The plant hypersensitive response: concepts, control and consequences

PETER BALINT-KURTI 1,2,*

1Plant Science Research Unit, USDA-ARS, Raleigh, NC, USA
2Department of Entomology and Plant Pathology, NC State University, Raleigh, NC 27695-7613, USA

SUMMARY
The hypersensitive defence response is found in all higher plants and is characterized by a rapid cell death at the point of pathogen ingress. It is usually associated with pathogen resistance, though, in specific situations, it may have other consequences such as pathogen susceptibility, growth retardation and, over evolutionary timescales, speciation. Due to the potentially severe costs of inappropriate activation, plants employ multiple mechanisms to suppress inappropriate activation of HR and to constrain it after activation. The ubiquity of this response among higher plants despite its costs suggests that it is an extremely effective component of the plant immune system.

Keywords: hypersensitive response, HR

INTRODUCTION
Simply put, the plant hypersensitive response (HR) is a rapid localized cell death that occurs at the point of pathogen penetration and is associated with disease resistance. While others had noted similar phenomena previously (Mur et al., 2008), it is believed that E.C. Stakman (Stakman, 1915) was the first to use the term ‘hypersensitive’. Discussing the extreme resistance displayed by certain grass hosts to *Puccinia graminis*, he noted that the ‘host plant in such cases is hypersensitive to the fungus’. Gauman (1950) defined HR similarly: ‘the hypersensitive reaction implies to us, a priori, rapid plant cell death following elicitation by a pathogen or metabolite thereof, reflecting electrolyte leakage due to membrane damage, the cessation of cytosol and cellular collapse … subsequent to this … is … necrosis of the collapsed cells and localization of the eliciting pathogen’. Goodman and Novacky (1994) describe HR by the following criteria: ‘A rapid cell death localized at the area of pathogen infection that results in some suppression of disease progress (sometimes although not always total)’.

HR is a widespread phenomenon, found in most if not all higher plants and induced by a number of classes of pathogen. HRs induced by fungi, oomycetes, bacteria and viruses are the most commonly observed, but HR can be induced by other organisms, such as insects (Rossi et al., 1998) and nematodes (Dropkin, 1969), that form sustained intimate interactions with the host plant. Cell death has also been observed in resistant interactions between parasitic plants and their hosts (Mohamed et al., 2003), though whether this represents an HR is unclear (Swarbrick et al., 2008). HR is generally associated with race-specific resistance to biotrophic pathogens (pathogens which derive nutrition from living tissues). It is generally less effective against, and may actually be beneficial to, necrotrophs which require dead host tissue to complete their life cycle (see below). The situation is more complex in the case of hemibiotrophs such as *Phytophthora infestans* or *Colletotrichum graminicola* (respectively, the causal agents of potato late blight and anthracnose in many cereals) in which early interactions with the host are biotrophic but subsequently switch to a necrotrophic lifestyle. In these cases HR may be beneficial to the host early but not late in the interaction (Jupe et al., 2013; Münch et al., 2008).

HR and associated responses have been reviewed before (Goodman and Novacky, 1994; Greenberg, 1997; Heath, 2000b; Kamoun et al., 1999; Künstler et al., 2016; Lam et al., 2001; Mur et al., 2008). For the most part these reviews have focused on the literature on the ultrastructure, biochemistry, genetics and physiology of HR and how it relates to other kinds of programmed cell death. This review does not dwell on these previously addressed subjects. Rather it emphasizes aspects of HR that have been the subject of less past attention: the concept, the control and the consequences of HR.

CONCEPTS

The genetics and molecular genetics of HR
Our understanding of HR is linked to the gene-for-gene concept discovered by H. H. Flor in the 1930s to the 1950s (Flor, 1971;...
Loeinger and Ellingboe, 1987). Working on the flax/flax rust system (Linum marginal Melampsora lini), Flor discovered a ‘gene-for-gene’ relationship between the plant and pathogen that determined whether the interaction resulted in disease or resistance/HR. Each dominant resistance gene (R-gene) in the host corresponded with a dominant avirulence gene (Avr gene) in the pathogen. Resistance was only conferred if both the R-gene and the corresponding Avr gene were present in the same interaction. The gene-for-gene relationship was subsequently determined to be broadly applicable across most species of higher plants that have been studied. Many R-gene and Avr genes have been cloned (Kourelis and van der Hoorn, 2018). In the large majority of cases, R-gene-mediated resistance is associated with HR.

Most (not all) R-genes encode cytoplasmically located proteins possessing both a nucleotide-binding site (NBS) and leucine-rich (LRR) repeat domains known as NBS-LRR proteins or NLRs. Furthermore, most NLRs carry either coiled coil (CC) or toll-interleukin receptor (TIR) domains at their N-terminal. While the similarities in NLR structure and function suggest a high level of conservation of mechanism, this is not necessarily the case. In particular, their mechanisms of activation seem to vary quite considerably (Wang and Balint-Kurti, 2015). Nevertheless, in general the N-terminal domains appear to be responsible for activating cell death pathways while the NBS and LRR domains are generally associated with regulating the activity of the R-protein (Kourelis and van der Hoorn, 2018; Wang and Balint-Kurti, 2015; Wang et al., 2015).

A related class of proteins known as pattern recognition receptors (PRRs) encode membrane-bound proteins that recognize broadly conserved microbial molecules known as microbe- or pathogen-associated molecular patterns (MAMPs or PAMPs). Upon recognition they activate a defence response known as MAMP/PAMP-triggered immunity (MTI/PTI) that is qualitatively similar to that induced by NLR, though quantitatively reduced and usually not including programmed cell death (Feechan et al., 2015).

NLRs originated in the earliest ancestors of photosynthetic plants and have been identified in basal-branching streptophytes (charophytes, liverworts and mosses) and all the land plants (Gao et al., 2018; Shao et al., 2019). While the functions of most plant NLRs have not been defined, the only function that has been definitively associated with them is as R-proteins. It is therefore not strictly correct to use the terms NLR protein and R-protein interchangeably as is often seen in the literature (e.g. Gao et al., 2018) since it is likely that many NLRs are not R-proteins. Furthermore some R-proteins are not NLRs; there are a number of classes of R-proteins that do not have the NLR structure (Kourelis and van der Hoorn, 2018).

Avr proteins are now considered to be a class of pathogen effector proteins; proteins that are produced by the pathogen and secreted into the host cells or apoplast specifically to enable the pathogenesis process (Lo Presti et al., 2015). Avr proteins are simply effectors whose presence can be detected by specific R-proteins leading to the activation of the defence response. Resistance triggered by effectors in this way has been termed effector-triggered immunity (ETI) (Jones and Dangl, 2006). The various mechanisms of Avr recognition by R-proteins and subsequent activation of the defence response have been reviewed extensively (Bonardi et al., 2011, 2012; Kourelis and van der Hoorn, 2018). In some cases the R- and Avr proteins directly interact while in others the action of the Avr protein on another host protein (known variously as the guardee or decoy) is responsible for activating the R-protein (Kourelis and van der Hoorn, 2018).

### How should HR be defined?

While the HR is the most obvious manifestation of the defence response associated with NLRs, there are many other aspects which have been reviewed previously (Hammond-Kosack and Jones, 1996; Heath, 2000b; Mur et al., 2008). Bursts of production of reactive oxygen species (ROS) and nitric oxide (NO) usually occur very early in the defence response and are often important for the initiation of HR (Delledonne et al., 2001). Other features commonly described include lipid peroxidation, transcriptional re-programming, ion fluxes and cell wall fortification.

Host–pathogen interactions inevitably drive evolutionary arms races such that genes involved in these interactions tend to evolve at a relatively rapid rate (Tiffin and Moeller, 2006). It is therefore likely that mechanisms of NLR–effector protein interaction and resulting resistance mechanisms including the HR may have diverged substantially between species and between interactions over evolutionary time. It has been noted previously that aspects of HR differ substantially in different interactions (Mur et al., 2008). Nevertheless, the mechanisms underlying HR and its physiological and ultrastructural consequences have often explicitly or implicitly been assumed to be highly conserved across higher plants between hosts and interactions. It is perhaps ironic that a group of interactions each of which are defined by exquisite specificity between individual R-genes and particular races of particular pathogens are nevertheless often assumed to function in identical ways after the initial recognition event. This review will likewise summarize findings made over a broad array of systems that induce HR in an attempt to make overarching conclusions; however, the reader is reminded of the likely variation in underlying mechanisms and effects of different HRs in different species and in different interactions involving the same host species.

The fact that cell death is a common phenomenon in plants with many different causes has also complicated our understanding of HR. The term HR has been invoked to describe a large range of phenomena whose only common feature may be the superficial macroscopic appearance of cell death. The term ‘hypersensitive-like cell death’ or similar is often used simply when cell death is observed without any explicit link to R-genes, the defence response or disease resistance (e.g. Chen et al., 2016; Király et al., 2008; Kumar and Kirti, 2015; Na et al., 2015; Wei et al., 2016).
This review will take a rather narrow view of HR, confined to the localized rapid cell death and excluding the other associated responses induced by the activation of NLR proteins. In most cases this NLR activation is due to the presence of the cognate pathogen-encoded effector proteins and is part of a defence response. However, this definition also includes categories in which HR is ‘illegitimately’ activated through NLRs, due to either mutation of the NLRs or manipulation by plant pathogens. While the cell death in these cases is associated with detrimental phenotypes (susceptibility or reduced growth) rather than resistance, here they will be considered to be legitimate examples of HR as they are triggered by activation of NLRs.

Excluded by this definition is the HR caused by a small class of R-genes called ‘executor R-genes’. These genes are activated at the transcriptional level by a class of effectors known as transcription activator-like effectors (TALEs). None of the six executor genes cloned so far are related to NLRs; two encode a putative flavin monooxygenase and four others encode proteins with predicted transmembrane domains (Kourelis and van der Hoorn, 2018; Zhang et al., 2015). The mechanism(s) by which executor R-proteins cause cell death have not been characterized but, due to their lack of structural or sequence homology to NLRs, it seems unlikely that they act through similar mechanisms to NLRs. This may be an example of convergent evolution; a rapid localized cell death in response to infection may be such an efficient method of containing the spread of biotrophic pathogens that several mechanisms to achieve this have evolved independently.

Can we learn about the control of HR from the study of lesion mutants?

A large class of mutations known variously as lesioned, lesion mimic, accelerated cell death, spotted leaf or lesions simulating disease mutants display lesions, or spontaneously forming patches of dead cells on their leaves. This class of mutants (here referred to as LES) have been characterized in several species, notably Arabidopsis, maize and rice (Fig. 1A). They were named based on their superficial similarity to disease-related phenotypes, specifically HR, though in most cases at the time of discovery there was no direct evidence for a mechanistic link. In fact the large diversity in lesion phenotypes (Fig. 1A and Johal, 2007) seemed to suggest a diversity of underlying mechanisms.

As the genes underlying LES phenotypes have been cloned it has become clear that a significant proportion of them are indeed associated with HR and the defence response. Bruggemen et al. (2015) lists about 80 genes conferring or suppressing LES phenotypes. A few are auto-active NLRs which usually occur when mutations in the NLR gene itself disrupts delicate auto-inhibitory intramolecular interactions causing inappropriately and apparently

![Fig. 1](image_url)
spontaneous activation in the absence of the cognate effector. Another group of LES genes appear to mediate their phenotype via interaction with the plant defence machinery, in some cases through direct interaction with NLRs (e.g. Li et al., 2009). Several others affect the processes regulating ROS in the plant. Therefore, in some cases at least, the phenotypes of LES mutants can inform us about aspects of HR. Some of these are discussed below.

Leaf flecking, a mild lesion phenotype observed on the leaves of some maize lines, is a trait familiar to most corn breeders (Fig. 1B), appearing in several widely used lines as well as in several other species such as barley (Makepeace et al., 2007), wheat (Nair and Tomar, 2001) and oats (Ferdinandsen and Winge, 1930). Recent work has indicated that in some cases flecking seems to be a mild form of misregulated HR (Olukolu et al., 2016; Vontimitta et al., 2015).

HR as a form of programmed cell death

One common definition of programmed cell death (PCD) is the death of a cell in any form, mediated by an intracellular programme. By this definition HR is clearly a form of PCD. A number of reviews have examined the symptomology of HR compared with much better understood forms of PCD (Birch et al., 2018; Goodman and Novacky, 1994; Mur et al., 2008). Many features of HR have been noted in apoptotic and/or autophagic cell death, types of PCD that have been best characterized in animal systems but which are believed to exist in some form in plants (Birch et al., 2018; Liu et al., 2005). These include cytoplasmic/protoplast collapse (Heath, 2000a), cessation of cytoplasmic streaming (Bushnell, 1981; Kitazawa et al., 1973; Naton et al., 1996) and disruption of the cytoskeleton (Chen and Heath, 1991; Gross et al., 1993; Kobayashi et al., 1994; Schadt et al., 2003), DNA laddering (Ryerson and Heath, 1996), formation of large vesicles (Liu et al., 2005) and involvement of the mitochondria (Xie and Chen, 2000). A nice summary of these and other features is given in Table 1 of Mur et al. (2008). The general consensus is that HR shares features with apoptosis and other forms of PCD but that it should be regarded as a specialized form of cell death (Coll et al., 2011; Mur et al., 2008; Van Doorn et al., 2011). Again, the reader should bear in mind that all HR is not identical (Mur et al., 2008).

CONTROL

HR control mediated through NLR expression and protein accumulation

HR needs to be tightly regulated. It must be completely suppressed under non-disease conditions since improper activation will lead to a spontaneous cell death phenotype which can be very detrimental to plant growth (e.g. Chintamanani et al., 2010). Conversely, it needs to be rapidly activated when required. These constraints have led to the evolution of multiple layers of control.

At the transcript level, NLR expression is generally low, often tissue-specific and can be induced during the defence response in many cases (Mohr et al., 2010; Tan et al., 2007). The various mechanisms by which NLR gene transcript abundance is controlled have been recently reviewed (Lai and Eulgem, 2018). They include regulation at the level of chromatin structure, by transcription factors, alternative splicing, post-transcriptional regulation by small RNAs and possibly by alternative polyadenylation, and nonsense-mediated decay. The presence of transposons in or near specific NLR genes is also likely to regulate transcription in certain cases.

Control of HR is also exercised at the level of protein accumulation and stability. In particular, the molecular chaperone HSP90 and two interacting co-chaperones RAR1 and SGT1 form a complex that interacts with many NLRs, stabilizing them and allowing their proper maturation and function (Zhang et al., 2016). The important roles that E3 ubiquitin ligases and the ubiquitin-mediated protein degradation pathway play in plant immunity are becoming increasingly clear (Zhou and Zeng, 2017). While this is still an active area of research, there is some evidence that specific E3 ligases are recruited to direct the degradation of specific NLRs (Huang et al., 2016). The regulation of NLR turnover by the ubiquitin-mediated protein degradation system has been reviewed in detail elsewhere (Dong et al., 2018; Feechan et al., 2015).

Silencing or mutation of any one of RAR1, SGT1 or HSP90 in many interactions is sufficient to abolish HR and to cause the reduction of NLR protein levels (e.g. Azevedo et al., 2006; Bieri et al., 2004; Hubert et al., 2003; Kim et al., 2018; Scofield et al., 2005). The role of SGT1 is not completely understood. In Arabidopsis, inactivation of one of the two functional SGT1 genes led to increased accumulation of the RPS5 NBS-LRR R-protein, suggesting that SGT1 antagonized the effect of RAR1 (Holt et al., 2005), acting to reduce levels of NLR proteins. In another case in Nicotiana benthamiana, silencing of SGT1 caused a reduction in steady-state levels of the R-protein, Rx (Azevedo et al., 2006). These contradictions have not been fully resolved, but the role of SGT1 may vary depending on the species and the particular NLR or its activation state (Azevedo et al., 2006). Translational control has recently been demonstrated to play an important part in regulating the plant defence system (Xu et al., 2017). While translational control of NLRs has not been demonstrated, this possibility does not seem to have been fully explored. Some studies have suggested that protein synthesis is required for HR (Keen et al., 1981; Nozue et al., 1977), while others have suggested the opposite (Doke and Tomiyama, 1975). The consensus is that protein synthesis is required (Greenberg, 1997) but it is of course quite possible that different cases of HR in different species may have somewhat different requirements.
Control of NLR activation mediated by intra- and intermolecular interactions

Arguably the most basic and conserved mode of HR control is the intramolecular interactions that occur between domains of the NLR. These have been well documented in a number of NLRs and while the specifics vary, in general the LRR domain usually plays an inhibitory role by suppressing the activity of the CC or TIR N-terminal domains which, when expressed alone, induce a constitutive HR (e.g. Wang et al., 2015).

As well as the interactions with SGT1, HSP90 and RAR1 discussed above, NLRs interact with a number of other proteins in the cell that modulate their activity. NLR activation is often associated with the formation of homo- and hetero-oligomers (Mestre and Baulcombe, 2006; Schreiber et al., 2016). A class of NLRs termed helper NLRs has been defined that is required for downstream signalling, including HR, initiated by effector recognition by so-called ‘sensor’ NLRs (Baggs et al., 2017). An extensive network of helper and sensor NLRs was characterized in tomato in which multiple complex and redundant interactions mediated immunity to oomycetes, bacteria, viruses, nematodes and insects (Wu et al., 2017). In some cases the genes encoding interacting helper and sensor NLRs are located together in the genome and are termed ‘paired NLRs’ (Baggs et al., 2017). In at least one case these paired NLRs have physically interacted (Williams et al., 2014). In a groundbreaking study Wang et al. (2019a, 2019b) demonstrated that, upon activation, the Arabidopsis ZAR1 NLR forms a homo-pentamer which is assumed to be able to initiate the defence response.

In many cases interactions between NLRs and their specific guardee or decoy proteins are required for inhibition of HR. For example, the guardee protein RIN4 interacts with a number of NLRs across different species and disruptions in RIN4 can induce inappropriate activation of HR (Toruño et al., 2019). The activity of the maize autoimmune NLR Rpf-D21 is modulated by interactions with at least two enzymes in the lignin biosynthesis pathway as well by interactions with genes encoded by other Rpf alleles (Olukolu et al., 2014; Wang and Balint-Kurti, 2016; Wang et al., 2015, 2016).

Control at the population level

In a randomly mating population, the negative effects of improperly activated HR are also mediated at the level of allele frequency. For example, the Arabidopsis NLR RPM1 has been shown to confer yield penalties in the absence of particular strains of Pseudomonas syringae to which it confers resistance (Tian et al., 2003), presumably because it triggers an inappropriate low-level defence response. It appears to have been maintained in the wild population through balancing selection due to its contrasting beneficial and detrimental effects, depending on the external conditions (Stahl et al., 1999). This may be the case for a number of R-genes that confer benefits in the presence of the appropriate pathogen but confer growth/yield penalties in their absence (Karasov et al., 2014).

Thermoregulation

Plant–pathogen interactions that induce HR are commonly temperature sensitive such that HR is not induced at temperatures above 20–30 °C (Bromfield, 1961; Goodman and Novacky, 1994). Examples include wheat/P. graminis (Harder et al., 1979), oat/Puccinia coronata (Zimmer and Schafer, 1961), the tobacco NLR R-gene N/tobacco mosaic virus (TMV; Jockusch, 1966), soybean/Pseudomonas spp. (Keen et al., 1981) and the tomato NLR R-gene Mi/nematode (Abdul-Baki et al., 1996; Branch et al., 2004; Dropkin, 1969).

This phenomenon is also commonly observed for auto-active NLRs (Heidrich et al., 2013; Negeri et al., 2013; discussed more below) and in hybrid necrosis controlled by NLRs (Bomblies et al., 2007; also discussed below; Muralidharan et al., 2014). In some cases chilling sensitive phenotypes, where leaf yellowing and cell death are observed at temperatures under 16 °C, were shown to be caused by mutated versions of NLRs (Bao et al., 2014; Huang et al., 2010).

In most reported cases, elevated temperature suppressed disease resistance as well as HR. For example, temperatures above 30 °C abolish HR and resistance to TMV mediated by the N gene (Whitham et al., 1996). In another example Wang et al. (2009) observed that, compared to 22 °C conditions, Arabidopsis grown at 28 °C exhibited slower HR and compromised resistance mediated by the NLR resistance genes RPS2, RPM1 and RPS4 in response to infection with strains of P. syringae pv. tomato (Pto) DC3000. However, in some cases this was not true; elevated temperatures of 30 °C suppressed HR mediated by the NLRs ZAR1 and RPS2 in Arabidopsis infected with Pto DC3000 and in most, but not all, accessions growth of the pathogen was still suppressed (Menna et al., 2015). More examples of disconnects between HR and disease-resistance phenotypes are discussed below.

The mechanisms underlying NLR temperature sensitivity are not completely understood. In some cases, protein levels may be important. The levels of the MLA NLR proteins conferring resistance to Blumeria graminis in barley were highly reduced when the temperature was shifted from 18 °C to 37 °C (Bieri et al., 2004), with a significant reduction observable within 30 min of the temperature change. Interestingly B. graminis is unable to colonize barley at these elevated temperatures so MLA proteins are likely not required under these conditions in any case (Aust, 1974). In most examples of temperature-sensitive HR, NLR protein levels cannot be measured since the necessary antibodies are not available. However, the levels of the NLR rpp4 that conferred chilling sensitivity in Arabidopsis and of the autoactive NLR SNC1 were not altered by temperature (Bao et al., 2014; Zhu...
et al., 2010), indicating that mechanisms other than those affecting protein accumulation may be important for NLR temperature sensitivity.

The autoactive NLR snc1-1 confers a dwarf phenotype and constitutive HR that is relieved at 28 °C and above (Zhang et al., 2003). In a seminal paper Zhu et al. (2010) showed that a mutation in the LRR motif of snc1-1 abolished the temperature-sensitive phenotype. As noted above, protein levels of snc1 did not appear to be altered by temperature, but the localization of the protein to the nucleus was absolutely correlated with the HR/dwarf phenotype (Zhu et al., 2010). Similar mutations in the N gene also abolished temperature sensitivity and that activity was again correlated with nuclear localization. In related work, also with the N gene, Padgett et al. (1997) showed that the temperature at which HR was abrogated depended on the precise sequence of the cognate Avr gene, suggesting that, in addition to the NLR structure itself and its localization, the precise nature of the NLR–effector interaction can influence the temperature sensitivity of HR.

As discussed above, NLRs appear to often function as oligomeric complexes. It has been suggested that higher temperatures may disfavor these interactions between proteins (Jones et al., 2016). While still untested, this may provide some explanation for the pervasive nature of the temperature-sensitivity phenomenon. The self-association of NLRs involves multiple domains, including the LRR (Schreiber et al., 2016; Wang et al., 2015). The mutation in snc1-1 that abolished the temperature-sensitive phenotype may have enhanced the ability of the protein to self-assemble, rendering the oligomerized state more resilient to the effects of high temperature.

Cheng et al. (2013) showed that while the Arabidopsis ETI response, including HR, is suppressed at temperatures above around 20 °C, the strength of the PTI response increased from 20 °C to 30 °C. Additionally, they examined plants mutant in the arp6 and hta9/hta11 genes, the wild-type versions of which are associated with nucleosome assembly. These lines have been reported to phenocopy warm-grown plants when grown at cooler temperatures (Kumar and Wigge, 2010). These mutants showed higher PTI and lower ETI (including HR) than wild-type plants when grown at low temperatures. These data suggest that, as well as being an intrinsic property of NLRs themselves, the wider plant thermosensing mechanism may also be involved in controlling the reduction in HR at higher temperatures.

Since it is so widespread, the temperature sensitivity of HR is very likely to be an adaptive trait (Alcázar and Parker, 2011; Cheng et al., 2013). In many cases pathogens do not grow well at elevated temperatures (temperatures above the normal ambient levels of their immediate environment). For instance, optimal growth rates of bacteria and fungi in soils from southern Sweden were reported to drop off above 25–30 °C (Pietikäinen et al., 2005). As discussed above, NLRs can have negative growth consequences in the absence of the pathogens to which each confer resistance, probably due to low-level activation of the defence response. It seems likely that the cost–benefit balance for NLR function might become more unfavourable at temperatures above which the pathogens cannot grow well, therefore the activity of NLRs might be down-regulated at these higher temperatures in order to mitigate potential negative growth effects. The observation that B. graminis is unable to colonize barley at the elevated temperatures at which MLA proteins are non-functional (Aust, 1974) supports this hypothesis. Another example is the maize NLR Rp1 which does not confer HR above 30 °C; Puccinia sorghi, the pathogen to which it confers resistance, does not infect well above 25 °C (Pryor, 1994). At substantially elevated temperatures the plant may be under considerable stress and down-regulating defence responses, in part by using temperature-sensitive NLRs, may be beneficial in order to maximize resources for survival growth and reproduction (Ramegowda and Senthil-Kumar, 2015).

Of course, the most predictable temperature fluctuations occur over the 24-h diurnal cycle. The Arabidopsis basal defence response is regulated in a circadian manner (Wang et al., 2011). The expression levels of several genes important for resistance peak around dawn, the time of peak spore dissemination. In this way, it was hypothesized, the plant is able to synchronize its maximal defence responsiveness to the period of maximal need. Dawn is also the coldest period of the day and so perhaps the temperature sensitivity of ETI is another way of fine-tuning this system.

An interesting approach to test the hypothesis that the temperature sensitivity of HR is adaptive would be to compare the temperature sensitivity profiles of NLRs derived from plants that evolved in different environments. One might expect that NLRs derived from plants that evolved in cooler environments might show temperature sensitivity at lower temperatures. To our knowledge this type of approach has not been pursued. The temperature sensitivity of NLR-based resistance has implications for agriculture in the face of climate change. Crops like wheat which are beset by a number of biotrophic pathogens and employ a large number of temperature-sensitive R-genes to combat them (Gousseau et al., 1985) may be particularly affected, though the exact ramifications are hard to predict (Garrett et al., 2016).

Other environmental requirements for HR

Light dependence of HR has often been observed (e.g. Chandra-Shekara et al., 2006; Guo et al., 1993; Negeri et al., 2013; Zeier et al., 2004). This is assumed to be linked to the light-dependent generation of ROS by chloroplasts (Allen et al., 1999; Ishikawa et al., 2014; Liu et al., 2007). The mitochondria are the other major source of ROS in the cell and the function of mitochondria, in particular the mitochondrial electron
transport chain, has been linked to HR in a number of studies (Cvetkovska and Vanlerberghe, 2013; He et al., 2019; Xie and Chen, 2000). High humidity has also been shown to suppress or delay HR in some cases (Klement and Goodman, 1967; Wang et al., 2005), though this might simply be due to delayed dehydration of the cells.

**Signal transduction, propagation and containment**

**Signal transduction**

It is remarkable for such a well-studied phenomenon that we do not understand the direct cause of cell death during HR. In mammalian apoptosis, a class of cysteine proteases called caspases orchestrate apoptotic cell death. These proteins have not been identified in plants (Dickman et al., 2017). It is generally assumed that R-gene activation initiates a signalling cascade that leads to, among other things, HR. The components of this cascade have proved to be elusive, however. Repeated screens for mutants compromised in HR have generally identified the same few genes: RAR1, SGT1, HSP90 and the R-gene itself (e.g. Hubert et al., 2009). Since RAR1, SGT1 and HSP90 are believed to work together to stabilize R-proteins, the implication from these studies is that the pathway from the NLR to cell death is extremely short and/or there is significant genetic or physiological redundancy among the components of the HR signalling pathway such that mutagenesis screens are ineffective in identifying them. The recent finding that upon activation the NLR ZAR1 forms a homopentamer that may form membrane pores suggests that the signalling pathway may indeed be very short or non-existent (Wang et al., 2019a, 2019b).

**Cell-to-cell propagation and containment of the signal**

In many cases HR is manifested as a single-cell phenotype (e.g. Thordal-Christensen et al., 1997; Hückelhoven et al., 1999), with the invaded cell being the only cell to show visible cell death (Fig. 2A). In other cases of HR initiated by incompatible interactions, the region of cell death appears to encompass tens or hundreds of cells, giving rise to spots on the leaf that are visible to the naked eye (Fig. 2B). In the case of multicellular HR, the question is whether HR has initiated in a single cell from which the cell death has then propagated, or whether each cell in the cluster of dead cells has independently initiated HR due to direct interaction with the effector protein. In the latter case this could be caused by a heavy initial inoculation such that many neighbouring cells may interact independently with a pathogen cell, or it may be caused by a phenomenon known as trailing necrosis in which HR does not completely stop pathogen growth, allowing the pathogen to grow or move from cell to cell, initiating HR in each cell in turn (Fig. 2C). This phenomenon has been documented in mutants or with treatments that partially suppress the defence response (Chivasa and Carr, 1999; Morel and Dangl, 1999).

It seems likely that the causes of multicellular HR and the precise appearance of the lesions vary depending on the interaction being studied and the precise circumstances, and are shaped by interaction-specific evolutionary forces that balance the damage to the plant due to the HR with the need to effectively control the pathogen. However, it does seem clear that in many cases there is a signal that is transmitted from cells undergoing the HR to their neighbours and, under the right circumstances, that this signal can cause HR cell death to spread to neighbouring cells. Perhaps the most compelling evidence for this comes from a study which investigated the interaction between HR and autophagy, the process by which cells degrade and recycle organelles and other components. The authors found that silencing ATG6, an important component of the autophagy mechanism, in Arabidopsis and tobacco conferred a runaway HR phenotype in which, once HR was initiated, cell death spread over the whole leaf and to neighbouring leaves instead of being restricted to the region in which it was initiated as it was in wild-type plants (Liu et al., 2005; Patel and Dinesh-Kumar, 2008) (Fig. 3). The tobacco HR in this study was caused by the recognition of a TMV protein p50-helicase by the N protein. Interestingly, in other work it was...
reported that TMV was detected in living cells on the edges of HR lesions induced by N (Wright et al., 2000). This suggests that the mechanism for suppressing the spread of HR may be strong enough in certain circumstances to inhibit HR even if the appropriate NLR and its cognate effector occur together in the cell.

Other evidence for the propagation of a cell death signal deriving from cells in which HR is initiated comes from the study of LES mutants caused by autoactive NLR mutants. In many cases spontaneous activation of HR in these mutants causes the production of macroscopic lesions (Bruggeman et al., 2015; Chintamanani et al., 2010). Genetic background has a profound effect on the size of the lesions induced by the autoactive maize NLR Rp1-D21 (Fig. 4A). The major loci responsible for these background genetic effects have been mapped (Chaikam et al., 2011; Chintamanani et al., 2010; He et al., 2019; Olukolu et al., 2013, 2014) and several of the causal genes have been identified. They include components of the lignin biosynthesis pathway (Wang and Balint-Kurti, 2016; Wang et al., 2016), the mitochondrial electron transport chain (He et al., 2019) and a polygalacturonase gene (Y. He et al., submitted). These genes are not absolutely required for HR, so they do not appear to be part of the primary signal transduction pathway but some may influence the strength of the response and its propagation from cell to cell.

Chimeras in which Rp1-D21 has been mutated in a section of the leaf show that HR neither initiates in or spreads to the sector that lacks Rp1-D21 (author’s unpublished data, Fig. 4B). This suggests that Rp1-D21 is required for both the spontaneous initiation of HR and for sensitizing the cell so it is ‘competent’ to respond to a death signal propagated from the neighbouring cell. Interestingly, defence-related gene expression was nevertheless elevated in the sectors carrying non-functional Rp1-D21, showing that Rp1-D21 was not required for all aspects of the response to the signal. This is presumably the case with other autoactive NLR mutants (Bruggeman et al., 2015). In a related study, Benetzen et al. (1988) used X-ray mutagenesis and visible leaf colour mutations to generate marked leaf sectors lacking the maize NLR Rp1, which confers resistance to common rust and is the wild-type allele of Rp1-D21. They showed that HR induced by the incompatible rust pathogen isolate was cell autonomous. Sectors lacking Rp1 were susceptible to the fungus and HR induced in wild-type sectors did not propagate to mutant sectors.

Taken together these data suggest that, once activated in a cell, the HR can transmit a signal inducing cell death in neighbouring cells. However, there appear to be other mechanisms responsible for the containment of this spreading cell death. The specific balance of these two processes may vary somewhat from situation to situation but in general HR lesions are restricted to one or just a few cells. When this balance is disrupted by genetic or experimental manipulation, larger necrotic lesions may develop.

These conclusions in turn suggest two further questions: What is the nature of the signal and what are the processes that act to suppress the cell death component of the response to the signal? As with many aspects of HR discussed here, the answer is unclear. It seems likely that the signal propagated from the cell undergoing HR usually includes ion fluxes and changes in the levels of ROS. Several LES and LES-suppressor genes encode ion channel proteins, particularly for calcium (Bruggeman et al., 2015). For example, the BONZAI1 family genes BON1, 2 and 3 function in calcium signalling and their mutants exhibit LES phenotypes (Yang et al., 2006). Their phenotype is dependent on the action of EDS1 and PAD4 (Yang et al., 2006), which are involved in the function of many NLRs (Wiermer et al., 2005), suggesting a strong link to HR. BON1 and BON3 are negative regulators of several NLRs (Li et al., 2009) and the autoimmune phenotype of the bon1 mutant is dependent on the NLR SNC1 (Gou and Hua, 2012; Hua et al., 2001).

The role of ROS is suggested by several lines of evidence. ROS production from both the chloroplast and the mitochondria has been implicated in the initiation and spread of HR, and several LES genes are associated with chloroplast or mitochondrial function (Bruggeman et al., 2015; He et al., 2019).
However, the best evidence for a role for ROS in propagation of a cell death signal may come from studies on the lesion simulating disease resistance 1 (LSD1) gene. Homozygous lsd1 mutants exhibit a spreading cell death phenotype which eventually encompasses the entire leaf (though not adjoining leaves) after initiation of cell death by treatment with incompatible pathogens or bioactive chemicals. Chemicals that generate ROS can initiate the spreading lesion phenotype in lsd1 mutants, and conditions that favour ROS accumulation can enhance it (Mateo et al., 2004), while addition of superoxide dismutase, an antioxidant enzyme that catalyses the dismutation of $O_2^-$, suppresses lesion formation. LSD1 encodes a protein with three zinc finger domains which was shown to interact with and stimulates the activity of several catalases (Li et al., 2013). Its activity is dependent on the presence of the NLR ADR1 (Bonardi et al., 2011).

**CONSEQUENCES**

**Resistance**

Perhaps surprisingly for what is the archetypal defence response, controversy remains on the precise role of HR in disease resistance. The argument for HR as a consequence or by-product of the resistance response, rather than a cause of resistance, has been made a number of times over the last half-century. Király et al. (1972) infected compatible hosts with the pathogenic oomycete Phytophthora infestans and the fungi *P. graminis* and *Uromyces phaseoli*. They killed the pathogens but not the host tissue with chemical or heat treatments and observed host cell death in the infected host but not in uninfected controls. They surmised that cell death observed during HR was a consequence of the cessation of pathogen growth. In the intervening years of course, the characterization of multiple NLRs has shown that cell death can occur during HR independent of microbial presence.

However, other studies have from time to time indicated that resistance and HR can be uncoupled, for example:

- Menna et al. (2015) reported that elevated temperature altered resistance and HR in quantitatively different and genotype-dependent ways.
- The TIR-NBS-LRR protein RPS6 confers resistance to *P. syringae* without visible cell death (Gassmann, 2005; Kim et al., 2009).
- The RIN13 gene enhanced resistance conferred by RPM1 but abolished visible HR (Al-Daoude et al., 2005).
- The *Arabidopsis* NLR RPS4 conferred resistance to *P. syringae* in accessions Col-0 and Ler, but while an HR is observed in Ler, no HR is observed in Col-0 (Gassmann et al., 1999).

In cases where R-proteins confer particularly rapid, high levels of resistance, HR may not occur. The tomato Cf-9 gene for resistance to the fungus *Cladosporium fulvum* confers resistance in tomato to an avirulent *C. fulvum* isolate expressing the cognate Avr9 gene without
HR (Hammond-Kosack and Jones, 1994). However, in artificial circumstances when the Cf-9 and Avr9 gene products are expressed together, high levels of cell death are observed (Hammond-Kosack et al., 1994). This phenomenon has been called ‘extreme resistance’. Another example of this is the potato Rx R-protein which confers resistance to potato virus X without HR (Tameling and Baulcombe, 2007). Much of this work and several further examples are summarized in a recent review (Künstler et al., 2016).

Ultimately, the question of whether HR cell death is a cause or consequence of resistance is perhaps not as interesting as it seems. While resistance and HR are unlinked in some situations, these remain the exception. The mechanisms of the resistance responses associated with activation of NLRs are multifaceted. In different cases it is likely that different aspects of the response are differentially effective in restricting pathogen growth and conferring resistance. In some of these cases cell wall fortification, ROS or calcium signalling responses may be the aspects that are most important and in those cases HR may not be necessary. In many other cases it is likely that HR is of primary importance. While the mechanisms of NLR activation vary between each NLR–effector interaction, they generally feed into common pathways in each particular host. It seems evolutionarily unfeasible that a host plant could evolve a series of subtly different NLR-triggered defence responses perfectly honed to each pathogen encountered. Rather it seems likely that a common set of responses is invoked with different aspects of the response, including cell death, playing roles of varying importance in resistance, depending on the pathogen and environment.

Susceptibility

In several necrotrophic systems, most notably in the wheat/Parastagonospora nodorum interaction causing Septoria nodorum blotch (SNB) (Oliver et al., 2012), host-specific toxins have been identified that cause cell death only on plants carrying dominant susceptibility (S) genes. In several cases the S-genes have been shown to encode NLRs or proteins similar to PRRs (Faris et al., 2010; Lorang et al., 2007; Nagy and Bennetzen, 2008; Shi et al., 2016). The gene-for-gene paradigm is inverted in this case since, rather than being hindered by the HR, the necrotrophic pathogen is able to derive nutrition from the surrounding dead cells (Friesen et al., 2007; Lorang, 2018). It seems that in these cases HR is ‘deliberately’ invoked by the pathogen to induce the host to trigger PCD/HR and provide dead cells on which the necrotrophic pathogen can grow. It is not clear how many necrotrophic pathogens use this strategy beyond the four or five systems that have been characterized already (Lorang, 2018), but new cases are being discovered regularly.

Speciation

The activity of NLRs is often delicately regulated by a combination of intra- and interspecific protein interactions. Since the consequences of inappropriate activation are so profound, it seems likely that NLRs and the proteins that regulate their activity co-evolve and that divergence of these proteins may occur within subpopulations of a species with low population gene flow. Within the genus Arabidopsis, the progeny of some crosses between species, or between distant accessions within a species, grow poorly and display a necrotic leaf phenotype (Chae et al., 2014; Vaid and Laitinen, 2019). In a number of these cases of so-called hybrid necrosis, the causal genes are NLRs, one from each parent (Bomblies and Weigel, 2007). As discussed above, interactions between NLRs are common and are often important in appropriate inhibition and activation (Kourelis and van der Hoorn, 2018). In these cases, it is assumed that the interaction of two NLRs that have not co-evolved within the same gene pool may cause their inappropriate activation. Similarly, the NLR-interacting protein RIN4 was associated with hybrid necrosis in crosses between two species of lettuce (Jeucken et al., 2009). Hybrid necrosis, caused by inappropriate activation of HR, has therefore been suggested to be an example of a post-zygotic reproductive barrier which can lead to reproductive isolation and ultimately to speciation (Bomblies et al., 2007). It is not clear how widespread this phenomenon is outside of Arabidopsis and its Brassicaceae relatives (Lafon-Placette et al., 2016). Hybrid necrosis has also been observed in wheat and related species and while the causal genes have not been identified, it has been characterized as an autoimmune phenotype (Mizuno et al., 2011). The severity of hybrid necrosis in both Arabidopsis and wheat is enhanced by low temperatures as would be expected if it were based on NLR activity.

Systemic resistance: exploiting HR to engineer disease-resistant plants

HR often can induce systemic acquired resistance (SAR): broad-spectrum systemic enhanced resistance to pathogenic infection following a localized infection by a necrotizing pathogen or following treatment with various chemical agents (Grant and Lamb, 2006; Vallad and Goodman, 2004). It is dependent on the phytohormone salicylate (salicylic acid, SA), and associated with the accumulation of pathogenesis-related (PR) proteins such as PR1, PR2 and PR5. The response to increased SA concentration is mediated through the proteins NPR1, NPR3 and NPR4, with NPR3 and NPR4 acting as SA receptors and mediating the action of the transcriptional regulator NPR1 which is considered the ‘master regulator’ of the SAR responses (Fu and Dong, 2013).

The high costs of producing and deregulating transgenic plants means that transgenically conferred disease resistance must be broad spectrum in order to be economically feasible as a commercial product. The ability of HR to induce SAR...
Plant hypersensitive response has encouraged approaches to manipulating HR to confer broad-spectrum resistance. Both HR itself and the induction of SAR can confer yield penalties (Durrant and Dong, 2004) so these approaches have focused on inducing HR and SAR at the specific times and places they are most required.

Initial efforts used pathogen-inducible promoters to induce HR by expressing autoactive NLRs or the cognate effector of an NLR endogenous to the host plant (Stuiver and Custers, 2001). These approaches generally failed since the disease resistance provided was insufficient or the yield penalties were too high (Hammond-Kosack and Parker, 2003). Both mild and extreme leaf flecking (as described above) are associated with broad-spectrum resistance (Olukolu et al., 2016). While more extreme flecking was also associated with a yield penalty, milder flecking was not. While much more research is required, this suggests that there may be circumstances under which the low-level activation of HR leading to SAR may be useful for imparting disease resistance without unreasonable yield penalties. One approach might be to use development-specific promoters that direct expression after anthesis, a period when many diseases become more prevalent, but after the majority of growth has been completed.

CONCLUSIONS

The ‘arms race’ between hosts and their parasites has had profound effects on the evolution of life on earth. The process of sexual reproduction itself may have evolved due to the need for the host to adapt to and evade disease pressure (Ebert and Hamilton, 1996). HR induced by NLR proteins is a remarkably widespread phenomenon across the plant kingdom and has profound effects on many aspects of plant growth and development beyond disease resistance. A sophisticated architecture has evolved to control HR activation with multiple levels of control (summarized in Fig. 5). Nevertheless inappropriate activation...
can still occur and leads to deleterious phenotypes such as lesion mimics which retard growth, susceptibility to necrotrophic pathogens and hybrid necrosis, and possible subsequent speciation (Fig. 5). Most species of plants carry more than 100 NLRs in their genomes (Arabidopsis has more than 100, tomato more than 400). The fact that plants maintain so many of these potentially lethal genes, as well as the cumbersome machinery to contain their deleterious effects, is a measure of how important disease resistance, and this mechanism in particular, has been during plant evolution.

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