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Hypersensitive response cell death in plant immunity

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Abstract

Pathogen recognition by the plant immune system leads to defense responses that are often accompanied by a form of regulated cell death known as the hypersensitive response (HR). HR shares some features with regulated necrosis observed in animals. Genetically, HR can be uncoupled from local defense responses at the site of infection and its role in immunity may be to activate systemic responses in distal parts of the organism. Recent advances in the field reveal conserved cell death-specific signaling modules that are assembled by immune receptors in response to pathogen-derived effectors. The structural elucidation of the plant resistosome – an inflammasome-like structure that may attach to the plasma membrane upon activation - opens the possibility that HR cell death is mediated by the formation of pores at the plasma membrane. Necrotrophic pathogens that feed on dead tissue have evolved strategies to trigger HR cell death pathway as a survival strategy. Ectopic activation of immunomodulators during autoimmune reactions can also promote HR cell death. In this perspective, we discuss the role and regulation of HR in these different contexts.

Introduction

To detect potential invaders and respond appropriately, plants have evolved a complex and fine-tuned immune system. Current models have both extracellular and intracellular plant immune receptors initiating signaling cascades in response to invasion (Cook et al. 2015). In turn, potential invaders have developed diverse virulence strategies to evade or subvert plant immunity.

A form of regulated cell death known as the hypersensitive response (HR) is a frequent consequence of pathogen recognition by the plant immune system. The term hypersensitivity stems from the abnormally rapid death of plant cells encountering biotrophic pathogens, which rely on plant living tissue for their survival (Stakman 1915). HR can be manipulated genetically and is under tight control to avoid runaway cell death beyond the site of infection. HR cell death resembles forms of regulated necrosis in mammals, such as necroptosis and pyroptosis, but it also features some apoptosis-like traits (Berghe et al. 2014; Galluzzi et al. 2018; Dickman et al. 2017; Salguero-Linares and Coll 2019). Cell contents leaked during HR cell death may alert other cells to a potential invasion.

HR cell death has been studied mostly in the context of plant defense against biotrophic pathogens or hemibiotrophic pathogens, the latter having an initial biotrophic phase followed by a necrotrophic phase. However, necrotrophic pathogens that feed on dead or dying tissue can hijack HR cell death for their own

benefit. Here, we provide a perspective on HR cell death signaling based on recent advances in the molecular interactions between plant and pathogens, plus we discuss autoimmunity as a trigger of HR cell death in the context of certain mutations or during hybrid necrosis.

Immune HR cell death as a consequence of pathogen recognition

The plant immune system is constantly evolving to detect invasive microbes or their effects on the plant. Initially, plasma membrane PRRs (Pattern Recognition Receptors) were thought to recognize conserved microbe-associated molecular patterns, whereas cytoplasmic NLRs (Nucleotide-binding domain Leucine-rich Repeat containing) sensed pathogenic virulence factors or their perturbations to the cell (Jones and Dangl 2006). However, as our knowledge of plant immunity has advanced, it has become evident that PRRs also respond to virulence effectors. NLRs may also “guard” conserved molecules that act as rheostats in plant immune responses (Cook et al. 2015).

In terms of domain architecture, plant NLRs resemble animal NLRs, with a variable N-terminal domain, a central nucleotide-binding domain and a highly polymorphic C-terminal leucine-rich domain (Figure 1). Plant NLRs are classified according to their N-terminal domains as Toll/interleukin-1 receptor (TIR) domain NLRs (also known as TNLs) or coiled-coil (CC) domain NLRs (or CNLs) (Cui et al. 2014a; Zhang et al. 2017). NLRs recognize effector molecules deployed by pathogens, either directly or indirectly, and then initiate signaling cascades that culminate in the expression of genes mediating host defense (Cui et al. 2014b). An emerging model in plant immunity is that NLRs work in functionally specialized pairs or even more complex networks, with sensor NLRs perceiving pathogen effectors and helper NLRs initiating downstream signaling (Bonardi et al. 2012; Wu et al. 2017).

Recognition of adapted biotrophic or hemibiotrophic pathogens by the plant immune system often leads to HR cell death. Thus, HR cell death is frequently described as an immune strategy to block pathogen colonization. However, this is not always the case, because there are numerous examples of HR cell death and inhibition of pathogen growth being genetically uncoupled (Yu et al. 1998; Greenberg et al. 2000; Balagué et al. 2003; Jurkowski et al. 2007; Coll et al. 2010; Sheikh et al. 2014; Menna et al. 2015; Lapin et al. 2019). As shown in Figure 2, HR cell death at the site of infection is crucial to initiate systemic signals that activate immunity in distal parts of the plant and eventually leading to resistance. This phenomenon is known as systemic acquired resistance or SAR (Fu and Dong 2013; Shine et al. 2019).

Although we are far from an integrated view of HR signaling, research in the last 30 years has substantially increased our understanding of the molecular mechanisms controlling HR. Downstream of NLR activation, HR involves a series of events that include calcium influxes, oxidative bursts originating in different cellular compartments, hormone signaling, mitogen-activated protein kinases, and transcriptional reprogramming (Adachi and Tsuda 2019). Most of these elements are shared between PRR and NLR signaling, and HR cell death has often been regarded as a consequence of surpassing certain signaling thresholds, rather than as a highly regulated phenomenon. However, this view is challenged by recent findings that shed light on HR-specific signaling.

Cell death signaling hubs and the resistosome

Recent work indicates the importance of signaling hubs downstream of NLR activation, which may partition cell death and immune responses (Wu et al. 2016; Castel et al. 2019; Wu et al. 2017; Qi et al. 2018; Lapin et al. 2019). The lipase-like protein ENHANCED DISEASE SUSCEPTIBILITY1 (AtEDS1) mediates all resistance outputs downstream of activated TNLs (Wiermer et al. 2005). As shown in Figure 2, AtEDS1 interacts with SENESENCE-ASSOCIATED GENE101 (AtSAG101) and this heterodimer functions together with the helper CNL family member N Requirement Gene 1 (AtNRG1) to form a cell death signaling module in *Arabidopsis thaliana* that can be transferred to unrelated plant species. In parallel, transcriptional reprogramming to enhance the basal defense response is mediated by the interaction of EDS1 with PHYTOALEXIN DEFICIENT 4 (AtPAD4) and a different helper CNL, ACCELERATED DISEASE RESISTANCE 1 (AtADR1) (Lapin et al. 2019). Helper NLRs have a high degree of redundancy in plant genomes, which may allow functional diversification and expansion of their corresponding sensor NLRs. For example, functionally redundant members of the helper NLR family NRC (NLR required for cell death) may contribute to immunity against different types of pathogens via their interactions with particular sensor NLRs (Wu et al. 2017). Studying interactions and outputs between the components of all these signaling modules is complex because they vary between plant species and according to the pathogen under study. In fact, we still do not know how the signals emanating from these modules execute cell death.

Clues were provided earlier this year by the reconstitution of a NLR supramolecular structure termed the resistosome (Wang et al. 2019a and Wang et al. 2019b). The resistosome has been hypothesized to directly induce HR by forming pores in the plasma membrane, an exciting idea that awaits testing. This immune complex, with stunning structural and mechanistic similarities to mammalian inflammasomes, is composed of the NLR HOPZ-ACTIVATED RESISTANCE1 (ZAR1) and two receptor-like cytoplasmic kinases (RLCKs) (Figure 3). In its resting state, ZAR1 is bound to ADP and the RLCK RESISTANCE

RELATED KINASE 1 (RKS1). RKS1 (RLCK XII) is a pseudokinase that interacts with the LRR (Leucine Rich Repeat) domain of ZAR1 (Roux et al. 2014). The bacterial pathogen *Xanthomonas campestris* uses a Type III secretion system to deliver the bacterial effector AvrAC into the plant cytoplasm, where it uridylates a decoy RLCK, PBS1-LIKE PROTEIN 2 (PBL2) (Wang et al. 2015). Unlike RKS1, PBL2 is an active kinase, but its catalytic activity appears dispensable for immune defense. Instead, modified PBL2 (RLCK VII) binds to RKS1 in the ZAR1-RKS1 dimer, causing conformational changes that release ADP and prime the complex for activation. Subsequent ATP binding drives formation of the resistosome via pentamerization of the ZAR1-RKS1-PBL2 complex. Intriguingly, formation of the resistosome exposes a funnel-like structure that is essential both for resistance to bacteria and for accumulation of the complex in the plasma membrane (Figure 3). This “death fold-switch” may act in an analogous manner to the membrane pores and ion channels formed by MLKL or gasdermins in mammals, or during NLR activation in fungi, potentially suggesting a common evolutionary origin of NLRs from plants and animals (Adachi et al. 2019).

Rather than being the direct cause of cell death, these potential pores could mediate specific ion influxes that activate HR-specific downstream signaling, such as activation of cell death executioner proteases (Feng and Tang 2019; Dangl and Jones 2019). For example, the metacaspase AtMC4 is rapidly activated by calcium that enters the cell upon loss of membrane integrity (Huang et al. 2018; Hander et al. 2019). Activation of AtMC4 results in cleavage of the precursor protein PROPEP1, which releases the danger peptide Pep1 to trigger wound-induced defense signaling. This program shares many components with pathogen-induced defense responses. Whether AtMC4 or other proteases are activated by resistosome pores will certainly be worth analyzing in the coming years.

PRR perturbation as an HR trigger

Plasma membrane signaling may have a very important role in HR signaling. When pattern recognition receptors (PRRs) in the plasma membrane sense certain microbial molecular patterns, they team up with co-receptors in specific nanodomains that initiate signaling cascades (Bücherl et al. 2017). For example, knocking out or overexpressing *AtBAK1* (*BRASSINOSTEROID INSENSITIVE1-ASSOCIATED RECEPTOR KINASE1*), a co-receptor of several different PRRs, leads to a potent HR cell death response and enhanced resistance to hemibiotrophic pathogens (Kemmerling et al. 2007; Domínguez-Ferreras et al. 2015). The fact that overexpression or elimination of a required element for PRR signaling leads to the same HR phenotype may indicate that perturbation or damage to components of PRR signaling is also monitored (Tang and Zhou 2015). This strategy would allow plant cells to defend against pathogen-

mediated inhibition of PRR pathways. Accordingly, inactivation of another PRR regulator, the plasma membrane receptor-like kinase AtBIR1, also results in HR cell death (Liu et al. 2016a).

Proteolytic pathways associated to HR

Signaling downstream of NLRs may impact finely tuned proteolytic pathways, including (selective?) autophagy and the concerted action of several proteases (Hofius et al. 2017; Salguero-Linares and Coll 2019). Various proteases in the cytoplasm (metacaspases, phytaspase, or the proteasome subunit PBA1), in the vacuole (vacuolar processing enzyme VPE), and those secreted to the extracellular space (cathepsin B, saspase, Rcr3, Pip1) have been shown to be essential for HR cell death (Salguero-Linares and Coll 2019). In fact, they need to be tightly controlled to limit cell death beyond the HR site. Hence the multiple levels of negative regulation exerted on, for example, the HR cell death protease METACASPASE1 (AtMC1) by the protease inhibitor SERPIN1, the scaffold protein LESION SIMULATING DISEASE 1 (AtLSD1), and the metacaspase AtMC2 (Coll et al. 2010; Lema Asqui et al. 2018). Moreover, AtMC1 has been shown to act additively to autophagy in controlling HR cell death (Coll et al. 2014). Although it is clear that autophagy promotes HR cell death, the mechanism and precise function (trigger or executioner?) remain unknown (Hofius et al. 2009; Munch et al. 2014; Coll et al. 2014). Intriguingly, to date no canonical proteolytic cascade has ever been characterized in plants. The coming years will hopefully provide a deeper insight into this HR-related proteolysis as the study of plant autophagy in plant-pathogen interactions has witnessed a tremendous expansion in the last few years (Avin-Wittenberg et al. 2018) and plant proteostasis is becoming a fully-fledged field of study.

Local vs peripheral regulation of HR

It will be important to pay closer attention to the spatio-temporal magnitude of HR in the coming years. This aspect has often been disregarded, with many studies of infected tissue not discriminating between HR versus non-HR cells. There are several examples of differential or antagonistic signaling between the cells undergoing HR and the surrounding area. This is true of the metacaspases AtMC1 and AtMC2, which antagonistically regulate HR cell death, and are expressed at the site of HR (AtMC1) or in the cells surrounding the HR zone (AtMC2) (Coll et al. 2010). The transcription factor AtMYB30, which mediates HR cell death and immune responses, has also been shown to be differentially regulated within HR and non-HR zones (Raffaele and Rivas 2013). Finally, signaling pathways downstream of the defense hormones salicylic acid and jasmonic acid are activated in spatially different domains during HR, with salicylic acid in the cell death zone and jasmonic acid in the surrounding area (Betsuyaku et al. 2018). Thus, it will be extremely important to define spatiotemporal markers of HR cell death, so that in the future, we can time and characterize the events leading to HR cell death. These markers will help

discriminate cells undergoing HR cell death from the surrounding tissue, which needs to activate protective mechanisms to survive, while integrating and transmitting danger/immune signals from dying cells to protect the organism against invasion.

Manipulation of immune HR cell death by necrotrophs as a virulence strategy

Necrotrophic pathogens have been regarded as generalists, but it is now evident that their interaction with the plant host is complex and highly regulated. Necrotrophs secrete toxins that kill plant cells and leave remnants from which the pathogen can feed. These pathogens have evolved very sophisticated strategies to trigger cell death. The most common strategy seems to be hijacking HR cell death pathways by subverting components of the plant immune system.

Secreted toxins, also known as necrotroph effectors (NE), are recognized by the so-called NE sensitive genes and trigger HR cell death (Figure 2). Several NE sensitive genes possess classical NB (Nucleotide Binding) and LRR domains, and they often have roles in defense against biotrophic or hemibiotrophic pathogens (Lorang et al. 2007, 2012; Faris et al. 2010). Thus, NE genes appear to be a double edged sword, being effective at eliciting an HR response to contain biotrophic pathogens, but able to be hijacked by necrotrophic effectors to confer plant susceptibility. A classic example is LOV1 (LONG VEGETATIVE PHASE1), an NLR from *A. thaliana* that confers susceptibility to *Cochliobolus victoriae* (Lorang et al. 2007). This necrotrophic fungus secretes the effector victorin, which activates LOV1 and triggers a resistance-like response that culminates in HR cell death and proliferation of the pathogen (Lorang et al. 2012).

The intricate mechanisms regulating necrotroph-host interactions have also been showcased by the study of *Sclerotinia sclerotiorum*. This necrotrophic fungus triggers HR by secreting oxalic acid into plant cells (Kim et al. 2008). During the initial phases of the infection, oxalic acid reduces levels of reactive oxygen species and creates a reducing environment that favors pathogen proliferation. At the same time, host defenses are dampened and the infection progresses unnoticed. At later stages, and once the infection is well established, oxalic acid triggers an increase in reactive oxygen species that causes cell death (Williams et al. 2011). Oxalic acid has also been shown to inhibit autophagy-mediated cell death, which could provide an additional mechanism to camouflage infection and prevent activation of defense responses (Kabbage et al. 2013).

New necrotroph effectors and their plant susceptibility targets are emerging from the interaction between wheat and the necrotrophic fungus *Parastagonospora nodorum*. For example, the effector ToxA is recognized indirectly by the NLR Tsn1 from wheat, which results in HR cell death and disease (Faris et al. 2010). Another *P. nodorum* effector, Tox1, remains in the extracellular space and is proposed to have a dual role in infection. It binds to chitin in the fungal cell wall to protect it from degradation by host chitinases, while also inducing an HR-like response via its recognition by Snn1, a wall-associated receptor kinase (Liu et al. 2016b; Shi et al. 2016). Adding to the complexity, the susceptibility triggered by a necrotrophic effector can vary depending on the genetic backgrounds of the host and pathogen (Peters Haugrud et al. 2019). The identification of new susceptibility gene candidates in the host holds great potential for the generation of plants that are more resistant to necrotrophic fungi, which are a serious threat to agriculture. Understanding precisely how necrotroph effector genes interact with their corresponding plant susceptibility genes may allow engineering of new plant protein targets that evade the effectors without compromising plant fitness and yield.

HR cell death as a consequence of autoimmunity

HR cell death can also be observed in plants in the absence of pathogens. This autoimmunity leads to ectopic defense activation and spontaneous cell death in the form of macroscopic disease-like lesions (Chakraborty et al. 2018). Plant autoimmunity can be triggered by gain or loss-of-function of plant immune modulators (NLRs and non-NLRs), autophagy, and impaired metabolic processes. In the 90's, lesion mimic mutants (LMMs), which are plants with spontaneous or mutagenesis-induced mutations showing HR-like cell death in the absence of pathogen, emerged as a promising tool to characterize HR cell death. Characterization of these genes, mostly in *A. thaliana* and rice, has highlighted the importance of several cellular compartments and pathways in HR signaling, including chloroplasts and light energy, sphingolipids and fatty acids, ROS and ion fluxes, autophagy, and plasma membrane signal perception (Bruggeman et al. 2015). Forward genetic screens targeting LMM revertants have identified additional components of defense signaling pathways, which has led to the idea that LMM phenotypes can be caused by loss of a pathogen effector target that is guarded by a NLR. Subsequent activation of the NLR promotes HR cell death (Lolle et al. 2017; Rodriguez et al. 2016).

The study of autoactive NLR alleles has also been informative. For example, the *snc1-1* (Suppressor of NPR1, Constitutive 1) mutant is a constitutively active variant of the SNC1 TLR that causes autoimmunity and HR cell death (Li et al. 2007). Autoactive SNC1 has been shown to activate immune responses in the nucleus, where it represses small RNAs involved in NLR silencing (Cai et al. 2018) and it associates

with a transcriptional corepressor that blocks expression of negative regulators of immunity (Zhu et al. 2010). To ensure appropriate activation of SNC1-dependent immunity, multiple repression mechanisms directed towards this protein have been shown at the transcriptional level as well as post-transcriptionally (Cheng et al. 2011; Huang et al. 2014; Niu et al. 2019; Dong et al. 2015; Gou et al. 2017; Zhu et al. 2010; Wang et al. 2017a; Zhang et al. 2018; Wang et al. 2019c, 2017b; Johnson et al. 2015, 2017; Cai et al. 2018). The Rp1-D21 gene in maize, which derives from an intergenic recombination event between two NLR genes, Rp1-D and Rp1-dp2, provides another example of NLR autoactivation resulting in HR cell death (Chintamanani et al. 2010). Intramolecular interactions drive activation of Rp1-D21, although HR cell death requires light and temperatures below a certain threshold (Wang et al. 2015; Negeri et al. 2013). Recently, it was shown that two key enzymes of the lignin biosynthetic pathway form complexes with this hybrid NLR and modulate its activity (Wang and Balint-Kurti 2016).

Autoimmunity leading to ectopic HR cell death can also be a consequence of hybrid necrosis, which is a common type of incompatibility found in the progeny of many crosses within and between species (Figure 2). In contrast to hybrid vigor, hybrid incompatibility challenges plant fitness and can result from mismatched NLRs (Chen et al. 2016; Vaid and Laitinen 2019). Indeed, genes causing hybrid necrosis are often associated with plant defense responses (Alcazar et al. 2008). Allelic interactions at the ACD6 (ACCELERATED CELL DEATH 6) locus in *A. thaliana* lead to hybrid necrosis and the enhanced expression of defense genes (Świadek et al. 2017). In fact, ACD6 acts as a quantitative resistance gene that balances growth and pathogen resistance in natural populations of *A. thaliana*, and it has been shown that deleterious autoimmune ACD6 alleles are modulated by natural variants of SNC1 (Zhu et al. 2018).

The hybrid necrosis hot spots in the *A. thaliana* genome are often densely populated with NLRs. These immune receptor loci act as hyper-modulated complexes that recombine between natural genetic variants and cause imbalanced NLR activity (Chae et al. 2014). The Bateson-Dobzhansky-Muller model explains pairwise heteromeric interactions between distinct unlinked NLR loci that lead to hybrid necrosis and enhanced defense (Phadnis and Malik 2014). On the one hand, the polymorphic nature (high levels of sequence divergence) of these immune loci gives an advantage during the host response to pathogen challenges, while on the other hand it positively correlates to hybrid necrosis impacting plant fitness. Different NLR pairs have been involved in hybrid necrosis phenomena (Bomblies and Weigel 2007; Tran et al. 2017; Atanasov et al. 2018). Many questions regarding hybrid necrosis remain unanswered: How is the NLR-mediated defense response propagated without pathogen challenge? What is the role of environmental factors and genetic distance in hybrid necrosis induction? How can the deleterious fitness

effects be mitigated during interspecific crossing while preserving the resistance trait? Our understanding of the mechanisms regulating HR cell death triggered by autoimmunity is still very limited. A deeper understanding of NLR activation and signal transduction will help us integrate and advance the current knowledge.

Concluding remarks

In plant immunity, HR cell death is often used to score resistance to pathogens. However, the mechanisms regulating this complex phenomenon are far from understood. The intricate interplay between sensor and helper immune receptors is starting to emerge, and will help shed light on how cell death is triggered and executed upon pathogen perception. Cell death-specific modules are being unveiled as integrators of signals emanating from activation of diverse sensor NLRs. HR cell death is an important part of the immune response to protect distal parts of the plant against future invasions.

The plant resistosome has been described as an inflammasome-like supramolecular structure that assembles upon recognition of pathogenic effectors to initiate defense responses. The activated resistosome features a funnel-like structure that is required for insertion of the complex into the plasma membrane and HR cell death. It has been speculated that this structure creates pores in the membrane, which could mediate ion fluxes that activate cell death enzymes. Perturbation of the plasma membrane or its signaling components – including PRRs – may also be monitored by NLRs that can trigger HR cell death.

Besides immunity against biotrophic and hemi-biotrophic pathogens, HR cell death can also mediate susceptibility to necrotrophic pathogens. There are several examples of necrotrophic fungi secreting toxins (also known as necrotroph effectors) that directly or indirectly activate specific NLRs and cause HR cell death. These NLRs were probably selected in the course of interactions between a plant and biotrophic pathogen, and then hijacked by a necrotrophic fungus for its own benefit. This is an emerging area of research with great potential, because susceptibility genes can serve as targets for genome editing technologies aimed at increasing resistance against fungi in commercial cultivars.

The analysis of autoimmune phenotypes in plants is also providing a better understanding of the mechanisms regulating HR cell death. Autoactive or miss-matched NLR alleles confer constitutive immunity and ectopic HR-like cell death phenotypes, highlighting the importance of a multi-layered and finely tuned regulation of immune modulators to avoid deleterious fitness costs for the plant. The booming

field of plant immunity will surely deepen our insight into the mechanisms regulating pathogen-triggered HR cell death, helping us understand to what extent it is programmed.

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Figure legends

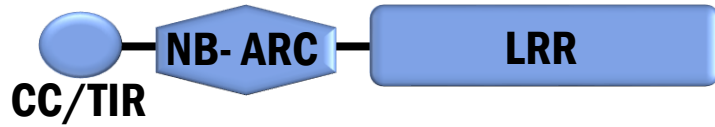
Figure 1. Plant NLRs. A) Schematic representation a plant NLR protein domains. The N-terminal region usually contains a TIR (Toll/Interleukin-1 Receptor homology) or a CC (Coiled-coil) domain. The central region is composed of a NB-ARC domain (Nucleotide Binding - APAF-1, R proteins, and CED-4). The C-terminal region contains a LRR (Leucine-Rich Repeat) domain. **B)** NLR activation. In the inactive, closed state, ADP is bound to the NB-ARC domain. Direct or indirect effector recognition, results in ADP release and ATP binding. This results in a conformational change that renders an open, active NLR. CC - Coiled-Coil domain

Figure 2. Pathways leading to hypersensitive response (HR) cell death in plant immunity. 1) HR can be triggered upon recognition of a biotrophic or hemibiotrophic pathogen via direct or indirect effector recognition by NLR immune receptors, often operating in pairs (sensor NLR + helper NLR). **2)** Cell death-specific modules have been identified, which translate the signal generated by effector perception via TNL (TIR-NLR) activation, into HR cell death. **3)** PRR signaling at the plasma membrane may be monitored by NLRs, with PRR signaling disturbance leading to HR cell death. **4)** HR cell death can be genetically uncoupled from local defense responses, but may have a role in activating systemic resistance responses. **5)** HR can occur as a result of autoimmune reactions, due to ectopic activation of NLRs or other defense signaling modulators or an NLR mismatch. **6)** Necrotrophic fungi can cause disease by hijacking the host HR cell death. A common strategy is activation of NLR receptors by toxins secreted by the fungi into the plant cytoplasm.

Figure 3. Mechanism of resistosome activation. 1) In its resting state, the NLR HOPZ-ACTIVATED RESISTANCE1 (ZAR1) is bound to ADP and the RLCK RESISTANCE RELATED KINASE 1 (RKS1). **2)** *Xanthomonas campestris* secretes the effector AvrAC into the host plant cells, which uridylylates the RLCK PBS1-LIKE PROTEIN 2 (PBL2). **3)** Uridylylated PBL2 binds to RKS1, causing conformational changes to the ZAR1-RKS1 dimer that release ADP and prime the complex for activation. **4)** Subsequent ATP binding results in formation of the resistosome via pentamerization of the ZAR1-RKS1-PBL2 complex. **5)** Conformational changes expose a funnel-like structure essential for accumulation of the complex in the

plasma membrane, bacterial resistance and **6)** cell death, which has been hypothesized to be mediated by pore formation at the plasma membrane upon insertion of the resistosome.

A. Plant NLR domains



B. Plant NLR activation

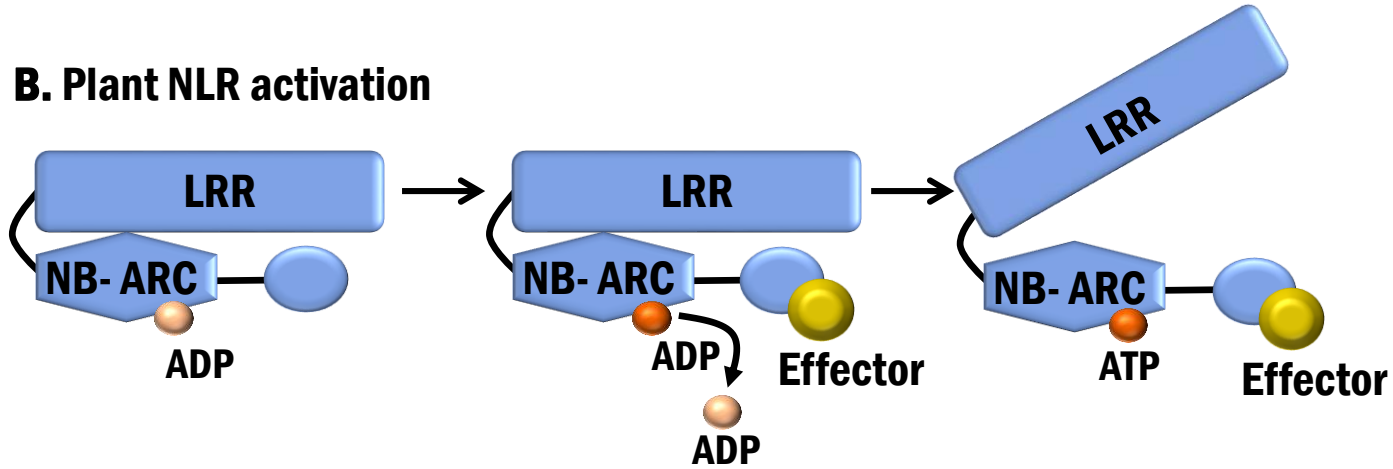


Figure 1

Figure 2

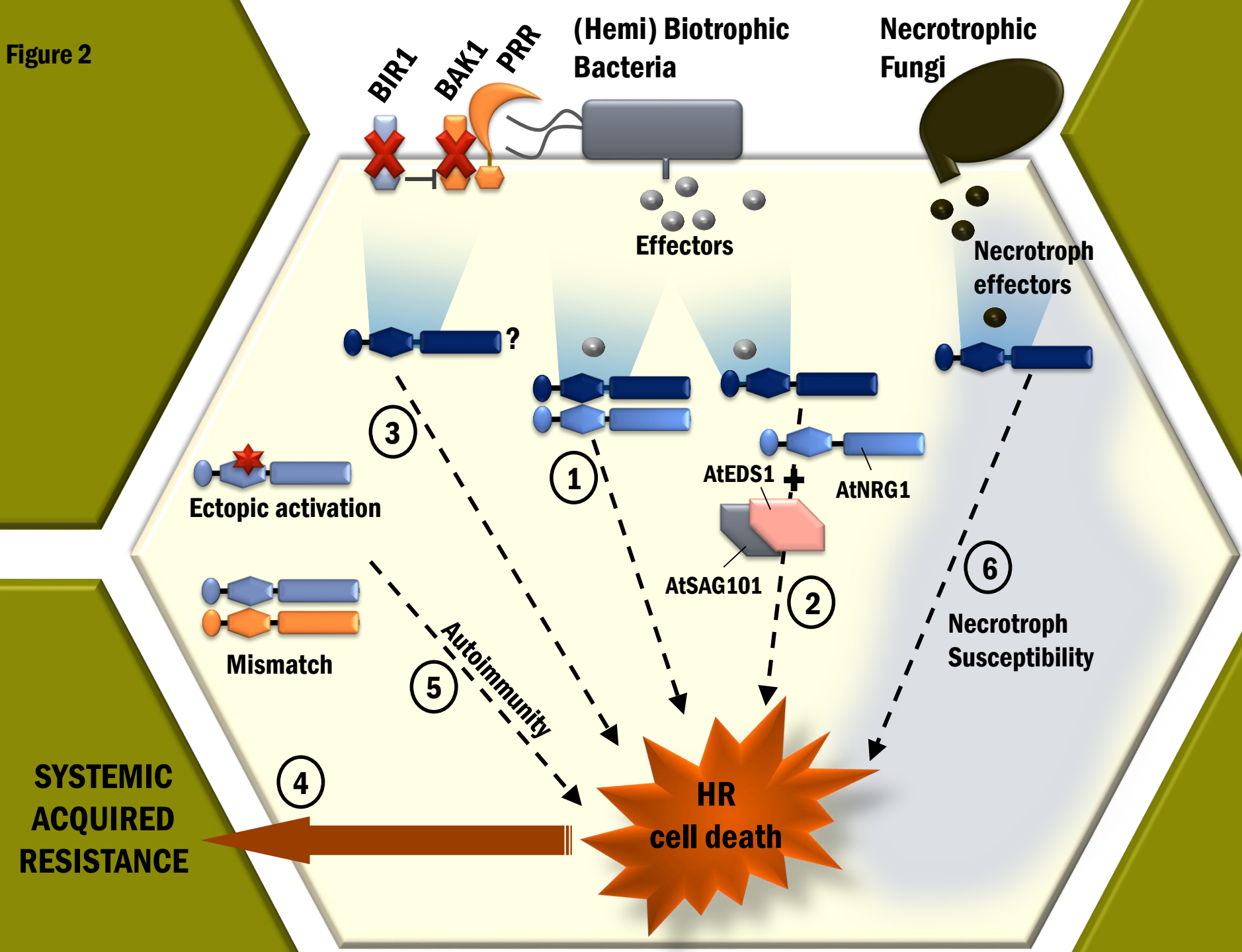


Figure 3

