis, pyroptosis and necroptosis (2, 3). Apoptosis is defined by specific  
65 morphological criteria that includes cell shrinkage, condensation of the chromatin and fragmentation  
66 of the nucleus, plasma membrane blebbing and formation and release of apoptotic bodies that are  
67 engulfed through a phagocytosis-like process named efferocytosis. At the molecular level, apoptosis  
68 involves a cascade of events that culminates in the activation of specific proteases belonging to the  
69 caspase family responsible for cell dismantling (2). Of note, apoptosis is a “silent form” of cell death  
70 that does not directly cause inflammatory response because of conserved plasma membrane integrity  
71 and efferocytosis. Efferocytosis has even been linked to the resolution of inflammation, required for  
72 the clearance of dead cells after infection, reducing the production of inflammatory factors by  
73 phagocytes and progressively allowing the restoration of homeostasis (4). On the opposite, pyroptosis  
74 and necroptosis are associated with the release of pro-inflammatory molecules allowing the  
75 establishment of adaptive immunity. They both involve pore-forming proteins (gasdermin-D  
76 (GSDMD) in pyroptosis and mixed lineage kinase domain-like (MLKL) in necroptosis) that trigger  
77 membrane permeabilization and osmotic imbalance leading to cell swelling. Many connections exist

78 between signaling pathways leading to apoptosis, pyroptosis and necroptosis and these cell death  
79 processes can occur simultaneously.

80 Recognition of invading microbes by plants can also trigger a specific cell death referred to as  
81 hypersensitive response (HR) which efficiently blocks the spreading of biotrophic pathogens in healthy  
82 tissues by limiting their access to the plant metabolites (5).

83 However, the molecular events involved in this HR have not yet been completely deciphered.  
84 HR-associated cell death is characterized by an early rupture of the plasma membrane associated with  
85 some apoptosis-like features such as the cytoplasm shrinkage, chromatin condensation and nuclei  
86 disruption (6). These are associated with plant-specific cell death feature including the dismantling of  
87 the tonoplast and vacuolar collapse (7). Consequently, the release of active hydrolases and proteases  
88 from collapsed vacuoles can trigger autophagy-like processes (8). Thus, HR appeared as a plant  
89 regulated necrosis displaying some feature of necroptosis or pyroptosis in animals (5, 9). As observed  
90 during necroptosis and pyroptosis, leakage of cellular content can constitute alert signals for  
91 neighboring cells and prepare them to cope with infections. All of these concerted events insure a  
92 global and effective defense response.

93 The theory that innate immune response is elicited by specialized receptors which recognize  
94 conserved microbial components referred to as pathogen-associated molecular patterns (PAMPs) was  
95 laid out by Medzhitov and Janeway (10), rewarded by the Nobel Prize in 2011. The first pattern  
96 recognition receptor (PRR) was described in plants as a cell surface receptor encoded by the rice  
97 disease resistant (*R*) gene *Xa21*, which confers resistance to the bacteria *Xanthomonas oryzae* pv.  
98 *Oryzae* (11). For many years, two major strategies to study the plant innate immunity have existed.  
99 The first was based on a genetic approach: certain varieties of a plant species express *R* genes leading  
100 to the establishment of hypersensitive cell death that locally limits the spread of a pathogen. On the  
101 microbe side, genes encoding effector proteins have been called avirulence genes (*Avr*). This is the  
102 basis of the gene-for-gene concept (*R-Avr*) described by Flor on flax and then widely used for genetic  
103 breeding of crop plants (12). The second used a biochemical approach coupled by pharmacological  
104 studies instead. Several teams have purified microbial-derived compounds, commonly referred to as  
105 elicitors (chitin, flagellin, elicitin,  $\beta$ -glucans...) able to trigger plant immune responses of which very  
106 few are capable of inducing HR cell death. They also characterized high-affinity plasma membrane  
107 binding sites interacting with elicitors and showing biochemical features of receptors. To combine the  
108 results of these two approaches and to get closer to the concept of PAMPs existing in mammals came

109 the concept of PAMP-Triggered Immunity (PTI) that takes into account the recognition of PAMPs by  
110 surface receptors and Effector-Triggered Immunity (ETI) related to the recognition of effectors  
111 (pathogen *Avr* gene products) by intracellular receptors (encoded by *R* genes). However, this PTI-ETI  
112 concept initially proposed by Jones and Dangl (13) was a bit controversial because it was too binary  
113 (ETI or PTI) and did not reflect all the existing shade of gray levels of plant immune responses, notably  
114 during symbiotic interactions. Recently, new models have emerged in the plant innate immunity with  
115 the concept of invasion patterns (IP) (14) and signs of danger perceived by a complex plant surveillance  
116 system that can produce secondary host-derived immunogenic factors termed phytochemicals (15).

117 This review aims to compare the immune responses existing in mammals and plants, mainly  
118 focusing on recent advances in the discovery of immune receptors and the involvement of signaling  
119 pathways leading to cell death. From this comparison emerged similarities and specificities of these  
120 multicellular eukaryotes that unravel future perspectives of research.

121

### 122 **MEMBRANE-ASSOCIATED PRRs**

123 Cells employ a large number of cell surface or endosomal receptors to sense PAMPs and  
124 endogenous danger signals referred to as damage-associated molecular patterns (DAMPs) to engage  
125 defense responses. In vertebrates, membrane-bound immune receptors belong to the Toll-like receptors  
126 (TLRs) family, which are located either at the cell surface or within the endosomal compartment and  
127 cell surface C-type lectin receptors (CLRs). On their side, plant PRRs are mainly plasma membrane-  
128 localized and are divided into two categories: the receptor-like kinases (RLKs) and the receptor-like  
129 proteins (RLPs) (Figure 1). In both plants and vertebrates, recognition of PAMPs/DAMPs by  
130 membrane PRRs primarily activates transcriptional programs that culminate in the production of  
131 microbicidal molecules and in the implementation of an adaptive response of the host to pathogen  
132 attack.

133 Membrane-bound PRRs are composed of an N-terminal extracellular domain that functions as a  
134 ligand recognition and binding domain, a transmembrane intermediate and a C-terminal cytoplasmic  
135 signal transducing domain (Figure 1). In animals, PAMPs are recognized by tandem copies (19-25) of  
136 LRR (leucine-rich repeat) in TLRs and by C-type lectin-like domains in CLRs (16). Thirteen TLR  
137 paralogs were described in vertebrates. Cell surface TLRs (TLR1, 2, 4-6 and 10) recognize components  
138 of microbial membrane such as lipids, lipoproteins, membrane anchored proteins, or extracellular

139 proteins bound to pathogens such as heat shock proteins (HSP) 60 and 70 while TLRs found within  
140 endosomal compartment (TLR3, 7-9 and 11-13) likely sense virus and bacteria-derived nucleic acids  
141 or endogenous nucleic acid in pathological conditions. On the other hand, CLRs are dedicated to the  
142 defense against fungal infections (16). CLRs can also sense commensal fungus and thus contribute to  
143 maintain homeostasis (17, 18). Molecular mechanisms of signal transduction in animal cells are well  
144 characterized. They involve the presence of conserved modular domains found in receptors, adaptor  
145 proteins or signaling effectors and that mediate through homotypic interaction the assembly of  
146 oligomeric signaling platform favoring the activation by proximity of signaling effectors. In TLRs, the  
147 intracytoplasmic signal transduction domain is the conserved Toll/IL-1 receptor (TIR) domain, also  
148 found in the adaptor proteins myeloid differentiation factor 88 (MyD88), MyD88 adaptor-like (MAL),  
149 TIR-domain-containing adaptor-inducing IFN- $\beta$  (TRIF), TRIF-related adaptor molecule (TRAM) and  
150 sterile  $\alpha$ - and armadillo-motif-containing protein (SARM). Ligand binding triggers TLR homo- or  
151 hetero-dimerization, conformational change in their intracellular TIR domain and the consecutive  
152 recruitment *via* TIR-TIR homotypic interaction of adaptor proteins to form a signaling platform and  
153 initiate downstream signaling pathway. TLR stimulation engages MAPKs and/or NF- $\kappa$ B and  
154 ultimately promotes inflammatory response that constitutes the first line of defense in mammals and  
155 appears critical to maintain homeostasis and tissue integrity. This includes the production of  
156 microbicidal molecules, pro-inflammatory cytokines and immune cell differentiating mediators  
157 responsible for the recruitment and activation of specialized immune cells to the site of infection  
158 (Figure 2) (19). However, in some situations such as a sustained infection, the presence of pathogens  
159 that resist to inflammatory defense or in some pathological conditions (*e.g.* some cancers, X-linked  
160 lymphoproliferative syndrome type 2 (XLP-2)) (20, 21), some TLRs such as TLR3 that recognizes  
161 virus-derived double stranded RNAs and RNAs released from damaged cells, and TLR4 that senses  
162 LPS from Gram-negative bacteria, can also trigger cell death (22-24). In CLRs, the signal transduction  
163 motif is the immunoreceptor tyrosine-based activation motif (ITAM) or ITAM-like motif that mediate  
164 the binding and activate phosphorylation of the spleen tyrosine kinase (Syk). Generally, CLR  
165 stimulation does not trigger cell death but results in MAPKs, NF- $\kappa$ B or interferon-regulatory factors  
166 (IRFs) activation (16).

167 Plants have evolved hundreds of membrane PRRs able to recognize a wide variety of PAMPs  
168 such as flagellin, peptidoglycan, chitin, elicitin, polygalacturonase, xylanase... (25, 26) or DAMPs  
169 such as fragments of the plant cell wall extracellular matrix (oligogalacturonides from pectins,  
170 cellobiose and cellodextrines from cellulose and xyloglucans from hemicellulose) (27, 28),

171 extracellular ATP, NAD<sup>+</sup> or the secondary endogenous phyto-cytokines such as systemin, RALFs,  
172 PIPs and PEPs plant peptides (15). The diversity of sensed PAMPs is made possible thanks to the  
173 presence of different extracellular domains (Figure 1). For example, LRRs found in flagellin sensing 2  
174 (FLS2) sense flagellin or its 22-amino acid epitope flg22 (29, 30), whereas Lysin motif (LysM)  
175 specifically recognizes chitin oligosaccharides in chitin elicitor receptor kinase 1 (CERK1) associated  
176 with LYK4/5 (31-34) or peptidoglycan with lysin-motif proteins LYM1/LYM3 (35). Epidermal  
177 growth factor (EGF)-like domain present in the wall-associated kinase 1 (WAK1) senses  
178 oligogalacturonides released during the degradation of the plant cell wall by fungal hydrolases (36, 37)  
179 whereas the lectin domains present in AtLecRK1.9 (DORN1) and AtLecRK1.8 perceive extracellular  
180 ATP and NAD<sup>+</sup>, respectively (38, 39).

181 Unlike animal PRRs that require the recruitment of adaptor proteins to transduce signal, plant  
182 membrane-associated RLKs are endowed with kinase activity thanks to the presence of cytoplasmic  
183 kinase domain (KD) (Figure 1). PAMP-sensing induces oligomerization of RLKs and kinase activation  
184 that directly triggers numerous cellular responses (Figure 3) such as ion fluxes across the plasma  
185 membrane, a burst of reactive oxygen species (ROS), a phosphorylation cascade activating MAPKs  
186 and transcription factors leading to the expression of defense genes, which encode enzymes involved  
187 in the production of defensive secondary metabolites (*e.g.* phytoalexins, callose and lignin that  
188 reinforce plant cell wall) (26). Because of their very short cytoplasmic domain (about 24 amino acids)  
189 devoid of kinase activity, RLPs are not able to transduce signal but function as a co-receptor  
190 heterodimerized with RLKs that finally elicit a similar cascade of immune signaling events. Most of  
191 the PAMPs and DAMPs recognized by plant cell surface PRRs are unable to elicit specific plant cell  
192 death. Only some proteinaceous elicitors secreted by pathogens in the apoplast can trigger HR in a  
193 plant species dependent manner.

194

### 195 **NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN (NOD)-LIKE RECEPTORS** 196 **(NLRs)**

197 Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), also generalized as  
198 nucleotide-binding domain (NBD)-containing LRRs (NB-LRR in plants), are a class of immune  
199 proteins found across both plant and animal kingdoms, with some exceptions in taxa such as Algae,  
200 Nematoda and *Drosophila*. They were previously classified in plants as R-proteins in the gene-for-gene  
201 model. In the animal kingdom, NLRs are the most represented family of cytosolic immune receptors,

202 along with ALRs (AIM2 (absent in melanoma 2)-like receptors) and RLRs (RIG-I-like receptors)  
203 (Figure 1). NLRs sense cytosolic PAMPs (*e.g.* bacteria-secreted toxins, components of bacteria with  
204 pore forming activity, internalized LPS, viral proteins) but also markers of intracellular stresses acting  
205 as DAMPs such as ATP, uric acids, reactive oxygen species (ROS), metabolic products or cell-derived  
206 peptides that are released by the cells in response to endogenous (*e.g.* ER stress, disruption of ion  
207 gradients) or environmental stresses. ALRs recognize cytosolic DNAs and RLRs sense cytosolic RNAs  
208 that include virus nucleic acid as well as endogenous microRNAs (miRNAs). Stimulation of cytosolic  
209 immune receptors can trigger inflammatory response. However, for most of them, the main response  
210 is the release of the pro-inflammatory molecules IL-1 $\beta$  and IL-18, and pyroptosis (Figure 4). NLR  
211 stimulation can also indirectly lead to apoptosis, or necroptosis, or activate autophagy process to clear  
212 pathogen (40). In plants, NLRs directly or indirectly detect pathogen-secreted effectors (*i.e.* virulence  
213 proteins) to generally promote HR cell death.

214 Although NLRs are found in both animals and plants, they seem to result from an independent  
215 evolutionary process (41). They are characterized by the presence of a central NBD (also named NOD)  
216 that may be originated from a prokaryotic class of AAA<sup>+</sup> ATPases. Both mammals and plants would  
217 have selected the NBD for the flexibility of its architecture. It catalyzes the ADP/ATP exchange which  
218 promotes the NLR oligomerization and activation. The ATP-bound active forms are generally unstable  
219 and rapidly recycled into inactive form or degraded. This mode of activation allows the NLR to quickly  
220 react after detection of pathogens and enable to preserve the organism from a costly and useless  
221 mobilization of defenses in the absence of pathogen. Animal NLRs are characterized by a “NACHT”  
222 [NAIP (neuronal apoptosis inhibitory protein), CIITA (MHC class II transcription activator), HET-E  
223 (incompatibility locus protein from *Podospora anserina*) or TP1 (telomerase-associated protein)]  
224 NBD subtype while plants NLRs possess an “ARC” (Apaf1, Resistance, CED4) NBD subtype, also  
225 found in some animal adaptor proteins involved in apoptosis such as Apaf-1 (42).

226 In addition to NBD, LRR is common to both sides. As in animal TLRs, this domain is involved  
227 in sensing microbe effectors or modified host-proteins. As an alternative, some animal NLRs own other  
228 motif domains with sensing activity such as WD/WD40, HEAT, Ankyrin, or TPR (tetratricopeptide)  
229 motifs. LRR domain is widespread among immune receptors of any kinds, probably because of its pre-  
230 disposition for forming mismatches thus easily creating diversity and therefore new potential  
231 recognition sites, as suggested by Baggs *et al.* (43). After invasion pattern recognition, LRRs undergo  
232 a conformational change allowing NLR switch from an inactive NBD-ADP-bound closed

233 conformation to an active NBD-ATP-bound open conformation and the recruitment of downstream  
234 signaling effectors (44, 45). LRR has also the ability to negatively regulate the NBD through  
235 intramolecular interactions that prevent its oligomerization (46).

236 The domains found in the N-term part of the protein are involved in the transduction of  
237 downstream signaling (45, 47). In animals, these domains belong to the death-fold superfamily which  
238 are homotypic interacting domains also found in adaptor and signaling molecules. The pyrin effector  
239 domain (PYD) is the most represented and characterizes the NLRP (NOD-like receptor protein) sub-  
240 family of NLRs (also named NALP). The NLRC sub-family contains one or two caspase-activation  
241 and recruitment domains (CARD), NLRA the acidic transactivation domain and NLRB the baculoviral  
242 inhibitory repeat-like domain (BIR) (Figure 1) (40).

243 In plants, if present, the N-term accessory domain could be of 3 main types: TIR defining the  
244 TIR-NB-LRR (TNLs) group, CC (Coiled-Coil) which defines the CNLs subgroup of NLRs, or CCR  
245 (the CC domain subtype with high similarity with the non-NBD-LRR resistance gene RPW8) that  
246 characterizes RNLs (48, 49). In addition, different structure variants lacking one or two of the  
247 previously described domains can also be found (42, 50, 51). Some of these truncated forms, also  
248 termed “adapters” or “helpers”, amplify the immune response in plants or could serve as effector baits.  
249 Because of the wide diversity and shorter lifespan of pathogens, different NLR-mediated detection of  
250 pathogens have emerged, allowing them to bypass the recognition issue due to their obvious slowly  
251 evolution (43, 52). In addition to the classic direct detection of one effector by its related NLR, different  
252 strategies for activating NLRs have been observed such as the “guard and decoy concept” (42). In this  
253 strategy, a decoy protein is in close relation with and constitutively represses the activity of a guard  
254 NLR. Effectors, or endogenous danger signals mediate decoy modification such as direct cleavage,  
255 phosphorylation, acetylation or uridylation (53-56). These post-translational modifications finally  
256 disrupt the inhibition signal allowing the NLR to be fully active (42). In this way, many pathogen  
257 effectors can be only detected by monitoring a small number of targets, whether directly involved in  
258 defenses (guardee model) or not (decoy model). Moreover, as NLRs are often working by pairs or  
259 oligomers, it is not rare to observe an “autoimmune” phenotype, *i.e.* a constitutive activation of NLRs  
260 in the absence of pathogen. In addition to result from mutations within the molecule (57, 58), this  
261 phenotype might also be the consequence of the absence of its related inhibitor, as well as an  
262 inappropriate negative interaction between closely related NLRs (59, 60). This is particularly common  
263 in the case of crossed plant populations, where inappropriate allelic combinations generate  
264 underdeveloped or self-deteriorating seedlings due to the fitness imbalance between growth and

265 defense (61, 62). This phenomenon, also known as hybrid incompatibility, thus facilitates the natural  
266 selection of related units. In connection with this, integration of decoy domains inside the NLR protein  
267 may have been selected more easily, as the probability of recombination being more important in  
268 genetically distant partners than in linked proteins. This then gives rise to the last NLR activation  
269 strategy described by Jones et al. (42), the “integrated decoy” model, exemplified by the RRS1 TLR  
270 that contains an integrated WRKY transcription factor domain, target of numerous effectors, or the  
271 NLR RGA5 that holds an integrated heavy metal-associated copper binding domain.

272

### 273 **DOWNSTREAM SIGNALING EVENTS LEADING TO CELL DEATH IN MAMMALS AND** 274 **PLANTS**

275 In Animals, although many interplays between cell death signaling pathways exist, pyroptosis is  
276 primarily the result of the stimulation of intracellular immune receptors (NLRs and cytosolic DNA  
277 sensors) while apoptosis and necroptosis are mainly triggered by membrane-associated TLRs. In plants  
278 the mechanisms of induction of HR are less well characterized.

#### 279 **NLR-induced pyroptosis in animals**

280 The signaling pathway induced by NLR stimulation has been extensively studied in animals  
281 and is about to be well characterized (for review, see (63)). Sensing of PAMPs or DAMPs by the C-  
282 term domain triggers NLRs oligomerization and the recruitment of downstream adaptors or signaling  
283 proteins to the N-terminal death fold domain *via* homotypic domain interaction, forming a large,  
284 cytoplasmic, ring-like multi-protein complexes. The best characterized NLR-associated multi-protein  
285 complexes are known as inflammasomes and result in pyroptosis. However, some NLRs such as  
286 NOD1 and NOD2 from the NLRC subfamily are not able to induce the assembly of an inflammasome  
287 but of a NODosome that ultimately results in the activation of a transcriptional program through NF-  
288  $\kappa$ B and/or MAPK signaling pathways (Figure 4) (64-66).

289 Inflammasome is built by the association of a cytoplasmic immune receptor and the pro-caspase  
290 1 effector, a cysteine protease from caspase family (Figure 4). Pro-caspase 1 is composed by a CARD-  
291 containing prodomain and two active subunits. Its recruitment into the inflammasome *via* CARD-  
292 dependent homotypic interactions induces an activating dimerization and subsequent auto-cleavage of  
293 the p10 and p20 subunits that assemble into the tetramer active form. Once activated, caspase-1 induces  
294 the processing of the pro-IL-1 $\beta$  and pro-IL-18 into mature cytokines. Caspase-1 can also catalyze the  
295 cleavage and activation of the pore-forming protein gasdermin D. Gasdermin D belongs to the pore-

296 forming protein family gasdermin (GSDM) characterized by the presence of an N-terminal pore-  
297 forming domain (PFD). It is synthesized as a precursor composed of two domains linked by a loop.  
298 Caspase-1 cleaved Gasdermin D within the loop, releasing the PFD that can oligomerize and anchors  
299 into the inner plasma membrane to form pores. Inflammasome-mediated Gasdermin D activation  
300 results in IL-1 $\beta$  and IL-18 release, ion unbalance that culminates in cell swelling (67, 68). The cleavage  
301 of gasdermin D can also be performed by the human CARD-containing caspase-4 and -5 (mouse  
302 caspase-11) that is activated in the so-called non-canonical inflammasome thanks to their ability to  
303 directly sense LPS by their CARD domain (69). Interestingly, Gasdermin D is also able to form pores  
304 into bacterial membranes and into membrane organelles such as mitochondria or endoplasmic  
305 reticulum that can result in potassium efflux, calcium mobilization and ROS generation (70).

306 Among NLRs, NLRP1, -3, -4, -6, -7 and NLRC4 can form inflammasome. Moreover, the  
307 cytosolic DNA sensors AIM2 and IFI16 also have the ability to form it (71-73). For NLRP3 and AIM2  
308 that do not contain a CARD domain, the molecular adaptor ASC (apoptosis-associated speck-like  
309 protein containing a CARD domain), that owns both a pyrin and a CARD domain, is recruited as an  
310 intermediate bridge to link the sensor to the pro-caspase-1 (Figure 4). ASC adaptor is also observed in  
311 the NLRC4 and NLRP1 inflammasomes, stabilizing the interaction between the NLR and the pro-  
312 caspase-1 (74). The activation process of NLRP3-inflammasome is the most documented (75). It  
313 involves a priming step that can be provided by sensing LPS by TLRs which induces NF- $\kappa$ B-dependent  
314 expression of NLRP3 and ASC (76). As the intracellular amount of these proteins have reached a  
315 sufficient level, NLRP3-inflammasome activation can be completed by sensing DAMPs (such as ATP)  
316 or some PAMPs (viral RNA or proteins, bacterial-derived compounds). Some post-translational  
317 modifications such as phosphorylation (77) and de-ubiquitination (78) could also be of importance for  
318 the priming step.

### 319 **NLR-mediated HR in plants**

320 ETI-related HR cell death is frequently associated with early signaling events such as NLR  
321 oligomerization, activation of a MAPK cascade, ROS generation, transcriptional reprogramming and  
322 a latter accumulation of phytohormones associated to plant immune responses (79, 80). Once the  
323 pathogen is detected, through the direct recognition of an effector or *via* a modification of a host  
324 molecular target, larger immune receptor complexes are built. Recently, an NLR supramolecular  
325 structure termed resistosome and showing similarities with the mammalian inflammasomes has been  
326 discovered in plants. In this case, the bacterial pathogen *Xanthomonas campestris* injects into the host

327 plant cells the AvrAC effector *via* its type III secretion system which uridylylates the PBS1-like protein  
328 2 (PBL2) decoy receptor-like cytoplasmic kinase (RLCK). This modification (PBL2<sup>UMP</sup>) triggers its  
329 association with the second RLCK resistance-related kinase 1 (RKS1) that interacts with the NLR Hop-  
330 Z-activated resistance 1 (ZAR1). This allows the NBD to become active by exchanging its ADP to  
331 ATP (81, 82). Subsequent ATP binding triggers the pentamerization of the ZAR1-RKS1-PBL2  
332 resistosome complex (Figure 3). The assembled supramolecular complex forms a funnel-shaped  
333 structure with a pore diameter ranging from ~10 to 30 Å. Because of its structural resemblance with  
334 the hemolytic pore forming protein fragaceatoxin C and the partial requirement of its association with  
335 the PM for the induction of cell death, Wang and collaborators hypothesized this complex to be pore-  
336 forming. The ZAR1 resistosome would thus disrupt the PM integrity and/or alter the ions homeostasis  
337 by acting in a similar manner to the MLKL and gasdermins in mammals (9). Nonetheless, they are not  
338 ruling out that the ZAR1 resistosome could also serves as a docking site for others immune actors.  
339 Since NLRs have different accessory N-term domains they can be directly involved in signaling  
340 platforms to finely tune cell death and immune responses in plants. In that way, the Arabidopsis helper  
341 NLR AtNRG1 (N-requirement gene 1) forms a cell death signaling hub when it is associated with the  
342 heterodimer formed by the lipase-like protein enhanced disease susceptibility1 (AtEDS1) interacting  
343 with the senescence-associated gene101 (AtSAG101) (83-85). However, if AtEDS1 interacts with  
344 phytoalexin-deficient 4 (AtPAD4), this molecular complex associates with another helper NLR  
345 AtADR1 (accelerated disease resistance 1) to promote the expression of immune genes *via*  
346 transcriptional reprogramming (85).

347 In Arabidopsis, an HR cell death pathway is regulated by a MAPK cascade, involving the MAPK  
348 kinase kinase MEKK1, the MAPK kinase MKK1/2, and the MAPK MPK4, itself monitored by the  
349 CC-NLR protein SUMM2 (suppressor of *mkk1/2*, 2) (86). Indeed, the Arabidopsis *mkk1*, *mkk1/2*, and  
350 *mpk4* mutants or silencing of *MEKK1* by RNAi exhibited spontaneous cell death and constitutive  
351 immune responses, such as defense gene activation and ROS production (87-92) whereas SUMM2  
352 suppressed the cell death of *mkk1*, *mkk1/2*, and *mpk4* mutants (86). A screening of Arabidopsis T-  
353 DNA insertion lines identified SUMM2, MEKK2, and Calmodulin-binding receptor-like cytoplasmic  
354 kinase 3 (CRCK3) to be vital regulators of MEKK1 depletion-induced cell death (93). At the opposite,  
355 overexpression of CRCK3 induced a SUMM2- and MEKK2-dependent cell death (92). Altogether,  
356 these results suggest that a dedicated plant MAPK cascade plays an important role in the HR signaling,  
357 which is under the tight control of different regulator proteins.

358 The onset of HR is also often associated to the accumulation of ROS. Most of the apoplastic ROS  
359 generated during plant–pathogen interactions is produced *via* plasma membrane-localized enzymes  
360 with homology to the mammalian phagocytes NADPH oxidases (NOXs) and called respiratory burst  
361 oxidase homologs (RBOHs) in plants (94). These enzymes generate apoplastic superoxide ions ( $O_2^{\cdot-}$ )  
362 that rapidly dismutate to hydrogen peroxide ( $H_2O_2$ ), a well-known microbicide. Following infection  
363 by a bacterial pathogen possessing the avirulence gene *AvrRpm1*, HR cell death is reduced in  
364 *Arabidopsis AtrbohD* mutant and *AtrbohD/F* double mutant plants, indicating that RBOHs and ROS  
365 promote cell death (95). This process required the concomitant production of nitric oxide (NO; see  
366 below). Nevertheless, infection with an avirulent oomycete pathogen in *Arabidopsis AtrbohD/F* double  
367 mutant plants caused more HR cell death and resistant phenotype even though the ROS was suppressed  
368 (95). Similarly, *Arabidopsis ncal* (no catalase activity 1) and *cat2* (catalase 2) mutants, supposed to  
369 have an increased  $H_2O_2$  level, surprisingly showed reduced cell death when infected by a bacterial  
370 pathogen expressing *AvrRpm1* (96). At the molecular level, the discovery that RBOHD activity is  
371 positively and negatively regulated by many post-translational modifications *via* different  
372 phosphorylation or ubiquitination events suggests a finely tuned control of the spatio-temporal ROS  
373 production during plant-pathogen interaction (97-100). Thus, the connection between ROS and HR  
374 cell death still needs clarifications. Interestingly the *Arabidopsis* LRR-RK HCPA1 has been recently  
375 shown to perceive the extracellular  $H_2O_2$  *via* cysteine oxidation to trigger  $Ca^{2+}$  influx, which then leads  
376 to immune responses such as stomatal closure to delay the pathogen penetration through this natural  
377 opening in plants (101).

### 378 **TLR-mediated apoptosis and necroptosis in animals.**

379 As described above, TLR-mediated signal transduction involves the assembly of multiprotein  
380 signaling platforms thanks to the presence of homotypic interacting domains in the receptors, adaptors  
381 and effector proteins (19). Ligand binding triggers TLR homo- or heterodimerization, conformational  
382 change in their intracellular TIR domain and the consecutive recruitment via TIR-TIR homotypic  
383 interaction of adaptor proteins. Schematically, TLR signaling pathways are subdivided into MyD88-  
384 dependent and TRIF-dependent signaling. Briefly, MyD88 can bind most of endosomal and cell-  
385 surface-TLRs. In turn, it promotes the recruitment of the serine/threonine IL-1R-associated kinase  
386 (IRAK) family members, *via* homotypic interaction with its C-term death domain (DD), to form a  
387 multiprotein complex named Myddosome. IRAK4 catalyzes a phosphorylation reaction that leads to  
388 the recruitment of the E3-ubiquitin ligase TRAF6 (tumor necrosis factor receptor (TNFR)-associated  
389 factor 6), the subsequent recruitment and activation of TAK1/TAB1/3 and IKK complexes which

390 engages MAPKs and NF- $\kappa$ B, and that ultimately leads to the expression of pro-inflammatory cytokines  
391 that include TNF $\alpha$  (tumor necrosis factor- $\alpha$ ) (19) (Figure 2).

392 The endosomal TLR3 and the cell surface TLR4 recruit the adaptor TRIF. While TLR3-TRIF  
393 binding is direct *via* TIM-mediated homotypic interaction, TLR4 requires the adaptor TRAM that  
394 bridges TLR4 to TRIF. TRIF can recruit TRAF3 and/or TRAF6 thanks to the presence of TRAF-  
395 binding motifs in the N-terminal part of the protein. TRAF6 promotes subsequent MAPK or NF- $\kappa$ B-  
396 dependent transcriptional program while TRAF3 engages the IRF3-activating signaling pathway and  
397 the expression of type I IFN genes (19) (Figure 2). In addition to the TIR and TRAF-binding domains,  
398 TRIF owns a C-terminal RIP homotypic interaction motif (RHIM) also found in the receptor-  
399 interacting kinases (RIPs) RIP1 and RIP3 (102).

400 The serine/threonine kinase RIP1 has been identified in 1995 because of its capacity of binding  
401 death receptors from tumor necrosis factor receptor (TNFR) superfamily (103). Thus, RIP1-dependent  
402 signaling pathway can be activated by TLR3 and TLR4 as described above and also indirectly by the  
403 other TLRs *via* the NF- $\kappa$ B-dependent production of TNF $\alpha$  and autocrine stimulation of TNFR1. RIP1  
404 appeared as the core component of signaling platforms, at the crossroad between inflammatory  
405 response, apoptotic and necroptotic cell death signaling pathways (for review see (104) (Figure 2).  
406 When modified by non-degradative ubiquitin chains, RIP1 constitutes a scaffold for the recruitment of  
407 the kinase complexes TAK1/TAB1/TAB2 and IKK that activate MAPK and NF- $\kappa$ B-dependent  
408 transcriptional response. In a non-ubiquitinated form, RIP1 promotes the assembly of a secondary  
409 cytoplasmic cell death signaling platforms thanks to its kinase activity. Associated with the adaptor  
410 FADD (Fas-associated protein with death domain) and caspase-8, it promotes caspase-dependent  
411 apoptotic cell death *via* the activation of the proteolytic cascade involving the caspase-3 (105). RIP1  
412 can recruit its closely related protein RIP3 via their respective RHIM domain and forms a necrosome.  
413 (Figure 2). Independently of RIP1, RIP3 can also be directly engaged by TLR3 and TLR4 *via* a RHIM-  
414 dependent binding to TRIF, and also by the cytosolic DNA sensor DAI from RLR family that owns a  
415 RHIM domain (106).

416 RIP3 is the main effector of necroptosis (107). It is activated by homodimerization and  
417 autophosphorylation. RIP3 promotes the activating phosphorylation of MLKL (mixed lineage kinase  
418 domain-like) (108). Once activated, MLKL oligomerizes and translocates to the plasma membrane  
419 where it interacts with phosphatidylinositols and forms pores or cation channels responsible for

420 membrane permeabilization and disruption and cell death (107, 109). Necroptosis has been associated  
421 with the production of ROS. Deletion of RIP3 completely blocked ROS production suggesting that this  
422 event occurred downstream of necrosome activation (110).

423 The concept of necroptosis has emerged over the two last decades but its contribution to the  
424 control of pathogen infections is still not very well understood. Experimental necroptosis model usually  
425 required an inhibition of apoptotic signaling pathway, suggesting that necroptosis occurred as a  
426 secondary event (111). The role of RIPK3-mediated cell death in antiviral response was highlighted  
427 by the analysis of mice deficient in RIPK3 that appeared highly susceptible to Influenza A virus or  
428 vaccinia virus (110, 112). In the same manner, macrophages or lung epithelial cell death induced by  
429 some bacteria (that include *Salmonella typhimurium*, *Staphylococcus aureus*, *Staphylococcus*  
430 *marcescens* or *Streptococcus pneumoniae*) is inhibited by RIPK3 deficiency or necroptosis inhibitors  
431 (113-115). Necroptosis could constitute an important defense mechanism against infection with  
432 pathogens able to bypass apoptosis induction by expressing anti-apoptotic proteins.

### 433 **PRR-triggered signaling events leading to HR in plants**

434 Apoplastic elicitors which trigger HR are more the exception than the rule. Nevertheless,  
435 Avr2/4/5/9 proteins secreted by the fungus *Cladosporium fulvum* induce HR in tomato expressing the  
436 corresponding surface RLP Cf-2, Cf-4, Cf-5 or Cf-9, respectively (116-118). Similarly, the fungal  
437 endopolygalacturonases secreted by *Botrytis cinerea* trigger plant cell death in a specific Arabidopsis  
438 ecotype (Columbia-0) co-expressing the RLPs RBPG1 (responsiveness to *Botrytis cinerea*  
439 polygalacturonases1) associated with SOBIR1 (suppressor of BIR1-1) (119). Elicitin proteins secreted  
440 by different species of *Phytophthora* can also trigger HR in different solanaceous plants after  
441 recognition by the RLP ELR (elicitin response) which forms a molecular receptor complex with the  
442 RLK BAK1 (brassinosteroid insensitive 1-associated receptor kinase 1) (120).

443 *Phytophthora cryptogea* induces an immune response in tobacco plants characterized by a HR  
444 and a SAR conferring protection against numerous micro-organisms, including virulent ones (121).  
445 Cryptogein secreted by this oomycete is the major inducer of plant immunity and mimics the effects  
446 of the oomycete once applied to tobacco plants and cell suspensions (122, 123). Cryptogein is an  
447 elicitin protein of 10 kDa that acts as sterol carriers and could supply *Phytophthora* species with sterols,  
448 these latter being sterol auxotrophs (124). In vitro binding assays provided first evidences that  
449 cryptogein is recognized by a putative plasma membrane receptor (125). Even if its molecular identity  
450 has not been reported so far, it is plausible to assume that the RLP ELR fulfils this role (120).

451 The cellular and molecular processes leading the cryptogein-induced HR have been widely  
452 studied, mostly using tobacco cell suspensions. Cells undergoing cell death shows a vacuole shrinkage  
453 within few hours (126). This vacuole volume loss has been functionally linked to a fast and ample  
454 nitrate effluxes across the plasma membrane resulting from the activity to anion-permeable channels  
455 (126, 127). Accordingly, inhibition of these effluxes, as well as  $\text{Ca}^{2+}$  influxes from the extracellular  
456 space, suppressed or delayed cell death (128). A similar result was observed in cryptogein-treated  
457 tobacco cells in which the activity of protein kinases, including MAPK, has been suppressed (129). All  
458 together, these data highlighted that the machinery leading to cell death is a dynamic process requiring  
459 early signaling events. These latter also include the production of NO and ROS. More precisely,  
460 cryptogein triggers within minutes the activation of a plasma membrane NADPH oxidase (NtRBOHD)  
461 which produces  $\text{O}_2^{\cdot-}$  simultaneously dismutated into  $\text{H}_2\text{O}_2$  through the activity of superoxyde  
462 dismutases (130). Interestingly, a coordinated action of ROS and NO has been highlighted (131).  
463 Indeed, the production of  $\text{H}_2\text{O}_2$  is a prerequisite for NO synthesis and functions as impairment of  
464 NtRBOHD expression compromises NO production as well as its involvement in cell death. In turn,  
465 NO negatively regulates the level of  $\text{H}_2\text{O}_2$  through the formation of peroxynitrite ( $\text{ONOO}^-$ ) resulting  
466 from the chemical combination between NO and  $\text{O}_2^{\cdot-}$ . The formation of  $\text{ONOO}^-$  might mitigate the  
467 effects of  $\text{H}_2\text{O}_2$  and provide a mean to control the intensity of cell death. The possibility that NO also  
468 mitigates  $\text{H}_2\text{O}_2$  production and the amplitude of HR through the inhibition of NtRBOHD by S-  
469 nitrosation, a NO-dependent post-translational protein modification, has been reported in other plant-  
470 pathogens models (132). However, the occurrence of this mechanism in cryptogein-treated cells has  
471 not been confirmed (131).

472 Caspase-like activities have also been detected in plants during HR cell death. If genes encoding  
473 true orthologs of caspases (cysteine dependent aspartate-directed proteases) are absent in the plant  
474 genomes, many proteases involved in HR cell death have been identified such as metacaspases in the  
475 cytosol, vacuolar processing enzymes (VPEs) in the vacuole or saspase, cathepsin B or papain like  
476 cysteine protease (PLCP like Rcr3 or Pip1) in the apoplast (9). Interestingly, plant metacaspases are  
477 lysine- and arginine-specific, whereas caspases found in mammals are aspartate-specific, indicating a  
478 different substrate specificity of these plant enzymes. Based on their protein structure, the phylogenetic  
479 analysis of plant metacaspases indicated three major clades that can be divided into type I with, or  
480 without, a zinc finger motif in the N-terminus region, and type II harboring a linker region between the  
481 two subunits of 10 and 20 kDa of the caspase-like regulatory and catalytic domains (133). In  
482 Arabidopsis, the type I metacaspase AtMC1 promotes HR cell death during biotic stresses whereas

483 AtMC2 acts antagonistically by inhibiting plant cell death without any different pathogen  
484 dissemination in both *atmc1* and *atmc2* mutants (134). The type II metacaspase AtMC4 is a calcium-  
485 dependent cysteine protease which cleaves the PROPEP1 phyto-cytokine in order to release PEP1 in  
486 the apoplast, itself detected by the PEPR1 PRR in neighboring cells to amplify plant immune responses  
487 during the damage-triggered immunity (135). The recent resolution of the AtMC4 crystal structure  
488 exhibited the inhibitory role of the large linker domain which blocks activation and substrate access of  
489 the catalytic domain (136). Concerning VPEs, they have been shown to exhibit similar enzymatic  
490 properties as the animal caspase 1 except that they are active in the vacuole (7). They possess an  
491 autocatalytic conversion of the inactive proprotein (pVPE) into the mature active mVPE (137). In  
492 tobacco plants infected by the tobacco mosaic virus (TMV), caspase-1 inhibitors or VPE gene silencing  
493 reduces the caspase-1-like activity associated to the rupture of the vacuolar membrane normally leading  
494 to the virus-induced HR cell death (138). During plant immunity, bacterial harpin-induced cell death  
495 was compromised in *Nicotiana benthamiana* VPE-silenced plants (139) and inhibitors of caspase-1  
496 delayed the HR cell death normally triggered in tobacco cells by the oomycete elicitor cryptogein (126).  
497 In Arabidopsis, a *vpe* null mutant lacking the four genes ( $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -*vpe*) was unable to show  
498 any VPE or caspase-like 1 activity (140) and  $\gamma$ -*vpe* mutant was more susceptible to viral, bacterial or  
499 fungal infection (141). The extracellular protease Pip1 and Rcr3 also actively participate to the  
500 perception of the fungal pathogen *C. fulvum* in tomato. *C. fulvum* secretes Avr2 into the apoplast which  
501 associates with Rcr3 and Pip1. The mentioned complexes perceived by Cf-2, a receptor-like protein  
502 (RLP), trigger HR and induce resistance to *C. fulvum* (142). Recently, the first proteolytic cascade has  
503 been discovered in plants where the extracellular immune protease proRcr3 is cleaved by the subtilase  
504 P69B in mature Rcr3 that interacts with Avr2 before that the molecular complex binds to the Cf-2 RLP  
505 (143). Interestingly, this P69B subtilase has been previously shown to be itself the target of the matrix  
506 metalloproteinases SI2-MMP and SI3-MMP (144, 145), suggesting that these MMP are initiator  
507 proteases whereas Rcr3 play an effector role in this cascade, as shown for intracellular caspases in  
508 mammals.

509

## 510 CELL DEATH REGULATIONS IN MAMMALS AND PLANTS

511 In host-pathogen interactions, control of the regulated cell death is crucial for both partners.  
512 Host have to adapt this defense response to contain pathogen development while avoiding its own  
513 lethal outcome. At the opposite, pathogens need to modulate the regulated cell death to ensure their  
514 infection cycle.

515 **Host regulations**

516 Organisms need to adapt their response as the infection evolves. Thus, many interplays and  
517 cross-regulation mechanisms exist between the different immune cell signaling pathways. The  
518 stimulation of one receptor can cause different responses including the activation of transcriptional  
519 programs or the engagement of cell death pathways, depending on the nature, the duration and the  
520 intensity of the stimuli. These responses can occur simultaneously or successively and cells have the  
521 ability to change the response very quickly. In animals, the interplay between TLR and NLR signaling  
522 pathways is illustrated by the activation of NLRP3-inflammasome in a two-step process. The first  
523 priming step involves the TLR-mediated,  $\text{NF-}\kappa\text{B}$ -dependent expression of *NLRP3*. Then DAMPs or  
524 PAMPs can stimulate the NLRP3-inflammasome assembly and pyroptosis (76). Thus, NLRP3-  
525 inflammasome-mediated pyroptosis is only activated when the TLR-mediated immune response is not  
526 sufficient to neutralize pathogens.

527 As illustrated Figure 2, TLR4 is able to trigger  $\text{NF-}\kappa\text{B}$ -dependent pro-inflammatory response,  
528 IFN-response, necroptosis or apoptosis. This imply the presence of accurate mechanisms of regulation.  
529 In addition to promote the production of microbicidal molecules and pro-inflammatory mediators,  
530 TLR-mediated  $\text{NF-}\kappa\text{B}$  activation induces the expression of several survival proteins such as the cellular  
531 inhibitor of apoptosis (cIAPs) (146). cIAPs act as E3-ubiquitin ligases promoting poly-ubiquitination  
532 of RIP1. Therefore, they are required for the TLR-dependent activation of transcriptional programs  
533 while they inhibit RIP-dependent apoptotic and necroptotic pathways (21, 147). The presence of a  
534 second signal that neutralizes cIAP activity could convert the transcriptional signal to a cell death  
535 signal. It is interesting to note that some viruses such as baculovirus express proteins from IAP family  
536 (148) that block cell death of infected cells and allow viral propagation. The different cell death  
537 signaling pathways are also interconnected and have the ability to regulate each other (for review, see  
538 (75). Blocking apoptosis signaling pathway is generally a prerequisite for detecting necroptosis  
539 because the apoptotic caspase-8 can inhibit the activity of key components of the necroptosis signaling  
540 pathway including RIP1 and RIP3 (107, 111). On the contrary, caspase-8 can activate the NLRP3-  
541 inflammasome (149) or directly cleave the caspase-1 leading to pyroptosis (150). Conversely,  
542 inflammasomes can connect caspase-8 to induce apoptosis (151). The necroptotic effector RIP3 is also  
543 able to cause NLRP3-inflammasome activation and pyroptosis *via* ROS production (152, 153).

544 Although less documented, such cross-regulations between immune receptor-mediated  
545 signaling pathways should probably exist in plants. Mutations or overexpression of some plant immune

546 receptors such as the RLK CERK1, the co-receptor BAK1, its closest homolog BKK1 (BAK1-like 1)  
547 or the RLP BIR2 (BAK1-interacting receptor-like kinase 2) can trigger an enhanced cell death (154-  
548 157). This discovery suggests that a plant surveying system probably guard these immune receptors  
549 from inhibition by pathogen effectors to trigger HR (9, 158, 159).

550 The molecular mechanisms that dictate the response to immune receptor stimulation are not  
551 completely understood and are the subject of intense research. Because of their flexibility and speed of  
552 implementation, post-translational modifications (PTM) constitute a remarkable and effective process  
553 to modulate the intracellular signaling and to regulate the communication networks between cell  
554 transduction pathways. As reported above, the priming step required for the full activation of NLRP3-  
555 inflammasome has also been shown to involve some post-translational modifications of NLRP3 such  
556 as phosphorylation (77) and de-ubiquitination (78). In mammals, a nice example is given by RIP  
557 proteins (RIP1, RIP2 and RIP3) for which the recruitment into various multiprotein signaling  
558 platforms, the kinase activity and the ability of engage downstream signaling pathways is orchestrated  
559 by PTM, mainly ubiquitination and phosphorylation (160). The serine/threonine kinase RIP1 is  
560 recruited to the TLR3 and TLR4-associated signaling complex (Figure 2) and RIP2 is associated with  
561 the cytosolic NLR NOD1 and NOD2 (161) (Figure 4). As previously described, modification of RIP1  
562 and -2 constitute a molecular scaffold for the subsequent recruitment of the kinase complexes IKK and  
563 TAB1/TAB2/TAK1, and their activation by proximity that ultimately result in NF- $\kappa$ B and MAPK  
564 activation and gene expression (Figure 2) (146, 160, 161). The non-degradative ubiquitination also  
565 completely inhibits RIP1 kinase activity that is essential for the assembly of secondary cytoplasmic  
566 cell death signaling platforms leading to apoptosis or necroptosis (21, 160). Of note, some viruses have  
567 developed strategies to counteract the death of infected cells by modulating RIP ubiquitination (162).

568 Many post-translational modifications of signaling proteins have also been identified to finely  
569 regulate the plant immune responses. The ubiquitin-proteasome system (UPS) plays an essential role  
570 in plant immunity. Among UPS components, E3 ubiquitin ligases have been particularly studied. Wang  
571 et al. (163) showed that the E3 ligase OsPUB15 interacts with the homodimerized PID2K, a  
572 transmembrane receptor-like kinase, which confers rice resistance against *Magnaporthe oryzae*.  
573 Interestingly, the authors demonstrated that the overexpression of *OsPUB15* led to an enhanced  
574 resistance against the pathogen, correlated with up-regulation of some defense genes, excessive  
575 accumulation of ROS and plant cell death, suggesting that ubiquitination of PID2K could favor its  
576 activity. However, in this case, the observed lesions were so important that they conducted to the plant

577 death. Another example of the importance of UPS in plant immunity is provided by studies  
578 investigating the function of the ATPase cell division cycle 48 (CDC48). CDC48 is a highly conserved  
579 protein from yeast to plants and animals (also named VCP (vasolin-containing protein) or p97 in  
580 mammals). This chaperone-like protein catalyzes the disassembly of protein complexes and/or the  
581 extraction of ubiquitinated proteins from membranes or chromatin in order to deliver them to the  
582 proteasome. Therefore, it plays an important function in UPS and, more generally, proteostasis (164).  
583 Investigations of CDC48 function in plant immunity demonstrated that the tobacco CDC48 isoform  
584 rapidly accumulates in its hexameric active structure in tobacco cells exposed to cryptogein (165). A  
585 screening for its binding partners allowed to the identification of key regulators of the redox status,  
586 including cytosolic ascorbate peroxidase (cAPX) a pivotal enzyme for ROS removal (165, 166). In  
587 CDC48-overexpressing tobacco cells, the activity of cAPX was impaired, leading to severe decrease  
588 in the cell capacity to respond to oxidative stress (167). Accordingly, a faster and pronounced cell death  
589 was observed in those cells. Although speculative, the involvement of CDC48 in cell death could be  
590 also explained by its ability to promote the degradation of cell death repressors. In animals, several  
591 studies have reported a role for its ortholog p97 in viral spreading (poliovirus, herpes simplex virus,  
592 cytomegalovirus or influenza virus) by regulating the cycle of viral replication in infected cells (168).  
593 However, the mechanisms and the relationship with immune receptor-induced cell death have not been  
594 clearly demonstrated.

595 Histone deacetylases (HDAC) of type 2 (HD2s) have also been identified as an important  
596 regulator of the cryptogein-induced HR in tobacco. HD2s designs a plant specific family of nuclear  
597 histone deacetylases (169). Two HD2s tobacco isoforms, NtHD2a and NtHD2b, were shown to  
598 undergo a fast phosphorylation in tobacco cells treated with cryptogein (170). This process was  
599 followed by a decrease both at the transcript and protein levels. Interestingly, silencing of *HD2*-in cell  
600 suspensions or *in planta* led to a faster and amplified cell death manifested by exacerbated HR  
601 symptoms. Based on these data, it has been proposed that NtHD2a and NtHD2b act as constitutive  
602 negative regulators of HR by modulating the expression or activity of HR regulators or effectors which  
603 identities remain to be discovered. In a similar manner, a role for histone deacetylases in the acquisition  
604 of cell resistance phenotype has also been observed in mammal macrophages. An upregulation of  
605 HDAC8 has been correlated with the acquisition of a resistance phenotype to anthrax lethal toxin  
606 (LeTx). HDAC inhibitors sensitized cells to LeTx-induced pyroptosis while inversely upregulation of  
607 HDAC8 prevents LeTx-induced cell death (171).

608 As NLRs are often tightly linked to strong immune process including cell death, these proteins  
609 need to be finely tuned to avoid any deleterious impact on the plant fitness in the absence of pathogen.  
610 In accordance, animals and plants dispose of several regulation processes among which are miRNAs.  
611 These regulatory elements function similarly in animals and plants and are in the same way excised  
612 from long primary miRNA transcripts by Dicer or Dicer-like enzymes (such as DCL1) before being  
613 loaded into an RNA-induced silencing complex (RISC) and to repress the gene by DNA methylation  
614 or by cleavage, destabilization or translational inhibition of its messenger RNA (mRNA) (172). These  
615 miRNAs are involved in the regulation of different biological processes, and particularly studied in  
616 plants when related to development and defenses. In addition to interact with exogenous nucleic acid  
617 and defend plant cells against viral pathogens (173), some host miRNAs also targets their own  
618 transcripts encoding immune receptors such as the NLR proteins (174-177). This is believed to allow  
619 them to control their immune reactions in the absence of pathogen and therefore to avoid any  
620 unnecessary waste of energy. In addition, since some bacterial and viral pathogens infect their host by  
621 blocking its miRNA interference process, the decrease in these miRNAs would also, at the same time,  
622 lead to an accumulation of the previously repressed immune receptors, ultimately leading to a  
623 potentiation of defenses (174, 176, 178).

624 Plant immunity is also regulated by a complex network of phytohormones, which integrate signals  
625 from biotic and abiotic stresses in order to finely tune the spatio-temporal expression of the different  
626 immune responses. Among them, salicylic acid (SA) and jasmonic acid (JA) play major roles and their  
627 antagonism is believed to specifically adapt the plant immunity to biotrophic or necrotrophic  
628 pathogens, respectively (179). SA has been shown to positively regulate the HR cell death during  
629 interaction with a biotrophic pathogen whereas JA seem to be more important for the plant resistance  
630 against invading necrotrophs or insects. Actually, low level of SA downregulates HR cell death  
631 whereas high level of SA triggers plant cell death (180). Moreover this hormonal balance between SA  
632 and JA seems to finely regulate plant cell death locally as SA accumulates into the HR-related cell  
633 death zone whereas JA level increases in the surrounding area to act antagonistically with the SA-  
634 pathway (181).

635

### 636 **Pathogens interfere with cell death signaling pathways to their own benefits**

637 According to their infection cycle, some pathogens interfere with regulated cell death signaling  
638 pathways to their own benefits (182). So, it is generally accepted that viruses and biotrophic pathogens

639 whose survival is fully dependent on the intracellular machinery of host cells can delay or inhibit cell  
 640 death contrary to necrotrophic ones which take nutrients from dead cells. However, the classification  
 641 does not always reflect the complexity of the pathogen cycle infection. The strategies used by  
 642 pathogens to evade host defenses in order to favor their multiplication and spread have been widely  
 643 studied in animal cells. Many viruses or bacteria deliver anti-apoptotic proteins that directly block  
 644 apoptotic, necroptotic and/or pyroptotic machineries. Caspase-1 and/or caspase-8 involved in  
 645 pyroptosis and apoptosis (Figures 2, 4) respectively can be directly inhibited by serpin (serine  
 646 proteinase inhibitor) homologs encoded by poxvirus, the influenza virus protein NS1, the vaccinia virus  
 647 protein B15N or effectors molecules secreted by *Pseudomonas aeruginosa* or *Yersinia* spp. (183). RIP1  
 648 from TLR3 and 4 signaling pathway (Figure 4) is frequently found as a target. Virus or bacteria  
 649 effectors can modulate the post-translational modification of RIP1 such as phosphorylation or  
 650 ubiquitination, thereby affecting its kinase activity and cell death-promoting ability (apoptosis or  
 651 necroptosis). Thus, the latent membrane protein 1 (LMP1) from Epstein-Barr virus (EBV) and op-IAP  
 652 produced by baculovirus can promote the poly-ubiquitination of RIP1 (162, 184) and the *Yersinia*  
 653 *pestis* effector YopJ/P modulates the phosphorylation status of RIP1 by targeting the kinases TAK1  
 654 and IKK or MK2 (185). Pathogens can bypass host defense mechanism by blocking signaling  
 655 pathways just downstream of the pathogen recognition-receptor. This is illustrated by the  
 656 enterohemorrhagic bacteria type 3 that produces a protease that cleaves the RHIM domain owns by  
 657 RIP1, RIP3, TRIF, the adaptor proteins involved in TLR3 and TRL4-mediated signaling pathways and  
 658 the cytosolic DNA sensor DAI (186). On the other hand, RHIM-homotypic interaction that mediates  
 659 the assembly of the necrosome, as well as the recruitment of RIPs to sensors (Figure 4) can be affected  
 660 by the presence of viral RHIM-containing proteins such as the proteins ICP6 and ICP10 produced by  
 661 Herpes simplex virus (187), vaccinia virus innate immune evasion protein E3 (188), vIRA encoded by  
 662 the murine cytomegalovirus (189). Poxviruses encoded MLKL homologs that can sequester the cellular  
 663 RIP3 and inhibits necroptosis (190).

664         Biotrophic or hemibiotrophic phytopathogens have to keep plant cells alive to ensure their  
 665 infection cycle. In this way, they secrete many effectors which target receptors or key signaling  
 666 components to suppress host immunity triggered by their own invading patterns (191, 192). As  
 667 examples, RipAY produced by *Ralstonia solanacearum* inhibits SA-dependent defense responses and  
 668 HR induced by the effector RipE1 in *Nicotiana benthamiana* (193) and RipAK suppresses catalase  
 669 activity and HR of *Nicotiana tabacum* (194). *Phytophthora infestans* AVR3a targets E3 ligase CMPG1  
 670 and suppresses HR induced by the elicitor INF1 in *Nicotiana benthamiana* (195, 196). In addition, it

671 has been shown that *P. infestans* PexRD2 interacts with the kinase domain of MAPKKKε, a positive  
672 regulator of cell death, increasing the susceptibility of *Nicotiana benthamiana* to this pathogen (197).

673 Inversely, necrotrophic phytopathogens favor plant cell death to ensure the infection spreading.  
674 For example, the broad host range necrotrophic plant pathogen *Sclerotinia sclerotiorum* secretes oxalic  
675 acid (OA) which is considered as a key molecule for its pathogenesis. It has been shown that OA has  
676 opposite roles: i) to suppress host oxidative burst and then HR at early state of infection allowing the  
677 establishment of the pathogen ii) to activate plant cell death, *via* ROS production, facilitating disease  
678 development (198, 199). Besides OA secretion, *Sclerotinia sclerotiorum* produces several effectors or  
679 toxins inducing plant cell death (200). For some of them, secreted in apoplast such as SsNE1-SsNE5,  
680 the death-inducing signal is mediated by the BAK1/SOBIR1 receptor complex (200). The involvement  
681 of these RLK was already highlighted for the necrotizing activity of the xylanase BcXYG1 secreted  
682 by *Botrytis cinerea* (201). Others would be internalized in host cells as the "effector-like" protein  
683 SsSSVP1 which interacts with QCR8, a subunit of plant cytochrome complex in mitochondrial  
684 respiratory chain (202). This leads to the loss of function of QCR8 and to plant cell death induction.  
685 Actually, numerous phytopathogens secrete several toxins or effectors to induce cell death. Around  
686 180 apoplastic cell death-inducing proteins (CDIPs) have been identified and for some of them, the  
687 associated receptors are known (203, 204). Other toxins are internalized in host cells and interact in  
688 some case with NB-LRR (182). Thus, the Arabidopsis susceptibility to *Cochliobolus victoriae* is due  
689 to the interaction between the secreted toxin victorin with the NB-LRR LOV1. In this case, the  
690 pathogen co-opts HR to facilitate its development (205).

691 A beneficial effect of cell death for pathogens to ensure infection cycle has also been described  
692 in mammals. It is well illustrated by the Human immunodeficiency virus (HIV) that hijacks the immune  
693 surveillance by promoting the pyroptosis of immune cells (CD4<sup>+</sup> lymphocytes) (206).

694

695

696 **DISCUSSION**

697 Although number of questions still remain to address, the intense research of the scientific  
698 communities on innate immunity in mammals during the 3 last decades and recent technological  
699 advances gave rise to a relative clear scheme of the cell death-signaling pathways activated in response  
700 to immune receptors. By comparison, the understanding of the immune receptor-induced cell death  
701 signaling pathways remains incipient in plants although the use of Arabidopsis mutants allowed the  
702 identification of actors involved in HR signaling and/or regulation (207-209). Up to date, more than  
703 600 RLKs and 100 NLRs have been inventoried but few have been characterized and many have not  
704 yet been identified. The abundance of immune receptors, the different processes used for their  
705 activation as well as the diversity of cellular models make the decoding of cell death signaling pathways  
706 very difficult. The generic name HR does not reflect the complexity of signaling pathways and, as in  
707 mammals, recognition of PAMPs, DAMPs or effectors does probably not lead to the engagement of  
708 one unique cell death response but likely activates different cell death-signaling pathways with specific  
709 features and outcomes. The cell death signal also likely depends on cell type and plant species.

710 The plant immune response is associated with different biochemical modifications and cellular  
711 signals that include MAPK activation, oxidative and nitrosative bursts, calcium fluxes, phyto-hormone  
712 production, protease activation and transcriptional reprogramming (5). Studies analyzing their  
713 involvement in immune receptor-induced cell death reported controversial results and their direct role  
714 as effector in transducing cell death signal is still debated. A closer characterization of the spatial and  
715 temporal aspects of these cellular events could probably provide a better view of their involvement. By  
716 putting the animal models into perspective, we can hypothesize that stimulation of plant membrane  
717 PRRs or NLRs have the ability to engage (i) a signaling pathway leading to transcriptional  
718 reprogramming (e.g. MAPK) responsible for phytohormones production and the expression of defense  
719 genes, and (ii) a cell death signaling pathway that can culminate into ions imbalance and rupture of  
720 plasma membrane, both regulated by interplays and cross-regulation mechanisms.

721 The analysis of plant NLR structure showed that the signal transduction domains belong to  
722 conserved homotypic interacting domain family. This suggests that activation mechanisms involve the  
723 assembly of multiproteins, signalling platforms. A range of evidences suggests that plant NLRs form  
724 signalling platforms to promote cell death (39, 83-85, 204, 210, 211), as observed for mammals NLRs.  
725 The recent works of Chai and colleagues (210, 211) highlighting the presence of a large cytoplasmic

726 multiprotein complex named resistosome that can translocate into plasma membrane to form pore-like  
727 structures have provide very important elements into understanding the plant NLR-mediated cell death  
728 signalling. The similarities between the ZAR-1 resistosome and NLR inflammasomes as discussed in  
729 the recent review of Xiong et al. (212) suggest that the NLR-mediated cell death signalling pathway  
730 could be a conserved process.

731 While the role and activation mechanisms of caspases-1, -8 and -3 in PRR-induced signalling  
732 pathways start to be well characterized in mammals, the activation mechanisms of plant proteases and  
733 their importance in the immune-receptor-induced HR remain important questions to address. It is  
734 interesting to note that the lumen of the funnel-shape structure found in the resistosome has negative  
735 electrostatic potentials given by two negatively charged glutamic acid residues (82). Such negatively  
736 charged glutamate residue is thought to be critical for anion selectivity in several human  $\text{Ca}^{2+}$  voltage-  
737 dependent channels (213, 214). It is tempting to speculate that this selectivity for cations could be  
738 associated with a death process. Of interest, some metacaspases such as AtMC4 that process the  
739 PROPEP to a mature phytocytokines are activated by a massive calcium influx.

### 740 **Future applications for plant protection**

741 In Arabidopsis, the screening of vast mutant collections and naturally occurring ecotypes, as well  
742 as forward genetic approaches, has led to the successful identification of novel immune receptors  
743 involved in HR cell death. In crops, analyzing genomic variations within different cultivars but also  
744 the “wild” relative species and their introgression lines allowed to map the Quantitative Trait Loci  
745 (QTLs) related to disease resistance. Although QTLs will mostly carry *R*-genes, they may also contain  
746 PRR genes (encoding RLKs or RLPs). In a scientific point of view, it’s interesting to note that PRRs  
747 can be successfully transferred from one plant species to another to provide a novel source of resistance.  
748 A very effective demonstration was achieved in tomato (from the Solanaceae family), where the  
749 transfer of the EFR RLK receptor (from the Brassicaceae family) led to important resistance against a  
750 wide range of different agriculturally important bacterial pathogens (215). Different studies also  
751 showed that the ectodomain and kinase domains from distinct PRRs can be combined leading to  
752 chimera receptors with preserved signal transduction determined by the kinase domain. Such a  
753 chimeric receptor build from the chitin-binding ectodomain of OsCEBiP and the kinase domain of  
754 XA21 capable to initiate HR in rice highly improved resistance to fungus *Magnaporthe oryzae* and  
755 thus represents an interest for practical use in disease resistance engineering (216).

756 Analysis of the polymorphism occurring in plant immune receptors or cell death regulators in  
757 different cultivars or species may lead to the identification of more efficient variants. As an alternative  
758 to the transgenic approach, conventional breeding can be assisted by the use of molecular markers that  
759 assist to deliver the desired gene into the crop, and pyramid it with other genes important for the plant  
760 resistance such as *R*-genes.

761 All over, the immune receptor-based breeding, the transfer and creation of novel chimeric PRRs  
762 might be applicable as an alternative in agriculture disease and pest management, as a “tailored  
763 immune-receptor therapy” that might provide more durable and broader resistance when associated  
764 with *R*-genes.

In review

## 765 FIGURE CAPTIONS

766

767 **Figure 1. Structural comparison of the main immune receptors found in animals and plants.**

768 ALR, AIM2 (absent in melanoma 2)-like receptors; BIR, Baculovirus Inhibitor of apoptosis protein  
 769 Repeat; CARD, caspase recruitment domain; CC, coiled coil domain; CCr, CC-RPW8; CLR; C-type  
 770 lectin receptors ; CRD, Carbohydrate-Recognition Domain; EGF-like, Epidermal Growth Factor like;  
 771 HIN200(s), Hematopoietic Interferon-inducible Nuclear protein with a 200 amino acid repeat; ITAM,  
 772 Immunoreceptor Tyrosine-based Activation Motif; LRR, leucine-rich repeat; LysM, Lysin Motif;  
 773 NACHT, NAIP (neuronal apoptosis inhibitory protein), CIITA (MHC class II transcription  
 774 activator), HET-E (incompatibility locus protein from *Podospora anserina*) or TP1 (telomerase-  
 775 associated protein); NB-ARC, Nucleotide-Binding domain Apaf1, Resistance, CED4; NLR,  
 776 Nucleotide-binding and oligomerization domain (NOD)-Like Receptor [animals] or Nucleotide-  
 777 Binding Domain (NBD)-containing LRRs [plants]; PYD, Pyrin effector Domain; RD, Regulator  
 778 Domain; RLK, Receptor-Like Kinase; RLP, Receptor-Like Protein (contain a short cytoplasmic  
 779 domain devoid of kinase activity); RLR, RIG-I-like receptors; TIR, Toll/Interleukin-1 receptor; TM;  
 780 Transmembrane; TLRs, Toll-like receptors.

781

782 **Figure 2. TLR-mediated signaling pathway.**

783 The activation of TLR (toll like receptor) 1-2, 4-6 or 10 by lipids, lipoproteins or membrane-anchored  
 784 proteins and the activation of TLR7-9,11-13 by virus-derived nucleic acids induce the dimerization of  
 785 TLRs and the recruitment of Myd88 (myeloid differentiation factor 88) and IRAKs *via* homotypic  
 786 interaction domains, forming the Myddosome. IRAKs catalyze phosphorylation cascade leading to the  
 787 recruitment of TRAF6 (tumor necrosis factor (TNF) receptor associated factor 6). In turn, TRAF6  
 788 promotes the activation by proximity of TAK1 (tumor growth factor- $\beta$ -activated kinase 1)/TAB1-3  
 789 (transforming growth factor-activated kinase1-binding protein 1, 2 and 3) and the IKK (Inhibitor of  $\kappa$ B  
 790 kinase) complexes that result in the activation of MAPK (Mitogen-activated protein kinases), NF- $\kappa$ B  
 791 (nuclear factor-kappa B)-signaling pathways and pro-inflammatory response. TLR3 and TLR4  
 792 stimulation induces the recruitment of TRIF (TIR-domain-containing adaptor-inducing IFN- $\beta$ ) through  
 793 a TIR-TIR homotypic interaction. The adaptor TRAM (Trif-related adaptor molecule) serves as a  
 794 bridge between TLR4 and TRIF. In turn TRIF can recruit TRAF3 that engages IFN (Interferon)

795 response, TRAF6 that leads to MAPK and NF- $\kappa$ B activation, or the kinases RIP (Receptor Interacting  
 796 Protein) 1 and/or RIP3. When poly-ubiquitinated, RIP1 can recruit TAK1/TAB1-3 and IKK complexes  
 797 and activates the pro-inflammatory response. In a non-ubiquitinated form, RIP1 can assemble with  
 798 FADD and caspase-8 to form the ripoptosome that leads to caspase cascade activation and apoptotic  
 799 cell death or can activate RIP3 in the necrosome. RIP3 catalyzes the activating phosphorylation of  
 800 MLKL (mixed lineage kinase domain-like), which oligomerizes and translocates into the plasma  
 801 membrane to form pores and induces necroptosis. The DAI (DNA-dependent activator of IRFs) can  
 802 also directly recruit RIP3 *via* RHIM homotypic interaction to induce MLKL phosphorylation and  
 803 necroptosis in response to virus-derived nucleic acids. The necrosome has also the ability to induce  
 804 ROS (Reactive oxygen species) production resulting in NLRP3 (NOD (Nucleotide-binding  
 805 oligomerization domain)-like receptor protein) inflammasome and pyroptosis. The TLR-mediated  
 806 production of TNF- $\alpha$  can induce an autocrine stimulation of TNFR1 that can lead to RIP1 engagement  
 807 and an amplification of the signal.

808

809 **Figure 3. Signaling events leading to HR in plants.**

810 PRRs are activated by recognition of elicitor molecules resulting from the degradation of plant cells  
 811 (DAMPs) or released by the pathogens (PAMPs/elicitins, apoplastic avirulence factors: Avr). Then the  
 812 signal is transduced by a cascade of phosphorylation involving MAPKs, cytoplasmic protein kinases  
 813 (CPKs) and transcription factors (T.F.), mainly from the WRKY family. This phosphorylation can also  
 814 activate the NADPH oxidase RBOHD, leading to the production of ROS ( $O_2^{\cdot-}$  transformed into  
 815 hydrogen peroxide ( $H_2O_2$ ) by a superoxide dismutase (SOD)). An influx of intracellular  $Ca^{2+}$ , initiated  
 816 quickly after perception of  $H_2O_2$  by HPCA1 leads to the production of nitric oxide (NO), as well as the  
 817 activation of transcription factors *via* the calcium dependent protein kinases (CDPKs). This is followed  
 818 by a reprogramming of the transcriptional activity leading to the expression of defense genes involved  
 819 in the synthesis of phytohormones (salicylic acid (SA), jasmonic acid (JA)...), the antimicrobial  
 820 phytoalexins or even the release of hydrolytic enzymes (glucanases, chitinases...) from the  
 821 pathogenesis-related proteins family. In the meantime, effectors secreted by pathogens to counter the  
 822 plant's defenses can also be directly or indirectly (*via* the recognition of a modified host-protein)  
 823 recognized by NLRs. This recognition generally induces a conformational change in the protein (noted  
 824 here by an asterisk and a color change), allowing the exchange of ADP by an ATP and therefore the  
 825 activation of the NLR leading to macromolecular complexes such as resistosome. These larger-scale

826 molecular complexes have been proposed to act *via* the recruitment of other signaling actors leading  
827 to a potentiation of the defenses already in place or by the formation of pores in the plasma membrane.  
828 A hypersensitive response (HR) cell death is then observed locally to block the spreading of the  
829 pathogen. This will also be associated with the release of DAMPs and phytohormones which will  
830 transmit information to neighboring cells and organs to prevent future infections in healthy tissues.  
831 Some plant peptides (*e.g.* PEPs), can be matured by metacaspase-mediated cleavage and are released  
832 in the apoplast to prime immune responses in neighboring cells, thus enabling the establishment of a  
833 local resistance.

834

### 835 **Figure 4. NLR-mediated signaling pathway in mammals.**

836 The recognition of PAMPs/DAMPs (Pathogen-Associated Molecular Patterns/Damage-Associated  
837 Molecular Patterns) by NLRs (NOD (Nucleotide-binding oligomerization domain)-like receptor  
838 proteins: NLRCs, NLRPs) promotes the recruitment of procaspase-1 (Pro-Casp1) through homotypic  
839 domain interaction, forming a large cytoplasmic complex named inflammasome. In some situation, the  
840 adaptor ASC (apoptosis-associated speck-like protein containing a CARD domain) can take part to the  
841 complex, bridging the receptor to procaspase-1. The procaspase-1 undergoes auto-activation and  
842 processing of its 2 active sub-units (p10 and p20) which assemble into a tetrameric active form. Active  
843 caspase-1 catalyzes the cleavage of proIL-18 (proInterleukine-18), proIL-1 $\beta$  (proInterleukine-1 $\beta$ ) into  
844 mature cytokines and gasdermin-D releasing the PFD domain that can oligomerizes and anchors into  
845 the membrane to form pores. Processing of gasdermin-D can also be ensured by caspase-4 and caspase-  
846 5, which are activated after LPS binding. The gasdermin PFD can also fom pores into the mitochondrial  
847 membrane that induce K<sup>+</sup> release and ROS production. In addition, pores created in the plasma  
848 membrane by PFD also lead to IL1 $\beta$  and IL18 release and to an ion imbalance that finally results in  
849 pyroptosis. The recognition of PAMPs/DAMPs by NOD1/2 promotes the formation of the NODosome  
850 composed of the sensor and the protein RIP2 (Receptor Interacting Protein 2) through CARD-  
851 dependent homotypic interaction. RIP2 can then recruit TAB1/TAB2/3/TAK1 and IKK complexes that  
852 engage MAPK and NF- $\kappa$ B signaling pathways leading to the production of pro-inflammatory  
853 cytokines.

854

855

856 **CONFLICT OF INTEREST**

857 The authors declare that the research was conducted in the absence of any commercial or financial  
858 relationships that could be construed as a potential conflict of interest.

859

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862

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875

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**FIGURE 1**

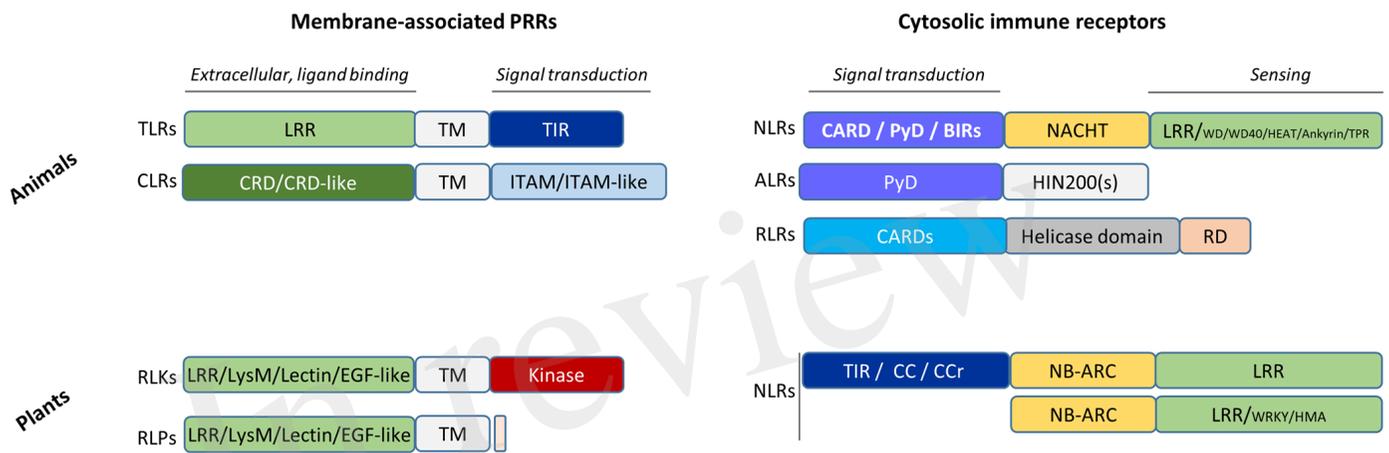


Figure 2.TIF

FIGURE 2

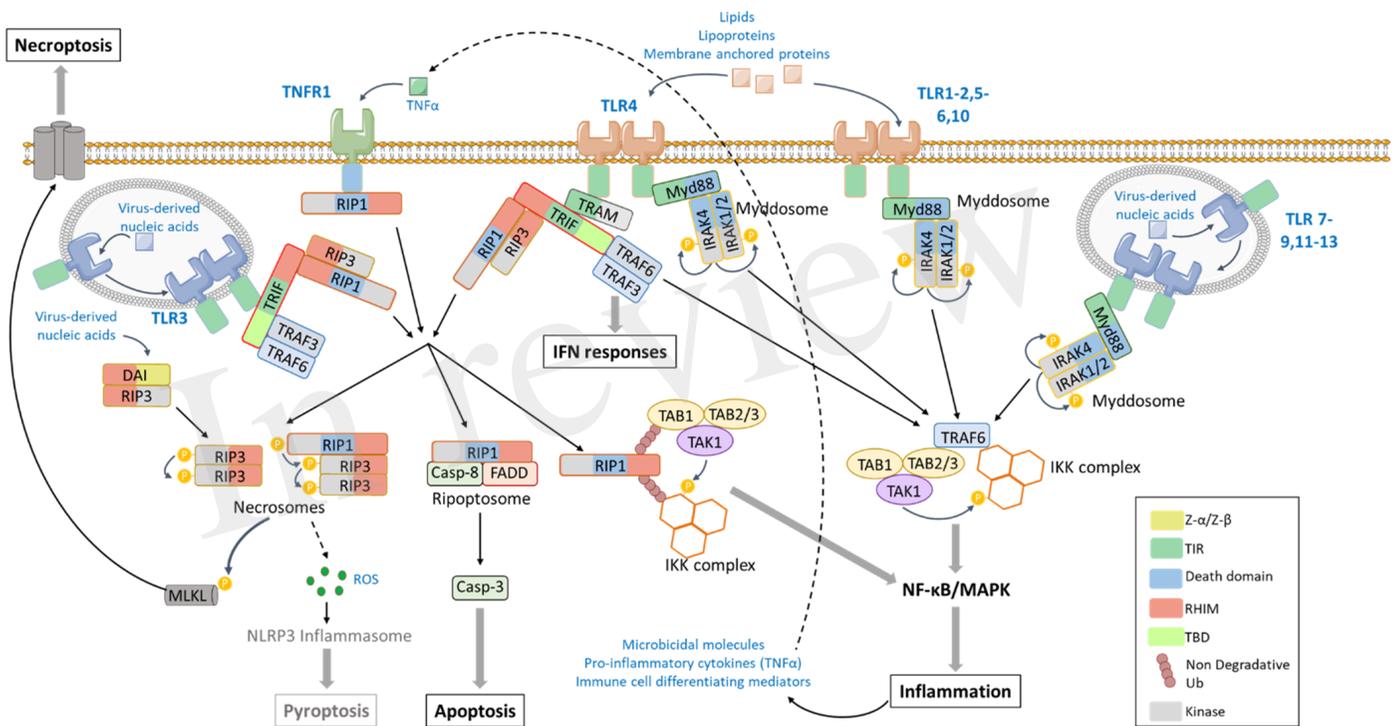


Figure 3.TIF

FIGURE 3

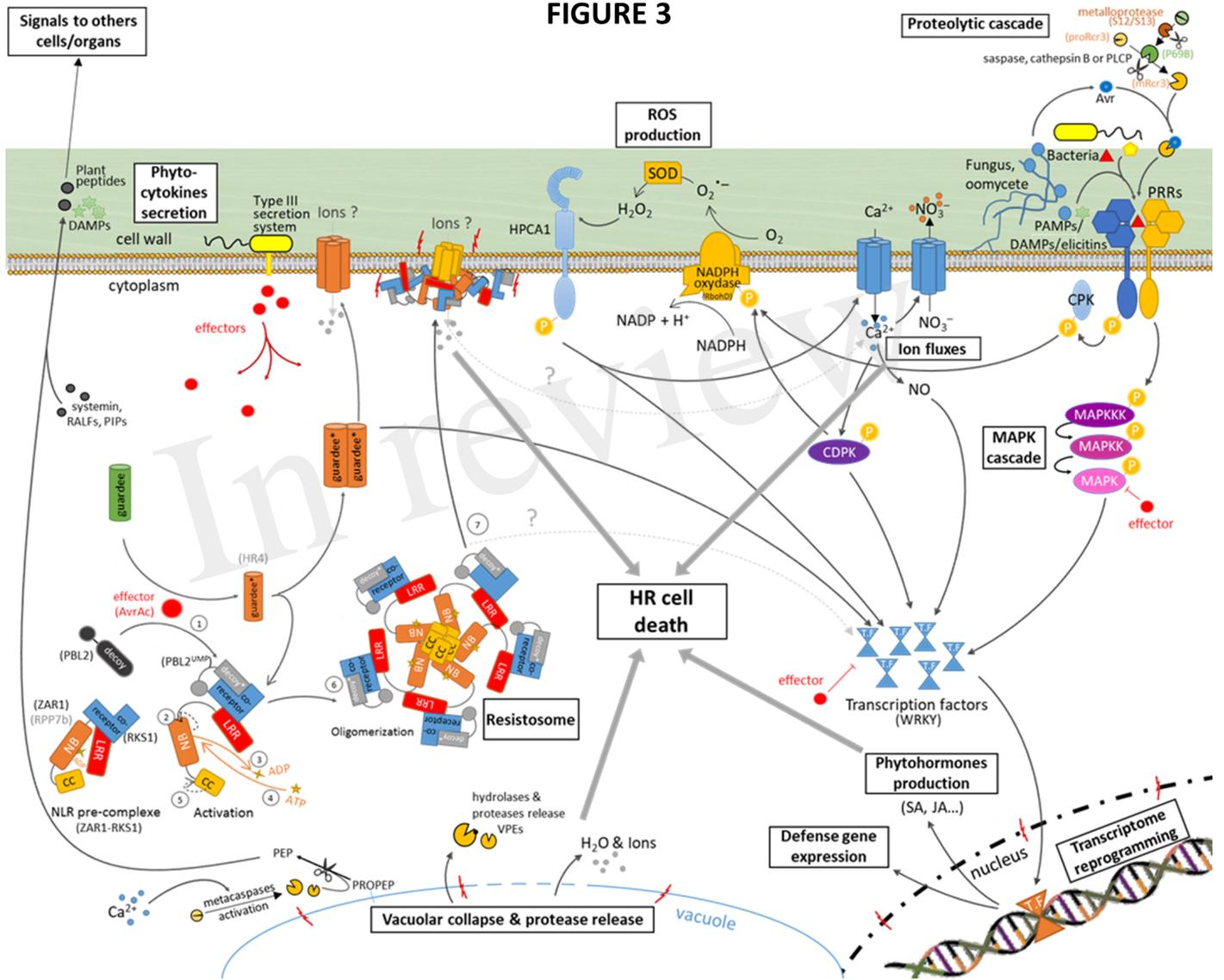


Figure 4.TIF

FIGURE 4

