A molecular roadmap to the plant immune system

Adam R. Bentham#, Juan Carlos De la Concepcion#, Nitika Mukhi#, Rafał Zdrzalek, Markus Draeger, Danylo Gorenkin, Richard K. Hughes & Mark J. Banfield*

Department of Biological Chemistry, John Innes Centre, Norwich Research Park, Norwich, NR4 7UH, UK

# Authors contributed equally, listed alphabetically by surname

* Corresponding author: Mark Banfield
Email: mark.banfield@jic.ac.uk

Running title: Molecular basis for pathogen detection by the plant immune system

Keywords: Plant immunity, cell surface immunity, intracellular immunity, resistance engineering, effectors, Nucleotide-binding leucine-rich repeat receptors (NLRs), Receptor-like kinases (RLKs), Receptor-like proteins (RLPs)
Abstract

Plant diseases caused by pathogens and pests are a constant threat to global food security. Direct crop losses, and the measures used to control disease (e.g. application of pesticides), have significant agricultural, economic and societal impacts. Therefore, it is essential we understand the molecular mechanisms of the plant immune system, a system which allows plants to resist attack from a wide variety of organisms ranging from viruses to insects. Here, we provide a roadmap to plant immunity, with a focus on cell-surface and intracellular immune receptors. We describe how these receptors perceive signatures of pathogens and pests and initiate immune pathways. We merge existing concepts with new insights gained from recent breakthroughs on the structure and function of plant immune receptors, which have generated a shift in our understanding of cell-surface and intracellular immunity and the interplay between the two. Finally, we use our current understanding of the plant immunity as context to discuss the potential of engineering the plant immune system with the aim of bolstering plant defences against disease.

Introduction

Plants suffer from disease. Their ability to respond to infection by microbial pathogens and pests is essential for survival. In agriculture, plant disease leads to a loss in crop yield and can have devastating effects on both subsistence, small-holder and industrialised farming (1-3), with subsequent impact on food supply chains and prices. Plant diseases have also shaped our world, with perhaps the best-known example being the Irish potato famine in the mid-1800s, where potato late blight disease (caused by the filamentous plant pathogen *Phytophthora infestans*) contributed to mass emigration from Ireland (4).

As a rich source of nutrients, plants are the target of microbial pathogens and pests including viruses, bacteria, filamentous pathogens (fungi and oomycetes), nematodes, and insects to complete their life cycle (5-8). Estimates of the impact of pre-harvest yield loss in crops due to disease vary, but at least 30% of global agricultural production is claimed annually (9). This can increase to 100% in localised outbreaks and represents a major contributor to food insecurity. In agriculture, plant diseases are largely controlled by chemicals, but this is unsustainable in the long-term due to environmental concerns and the necessity to rethink agricultural practices more generally in light of the climate emergency. Genetic forms of disease resistance offer the potential for environmentally friendly, low input, sustainable agriculture (10). Over the last 25 years, remarkable progress has been made in our understanding of the molecular basis of plant disease resistance mechanisms. Plant immune receptors, encoded by Resistance or ‘R’ genes have been cloned and characterised, and shown to be the genetic basis of disease resistance phenotypes used by plant breeders for > 100 years. Recent studies have extended our knowledge to reveal our first insights into the structural basis of plant immune receptor function (11-20).

The immune system of plants shares similarities with the innate immune system of animals (21-23). But as plants lack an adaptive immune system, they rely solely on innate immunity to recognise microbial pathogens and pests. Conceptually, plant immunity can be divided into cell-surface and intracellular immunity (24). A full list of the structurally characterised immune receptors and associated ligands can be found in Table 1. Cell-surface immune receptors detect common signatures of pathogens or pests outside the host cell via extracellular domains (ECDs), and initiate cellular responses to resist infection via their intracellular kinase domains (KD) (25). A subset of cell-surface immune receptors sense damaged ‘self’ as a surrogate for the presence of pathogens or pests (16). Intracellular immune receptors detect signatures of adapted pathogens or pests (26). Typically, these signatures are translocated proteins known as ‘effectors’, which are delivered inside cells to modulate host physiology to promote colonisation and proliferation (27,28) (Fig. 1). Activation of intracellular immunity is generally considered a more robust response and can be associated with localised cell death that constrains the spread of infection. While often presented as distinct signalling pathways, insights into how cell-surface and intracellular immune pathways in plants overlap and work synergistically to resist infection have recently begun to emerge (29,30).

There are many excellent reviews covering plant immunity and its subversion by microbial pathogens and pests published over the last ~15
years (22,25,31-39). Here, as part of this JBC “Plants in the Real World” thematic series, we provide an up-to-date overview of the general concepts of plant disease resistance mechanisms, with a focus on plant immune receptor function at the molecular level. We detail how these receptors perceive pathogen signatures at the cell-surface and inside host cells, and how this perception is translated into an immune response. This review summarises the general concepts of plant immunity before providing in-depth analyses of the more recent breakthroughs, that have greatly expanded our understanding of plant immune receptor function. Finally, in the context of current knowledge, we discuss how plant immune receptors could be engineered to deliver novel disease resistance properties to benefit global food security.

**Effectors: Master manipulators of plant cells to promote infection**

To best understand the interplay between the pathogens/pests and the plant immune system, we must first understand effectors and their role in promoting virulence. In the broadest definition, effectors are molecules used by a diverse array of organisms (including microbes, plants and animals) to modulate the activity of another organism. In this review, we use the term ‘effectors’ to define protein molecules secreted by microbial pathogens and pests to promote colonisation of their plant hosts (39). These effectors can be delivered to the extracellular space or deployed to the inside of host cells.

Effectors are also an Achilles’ heel for the pathogen/pest. As signatures of non-self, they can be perceived by plant immune receptors at both the cell-surface and inside cells. Intracellular perception of effectors, or their activities, is mediated and transduced by NLRs, as described elsewhere in this review.

**Section 1: Cell surface Immunity**

A major component of cell-surface immunity in plants are membrane localized receptor-like kinases (RLKs) and receptor-like proteins (RLPs) that detect signatures of non-self as signs of infection (31). RLKs/RLPs also have other roles in plants, regulating self-incompatibility, growth and development, reproduction, response to abiotic stress, and symbiosis (31,47-49). Also known as pattern recognition receptors (PRRs), cell-surface immune receptors monitor the extracellular environment for pathogen/pest invasion patterns (ligands known as MAMPs (microbial-associated molecular patterns) or DAMPs (damage-associated molecular patterns)) (50,51). Frequently, ligand-sensing cell-surface receptors require co-receptors to transduce perception of non-self into a response (52,53). Although proteinaceous receptors represent the major players in cell-surface immunity of plants, recent studies have highlighted an emerging role of membrane lipids in sensing infection (36).

Irrespective of their origin, invasion patterns recognized by cell-surface immune receptors tend to be evolutionarily constrained ligands derived from components essential to the fitness of the pathogen/pest. These essential components range from cell wall constituents or subunits of bacterial flagellin, to molecules secreted into the apoplast, to secreted proteins intended for the host cytosol (25). These specific ligands are perceived by cell-surface receptors at nanomolar concentrations, and initiate signalling cascades including production of reactive oxygen species (ROS),...
cytosolic Ca\textsuperscript{2+} bursts, activation of MAPKs, and changes in expression of various defence-related genes (50,53,54). Generally, cell-surface immune responses are considered less volatile when compared to intracellular immunity and do not result in host cell death to restrict infection. However, they constitute an effective host strategy against infection, leading to broad-spectrum resistance (55). This review focuses on the mechanisms of immune activation rather than the downstream effects of extracellular and intracellular immunity, for readers interested in the physiological effects of immune activation we recommend these reviews (56-58).

Signalling cascades downstream of cell-surface immune receptors are major targets of pathogen/pest effector proteins, which interfere with these processes to benefit infection. It is also worth noting many MAMPs are shared between pathogens and mutualistic microbes (48,59), and as such it is important to understand how plant’s use extracellular immune receptors to distinguish between pathogens/pests and mutualists. In this review we cover MAMP recognition from a pathogen/pest-detection perspective, and would direct readers interested in plant-mutualist interaction to these reviews (48,59).

**Structural and functional diversity of ligand recognition by cell-surface receptors**

RLKs contain a variable extracellular domain that mediates ligand recognition, a single pass transmembrane domain, and an intracellular kinase domain (KD) that transduces the signal to downstream immune components (60) (Fig. 2). Most plant RLKs identified belong to the family of non-RD kinases (defined by the absence of conserved arginine in the catalytic loop) and often associate in dynamic complexes with membrane-bound RLKs that are functional RD kinases (such as BAK1 and SERKs), which operate as co-receptors for perception to initiate immune signalling (61-63). While RLPs exhibit a similar overall structure to RLKs, they only contain a short intracellular tail, lacking a kinase domain, and require a partner co-receptor to signal (49,64).

Based on the type of ECD, RLKs and RLPs can be clustered into distinct sub-families including leucine-rich repeat (LRR), lysine motif (LysM), lectin, and epidermal growth factor (EGF) domain-containing receptors (52,65,66) (Fig. 2). The type of ECD mainly defines the nature of the ligand perceived by the RLK/RLPs, however a few anomalies persist. Amongst the best characterized cell-surface immune receptors are the Arabidopsis LRR-type RLKs, FLS2 (Flagellin-sensitive 2) and EFR (elongation factor Tu (EF-Tu) receptor) (67,68), and the LysM-type RLKs LYK5 (Lysin motif receptor kinase 5) and CERK1 (Chitin elicitor receptor kinase 1) (69,70). FLS2 (Fig. 3) and EFR recognize peptide epitopes from the N-termini of bacterial flagellin (flg22) and bacterial EF-Tu (elf18) respectively (71), while LYK5 and CERK1 bind fungal chitin oligomers (70).

**Recognition of peptide/protein ligands**

LRR-RLKs are a large subfamily of cell-surface receptors that preferentially bind peptides or proteins as ligands (72-74). In addition to the Arabidopsis FLS2 and EFR, LRR-RLKs from rice and solanaceous plants have been characterized. The rice cell-surface receptor Xa21 binds RaxX21-sY, a tyrosine-sulphated protein from bacteria (75). Cell-surface receptors from tomato (CORE) and tobacco (NbCSPR) bind to conserved epitopes derived from bacterial cold shock protein (76-78). Likewise, Arabidopsis RLP23 binds the epitope nlp-20, a conserved peptide derived from ethylene-inducing peptide1-like proteins of bacterial and filamentous pathogens (79).

While not an LRR-RLK, the Arabidopsis cell-surface receptor FERONIA (FER) uses a tandem malectin-like ECD to perceive RALF1 (Rapid alkaliniization factor 1) peptides. RALF peptides are cysteine rich peptides prevalent in the plant kingdom that regulate many aspects of plant life such as reproduction, growth, responses to environment, and immunity (80,81). Intriguingly, some functionally active RALF-like peptides have been characterised from fungal pathogens, however the role of these RALF-like peptides in pathogenesis is unknown (82). In addition to MAMP ligands, some LRR-RLKs perceive proteinaceous DAMPs such as Atpeps (plant elicitor peptides) and PIPs (PAMP-induced secreted peptides) respectively (83-86). Like LRR-RLKs, LRR-RLPs can also sense extracellular short peptide ligands, however they can also sense larger extracellular proteinaceous ligands, such as apoplastic effectors. In tomato, the LRR-RLPs Cf-2/4/9 perceive apoplastic effectors Avr2, Avr4, and Avr9 from Cladosporium fulvum respectively (87-91).
Recognition of carbohydrate ligands

There are several different classes of receptor that are capable of sensing different carbohydrate ligands. LysM-RLKs/LysM-RLPs and Lectin-RK LORE perceive carbohydrate MAMPs such as bacterial peptidoglycan (PGN), lipopolysaccharide (LPS), and fungal chitin (11,69,70,92,93). The ECD of the cell wall-associated kinase family (WAKs) comprise repeated EGF-like domains (94-97) that bind various types of pectins including pathogen/wound-induced short oligogalacturonic acid fragments (OG) as well as cell wall-associated longer pectins (97,98). Intriguingly, the DORN1 receptor, also predicted to be a Lectin-RK, perceives the non-carbohydrate ligand eATP (extracellular ATP) as a DAMP signal (99,100).

Ligand induced homo/heterodimerization of cell-surface receptors

Plant cell-surface immune receptors function in complex with co-receptors and intracellular kinases to activate defence (51,52,64). The LRR-RLK BAK1 is the best-characterized co-receptor to date (14,63,101). BAK1 forms heterocomplexes with peptide-binding immunity-related LRR-RLKs including FLS2 (Fig. 3), EFR, and PEPR1, and is required for immune signalling (13,14,101-103). Like BAK1, SOBIR1 is a regulatory LRR-RLK that serves as an adaptor for certain LRR-RLPs to trigger defence (104-106). Similar to LRR-RLKs, these RLP/adaptor complexes recruit BAK1 or other SERKs for signal transduction (107-109).

By contrast, the Arabidopsis carbohydrate-binding LysM-RLK CERK1 forms chitin-bridged homodimers (11). Homodimeric association has also been reported for the chitin-binding rice LysM-RLP CEBiP (110,111), but the rice CEBiP can also form heterodimers with rice CERK1 (11,112). Although oligomerisation is important, the precise role of homo- or hetero-interactions of LysM-RLK/RLPs in signalling recognition of chitin remains unclear (110).

RLCKs in downstream defence signalling

Ligand perception by plant cell-surface receptors typically results in homo- or heterodimerization that stimulates cis- and/or transphosphorylation of intracellular kinase domains (110). In turn, the kinase domains of cell-surface immune receptors activate receptor-like cytoplasmic kinases (RLCKs) to transduce immune signals (113-115).

The Arabidopsis RLCKs BIK1 and PBS1-like (PBL) proteins are substrates of distinct receptor/BAK1/CERK1 complexes at the cell-surface (113,116,117). For example, in the absence of ligand, BIK1 interacts with BAK1 and associated cell-surface receptor kinase domains (Fig. 3). On ligand binding, a series of cis/trans phosphorylation events promotes BIK1 dissociation from the complex (113,117). BIK1 then and activates various downstream immune signalling pathways including ROS burst, Ca²⁺ accumulation, and activation of MAPK pathways (118-120). Multiple RLCKs have been identified in plants that regulate a ROS burst by phosphorylating distinct sites in RBOHD, a membrane localised NADPH oxidase critical for ROS formation post-MAMP detection (119,121-123).

Regulation of cell-surface immune responses

To prevent inappropriate signalling, the activity of plant cell-surface immune receptors is tightly controlled (124). Plants use various strategies to help maintain cell-surface receptors in an inactive state in the absence of ligand binding, including the regulation of phosphorylation status, and ubiquitination by E3 ligases (124-127).

Phosphorylation is central to cell-surface immunity signalling cascades and is under tight regulation. Plants use phosphatases to negatively regulate cell-surface receptors to prevent the potentially harmful effects of autoinduction. For example, Arabidopsis PP2A (Protein Phosphatase 2A), a serine/threonine phosphatase, dephosphorylates BAK1/EFR to control defence signalling (128,129). Similarly, PP2C38 regulates ligand-induced phosphorylation of BIK1, moderating signalling by this key transducer of cell-surface immunity (124). A second strategy to negatively regulate cell-surface immunity is the use of pseudokinases, such as BIR1 and BIR2 that are catalytically inactive but interact with BAK1 in its resting state, preventing the association of LRR-RLKs (130-132). Ligand binding relieves this inhibitory interaction leading to the formation of activated immune complexes.

Regulation of immunity can also come from
controlled degradation through ubiquitination. Two closely related E3-ubiquitin ligases, PUB25 and PUB26, together with both a calcium-dependent protein kinase CPK28 and a heterotrimeric G protein, form a regulatory module and maintain BIK1 homeostasis (133). Similarly, PUB12 and PUB13 polyubiquitinate and mediate degradation of ligand bound FLS2 (134-136). Intriguingly, a recent study showed that monoubiquitination of BIK1 is necessary for its release from the FLS2/BAK1 complex and immune system activation (137). This demonstrates that a variety of post-translational modifications are important for both positive and negative regulation of cell-surface immune receptors.

In addition to regulating the pool of ligand-bound cell-surface receptors at the plasma membrane, plants also ensure the availability of ligand-free receptors for ongoing pathogen/pest perception. Cell trafficking components, including SCD1 (DENN domain protein) (138,139) and ESCRT-I (an endosomal sorting complex required for transport) (140,141) are involved in delivering these receptors to the cell-surface. Finally, it has been proposed that sets of cell-surface receptors may gather at discrete locations on membranes, forming discrete nano- or micro-domains (142,143). These nano-/micro-domains are proposed to use similar downstream signalling components, however different groupings of receptors would lead to different specificity in signal perception, resulting in different responses to stimuli. However, more work is needed to understand the specificity of these nano-/micro-domains and how they are clustered into spatially-distinct regions of the membrane (142,143).

**Next steps in understanding cell-surface immunity**

While hundreds of RLKs and RLPs have been identified in many plant species, only a subset have been characterized. The biological significance of the vast majority of these receptors remains elusive, and their underlying mechanism of ligand perception remains poorly understood. Understanding how cell-surface receptors with different ECDs perceive ligands will provide a foundation for engineering broad-spectrum resistance into crop plants (144,145). Further, our understanding of how RLCKs coordinate their association with different receptors and facilitate distinct signalling outputs is a key challenge for the future. We are yet to understand whether activated cell-surface receptor complexes form higher-order supramolecular signalling units at the plasma membrane, what the molecular identity of these activated immune complex might be, and how they may differ across different ligand/cell-surface receptor pairs. Beyond this, we must endeavour to understand the determinants of specificity of plant cell-surface receptors for MAMPs, as this will provide insight into how plants distinguish the MAMPs of pathogenic microbes from those of the beneficial mutualistic microbes.

**Case study 1: flg22 perception by the FLS2/BAK1 complex – An exemplar of ligand perception by cell-surface receptors**

Genetic screens in Arabidopsis identified FLS2 as the gene that recognizes a conserved 22-amino acid N-terminal epitope (flg22) of bacterial flagellin to initiate cell-surface immunity (67,68,146). FLS2 belongs to the LRR-RLK class XII subfamily and shares homology with TLR5, an LRR-containing receptor that perceives flagellin in mammals (147,148). Fig. 3 gives a detailed mechanistic view of how flg22 is perceived by FLS2.

Flagellin perception in Arabidopsis requires heterodimerization of FLS2 with BAK1 (68,103,149). The crystal structure of the ECDs of FLS2 and BAK1, in complex with flg22, revealed the structural basis of flg22 perception (13). The flg22 peptide is bound within the concave surface of the FLS2-ECD, via the leucine-rich repeat subunits LRR3 to LRR16. Flg22 interactions with FLS2 are divided into two regions, separated by a kink in the peptide. The N-terminal seven amino acids of flg22 interact with LRRs 3 to 6, with the C-terminal 14 amino acids binding LRRs 7 to 16. Numerous hydrogen bonding, electrostatic and hydrophobic contacts are formed between flg22 and FLS2. Interactions between the FLS2 and BAK1-ECDs are both receptor- and flg22-mediated, but the peptide acts as a ‘molecular glue’, stabilizing the heterodimer.

In the absence of flg22, the Arabidopsis RLCK BIK1 can associate with the FLS2 and BAK1 kinase domains. Ligand perception leads to activation and phosphorylation of BIK1 by BAK1.
Following phosphorylation, BIK1 is monoubiquitinated by the E3 ligases RHA3A/B. BIK1 has an N-terminal myristoylation motif, and plasma membrane localization of BIK1 is essential for ubiquitination. Monoubiquitinated BIK1 is then released from the FLS2–BAK1 complex and initiates ROS production and Ca2+ signalling through phosphorylation of plasma membrane-localised NADPH oxidases and cyclic nucleotide gated channels (137).

Section 2: Intracellular Immunity

Intracellular immunity in plants is conferred by nucleotide-binding, leucine rich repeat receptor proteins (NLRs). NLRs perceive the presence and/or activities of host translocated effectors, leading to defences that may result in programmed cell death to limit the spread of infection (150). Prior to the molecular identification of NLR receptors and effectors, the genetic basis of what we now call intracellular immunity was established as the ‘gene-for-gene’ model. The gene-for-gene model described a requirement for plants to utilize specialized immune receptors encoded by R (resistance) genes to counteract and respond to the effectors encoded by pathogen AVR (avirulence) genes (151).

NLRs comprise multiple domains with distinct functions

NLRs belong to the AAA+ class of “signal transducing ATPases with numerous domains (STAND)” ATPases that share a conserved central nucleotide-binding domain (NBD) across plant, animal and fungal kingdoms (152). The STAND superfamily includes APAF1, the primary component of the mammalian apoptosome (153), and NLRC4 and NLRP3, which are the best characterized NLRs of the metazoan immune system (21,154-158).

Classically, plant NLRs comprise a C-terminal leucine-rich repeat (LRR) domain, a central nucleotide-binding domain known as the NB-ARC (nucleotide binding domain shared with APAF1, R gene products and CED4 (159), and a variable N-terminal module, which is typically either a TIR (Toll/interleukin-1 receptor/resistance), CC (coiled-coil) domain, or a RPW8-like CC domain (CC-RPW8) (160). Interestingly, LRR domains appear in both cell-surface and intracellular immune receptors and are widely found to be ligand recognition motifs that mediate protein-protein interactions across kingdoms of life. The LRR domain has been implicated in effector recognition for some NLRs, although it is also likely to be important for autoinhibition of the receptor (21,161,162).

The NB-ARC domain functions as a molecular switch, with effector perception relayed through this domain via nucleotide exchange (ADP for ATP) (34). The N-terminal domains are required for immunity, and divide the NLRs into three major classes: TIR-NLRs, CC-NLRs and RPW8-NLRs (22). Transient expression assays in plants have shown that the N-terminal domains can initiate cell death autonomously, and in the absence of an effector (163). Recently, some NLRs have been shown to incorporate additional non-canonical domains into their architecture (164). Known as integrated domains (IDs), these domains can directly interact with effectors (12,18,165-167). Intriguingly, many NLR-IDs share sequence/structural homology with established virulence-associated host targets of effectors, such as transcription factors or proteins important for cell homeostasis (168). Overall, the individual domains of plant NLRs function together to deliver an effective immune response against pathogen/pests.

Effector Detection: Direct and indirect perception of effectors by plant NLRs

Conceptually, how plant NLRs perceive effectors has been grouped into three overarching models: the direct recognition model (non-ID), indirect recognition model (via guardees or decoys), and the integrated domain recognition model (via integration of effectors targets as integrated domains (IDs) into the NLR architecture) (Fig. 4A; Fig. 5).

Direct recognition

The LRR domain of NLR proteins has been implicated in direct interaction with effectors, as well as having a role in autoinhibition of receptor activity. Best characterised in Flax, this plant shows a variety of resistance phenotypes towards different strains of the flax stem rust pathogen (Melampsora lini) expressing different effector alleles (169). In particular, dissection of Flax NLRs from the L resistance gene loci (encoding L5, L6, and L7 NLRs among others), and how they perceive alleles of the effector AVRL-567, revealed polymorphisms in the LRR region that
underpin specificity (161,170). Similarly, polymorphisms between the Flax NLR variants P and P2 within the LRR domain determine different Flax stem rust resistance specificities (171). Even though genetic and biochemical evidence for effector perception by LRR domains is established, to date, the structural basis of such interactions has yet to be determined.

**Indirect recognition**

NLRs can act as ‘guards’ for host proteins targeted by effectors (known as guardees (168)). Guard/guardee interactions can be divided into two models. In both models, the NLR monitors the biochemical status of the guardee (for example detecting post-translational modification or cleavage/degradation). In the Guard Model, the guardee is important for host cell function, whereas in the Decoy model, the guardee is a mimic of an effector target, but does not have a function outside of immunity.

RIN4 is a plasma membrane localized negative regulator of plant immunity (172). This protein is a classic example of an effector “hub”, a host protein that is targeted by multiple effectors from different pathogens, and as a consequence, it is guarded by multiple NLRs (46). The Arabidopsis NLRs RPM1 and RPS2 monitor the biochemical status of RIN4, detecting modifications such as phosphorylation and degradation which lead to activation of immunity (172,173).

In tomato, Pto is a protein kinase that directly interacts with the NLR Prf (174,175). Pto is a decoy that mimics the intracellular domains of cell-surface immune receptors (174,175), and acts as a trap for effectors that pathogens have delivered to interfere with receptor signalling. Pto has no known function outside of this bait activity (176). Direct interactions between effectors and Pto leads to oligomerization of Prf and immune activation (175,176).

**Integrated Domain Model**

The integrated domain model is an evolutionary innovation in plant NLRs where a domain that mimics an effector target is positioned in an NLR architecture, serving as a sensor domain by directly interacting with effectors (Fig. 4A; Fig 5). A well-studied example of NLR IDs are the heavy metal-associated (HMA) domains of rice receptor proteins Pik-1 and the Pia sensor NLR (RGA5), which directly bind effectors of the fungal pathogen *Magnaporthe oryzae* (12,165). Biochemical, structural, and in planta studies have shown how these HMA domains interact with pathogen effectors, and demonstrate how different NLR variants perceive different alleles of the effectors (12,177-179). Interestingly, a single integrated domain in an NLR can perceive multiple effectors. For example, the WRKY transcription factor-like domain of the Arabidopsis NLR RRS1 interacts with two sequence- and structurally-divergent effectors (180). One of these effectors adopts a helix-loop-helix fold with an unknown virulence function (AvrRps4; presumed to be a protein-protein interaction module) (18,181), whereas a second is an acetyltransferase (PopP2) that acetylates both WRKY transcription factors and the RRS1-WRKY (18,181). The structural basis of interaction between the RRS1-WRKY and PopP2 has been elucidated (18,181), but the equivalent structure with AvrRps4 remains to be determined. The RRS1-WRKY case demonstrates the versatility of effector perception that integrated domains deliver to NLRs and suggests their utility for receptor engineering.

**Case Study 2: Integrated HMA domains – exemplars of integrated domains in NLRs**

Many different types of proteins have been found as integrated domains (IDs) in plant NLRs, and likely function in direct perception of effectors (182-186). The integrated heavy metal-associated (HMA) domains of the sensor NLRs of the rice Pik and Pia pairs are exemplars of IDs, and serve as model systems for understanding the principles of effector perception by these domains (12,165,177,179). Fig. 5 illustrates the integration of atypical domains into NLRs to facilitate effector perception.

The integrated HMA domains of Pik-1 and the Pia sensor (also known as RGA5) are likely derived from an expanded family of small plant proteins containing an HMA domain and, sometimes, a C-terminal isoprenylation motif (heavy metal associated plant proteins (HPPs) or heavy metal-associated isoprenylated proteins (HIPPs) (187)). These proteins may have a role in abiotic stress and detoxification of heavy metals, such as copper or cadmium (187). Additionally, some of these proteins act as susceptibility factors (host targets that can be exploited to assist infection) for diverse pathogens (188-190). This suggests that HPPs/HIPPs may be effector hubs,
repeatedly targeted by pathogens as part of infection strategies (45,191). This provides an evolutionary context for their integration into NLRs as “baits” for triggering immunity (164).

In rice, integrated HMA domains can be found at the C-terminus of the sensor NLR of Pia (165), and also between the CC and NB-ARC domain of the sensor NLR Pik-1 (12). Diversity in the location of domain integration implies these were separate integration events.

The HMA domain of the Pia sensor binds two rice blast effectors, AVR-Pia and AVR1-CO39, whereas the Pik-HMA binds variants of the rice blast effector AVR-Pik (12,177-179). Interestingly, these effectors bind to the Pia- and Pik-HMA domains via different interfaces, suggesting they have independently evolved to target HMA domain containing proteins, and rice has been able to use both these interfaces to bait effectors and trigger immunity (179).

As a consequence of arms-race co-evolution with AVR-Pik effector variants (177,192,193), the HMA domain is the most variable domain region of the Pik NLRs (194), and the rice Pik receptors also exist as an allelic series with differential recognition specificity for effector variants (192). Biochemical and structural studies of the interaction between different AVR-Pik variants and two allelic HMA domains revealed how subtle changes in the effector/HMA binding interface underpin variation in recognition specificity (177). Recently, the observation that subtle changes underpin specificity has been used in a proof-of-concept study to show that NLR IDs can be engineered to expand their recognition capacity to allelic effectors (195).

**NLR activation**

A general principle of NLR biology is that perception of effectors leads to conformational changes in the receptor. These changes can include domain rearrangements and oligomerization. While the details depend on the mode of effector perception, nucleotide exchange (ADP for ATP) in the NB-ARC domain of NLRs is a factor for activation. Numerous studies have shown the importance of conserved sequences such as the “P-loop” and “MHD-like” motifs in nucleotide-binding/exchange and NLR activation (196,197).

Conformational change and/or oligomerization of NLRs perturb the N-terminal CC or TIR domains to initiate immune responses. While recent studies have begun to shed light on the molecular basis of how these domains trigger immunity, whether these reflect general principles applicable for all NLRs remains to be determined. For example, for CC domains, the structure of the Arabidopsis NLR ZAR1 revealed a mechanism whereby oligomerization results in a “funnel” of the N-terminal helices, which then associate with membranes and may perturb cellular integrity (15,16) (Fig. 6). A sequence motif within the N-terminal helix of some NLR CC domains has been associated with ZAR1-like cell death immunity; known as the MADA motif (198). This suggests a subset of NLRs may function in a manner similar to ZAR1. However, how CC-NLRs that do not contain this motif function to initiate immunity has yet to be determined.

Many TIR domain structures from plant NLRs have been determined (17,199-202), and revealed multiple mechanisms of self-association to form scaffolds for protein-protein interactions that may be important for immune activation (203). Recently, the TIR domains of several NLRs have been shown to catalyse the hydrolysis of NAD+, suggesting a new mechanism for TIR-NLR activity (201,204). How NAD+ hydrolysis functions in plant immunity is currently unknown. Recently, the structure of the N. benthamiana TIR-NLR Roq1 was determined, marking the first structure of a TIR-NLR resistosome (205). The Roq1 structure provides insight into the novel recognition of its cognate effector, XopQ, through interaction with a unique integrated-like domain deemed the Post-LRR (PL) domain. Furthermore, it verifies the importance of specific TIR-domain self-association interfaces, alluding to self-association resulting in the opening of the TIR domain active site for NAD+ binding and hydrolysis.

**NLRs function as singletons, pairs and networks**

To compensate for the lack of an adaptive immune system, plants have a diverse NLR repertoire, which has enabled functional specialization. This has resulted in the evolution of NLRs that function as singletons, in pairs, and as parts of interconnected networks (206-208) (Fig. 4B).
To date, several NLRs have been identified that appear to function autonomously, both sensing the presence of pathogens/pests, and mounting a response. These are referred to as NLR singletons. Examples include NLRs of the Mildew resistance locus A (MLA) in Barley, Arabidopsis TIR-NLR RPP4 and CC-NLR RPS2 (173,209).

By contrast, other NLRs have specialized functions and can be broadly divided into two groups, sensors and helpers, and are generally referred to as NLR pairs (208). In these pairs, sensor NLRs perceive effectors, via the mechanisms discussed above, and helper NLRs are involved in converting effector perception into immune activation (168). NLR pairs can be genetically linked, often encoded at the same locus under the control of the same promoter. They are also always of the same class (CC-NLR or TIR-NLR). The best characterized genetically linked sensor/helper paired NLRs are the Arabidopsis pair RRS1/RPS4, the rice pair Pik, and the rice pair Pia (a.k.a RGA5/RGA4). Intriguingly, each of the sensor NLRs of these pairs contains an integrated domain. General mechanisms for how paired NLRs function are based on models of suppression or receptor cooperation (210). The Pia and RRS1/RPS4 NLR pairs can be transiently expressed in tobacco leaves without clear cell death phenotypes. However, cell death phenotypes can be observed in tobacco leaves when RPS4 or the Pia helper NLRs are expressed without their cognate sensors or effectors. Co-expression of the RRS1 or Pia sensor NLRs suppresses the autoactive cell death phenotype of the helpers (211). Co-expression of the paired NLRs with their cognate effectors relieves this suppression, resulting in cell death. By contrast, expression of the Pik-2 helper NLR does not result in cell death, and co-expression of the Pik-1 sensor NLR and the cognate effector is required for cooperative cell death (12,212).

However, a direct genetic link (head-to-head orientation or belonging to the same genetic loci) is not essential for NLR cooperation in immune activation, and some require complex NLR networks for function. The NLR ‘N-requirement gene 1’ (NRG1), is required for the resistance to tobacco mosaic virus (TMV) provided by the TIR-NLR, N (213). NRG1 is a member of the Activated disease resistance 1 (ADR1) family of RPW8-NLRs, and since the discovery of NRG1, the RPW8-NLRs have been found to be important for the full function of many other CC-NLRs and TIR-NLRs (214,215). Another NLR network has recently been uncovered in Solanaceous plants. The NRCs (NLR required for cell death) are a phylogenetically distinct class of helper CC-NLRs consisting of functionally redundant paralogs (216). Sensor NLRs that require NRCs provide resistance to diverse pathogens and pests including bacteria, oomycetes, nematodes, viruses and insects (216). They display distinct specificities for different NRC helpers, with some sensors signalling through only one, and others showing functional redundancy. Diversification of NLRs in the NRC network has allowed a varied arsenal of NLRs against a broad range of pathogens to have evolved.

Intriguingly, a new body of work has emerged which has begun to uncover interplay between cell-surface and intracellular immunity (29,30). These papers demonstrate cell surface immunity is required to potentiate intracellular immunity, enhancing NLR responses such as cell death. By contrast, NLR activity was shown to be important for cell-surface immunity receptor turnover, relieving attenuation of PRR signalling, and replenishing signalling components at the cell-surface. These new findings open the door to further studies analysing cross-network communications between cell-surface and intracellular immunity.

**Case Study 3: The Structure of ZAR1 – the first plant resistosome**

Recently, cryo-EM structures of ZAR1 were solved in inactive and active states. These are the first structures of full-length plant NLRs to be determined, and represent a major advance in our understanding of NLR biology (15,16). In the inactive state, the LRR domain in the ZAR1:RKS1 receptor complex makes autoinhibitory contacts with both the NB-ARC and CC domains, and a molecule of ADP is bound within the NB-ARC domain. PBL2 binding to RKS1 induces a disorder-to-order transition of the RKS1 activation loop, and a steric clash with the NB-ARC of ZAR1, which becomes displaced. This conformational change results in nucleotide exchange from bound ADP to ATP, and stabilization of a structure primed for oligomerization with other activated RKS1:ZAR1 heterocomplexes. The pentamer that results from the oligomerization events is known as the “Resistosome”. The conformational changes and oligomerization associated with
PBL2(mutex) binding promote unfolding of the ZAR1 CC domain, releasing the N-terminal helix (H1), from a four-helical bundle. The released H1 helix then associates with the H1 helices of neighbouring activated ZAR1 molecules, resulting in the formation of a funnel-like structure with a striking hydrophobic surface. There is evidence that the ZAR1 CC domain funnel is required for membrane association, and that this membrane association is linked to induction of cell death, potentially through ion efflux or membrane perturbation (15,16,217).

As this review was being finalised, the structure of the Roq1 TIR-NLR from *N. benthamiana* was determined by cryo-EM (205). This structure provides a significant advance in our understanding of plant NLR immunity as it represents the first structure of a TIR-NLR resistosome, and as such, should be considered alongside this ZAR1 case study.

**Next steps in understanding intracellular immunity**

Despite recent advances, key questions on NLR function remain to be addressed. The ZAR1 and Roq1 structures have provided a wealth of information that has significantly expanded our understanding of plant NLR biology. However, it is as-yet unclear how oligomerization of CC-NLRs into a resistosome mediates cell death. Furthermore, we lack structural information and evidence of resistosome formation for RPW8-NLRs. Even more perplexing is the role of TIR domains NADase activity, and how it leads to the activation of RPW8-NLRs. Even more perplexing is the role of TIR domains NADase activity, and how it leads to the activation of RPW8-NLRs. Where we are beginning to generate a picture of the complex interactions between NLRs in plants, it is still unclear how one of the most primary interactions, effector detection, is mechanistically relayed from sensor NLRs to helper NLRs in pairs and networks. Each of these areas, among many others, require further research to fully understand how NLRs provide resistance to pathogens/pests.

**Section 3: Engineering plant immunity**

Since their discovery, cell-surface and intracellular immune receptors have been targets of biotechnological approaches to improve disease resistance in plants. These approaches have included different scales, from transferring genes encoding plant receptors between species to specific amino acid mutations to modulate effector binding or receptor activity (38,218). Engineering requires a holistic view, incorporating a range of methods to deliver both broad and robust resistance. Broad low-level resistance is regularly found in nature, however due to monoculture reducing natural diversity, bespoke resistance to specific pathogens is often more desirable. While the GMO debate remains a focus of public discussion and governmental policy decisions, engineering and editing crop genomes offers potential solutions to food insecurity.

**Engineering resistance by transferring genes**

The transfer of traits conferring pathogen resistance is conceptually the most straightforward strategy to engineer disease immunity in plants. This method is used in classical plant breeding by selecting resistant phenotypes and crossing into desired cultivars. However, this approach is time-consuming and technically challenging (219). The recent development of new sequencing, phenotyping and plant growth technologies has allowed to overcome the limitations of this process (220-223).

As plant cell-surface immune receptors tend to perceive common signatures of pathogens/pests, and activate conserved signalling pathways in plants, they offer opportunities to transfer resistance between plant species. For example, the Arabidopsis EFR receptor is restricted to Brassicaceae species in nature, but delivered novel resistance specificity against bacterial pathogens when it was transferred to tomato and rice (224-226). Similarly, transfer of the rice cell-surface receptor Xa21 to Banana, Sweet orange, or tomato, increased resistance to *Xanthomonas* sp. (227-229). Further, an allelic FLS2 receptor from wild grape has been demonstrated to confer resistance to the crown-gall pathogen *Agrobacterium tumefaciens* when expressed in tobacco (230).

Building on these advances, mining the diversity of cell-surface immune receptors with expanded recognition specificities from diverse plant species, and their subsequent transfer to other plants, holds promise for engineering broad spectrum disease resistance (224,231,232).
Recent advances in mining the genomes of wild plant species using new genomics technologies (222,233-236) has allowed the rapid identification of candidate immune receptors for deployment in crops. Using such approaches, resistance to Asian soybean rust in Soybean has been established by transferring an NLR from Pigeon pea (237). Further, resistance has been shown against the potato late blight pathogen by introducing resistance genes from wild potato species (238,239).

Plant intracellular NLR receptors are highly diverse (240-242) and often work together with other NLRs in pairs or networks. Therefore, NLRs frequently require a specific genetic background to provide effective disease resistance. As a consequence, the functional transfer of NLR receptors between species, or even cultivars of the same species, has proven challenging (243,244).

**Bespoke engineering of NLR responses**

Based on recent advances in our understanding of the mechanisms of NLR function, a number of new approaches are being explored to enable more effective engineering of NLRs to help deliver disease resistance in target plants.

**Domain exchange and mutagenesis**

Domain exchange approaches between related NLRs have been explored for their potential to engineer disease resistance (245). Domain exchanges between the potato NLRs Rx and Gpa enabled the partial exchange of immune recognition from viruses to nematodes and vice-versa (245). Auto-active and loss-of-function phenotypes were also observed in the chimeras and suggested that more subtle variations may have more potential.

High-throughput random mutagenesis of NLRs has been used to explore whether these receptors can be improved by enhancing their activation sensitivity or by expanding their recognition specificity. Following such approaches allowed expanded recognition of viruses by the NLR Rx (246,247). This has been also applied to identify mutations that expanded the response of the potato NLR R3a, and its tomato ortholog I-2 (248), to effectors from Phytophthora species (249). However, the translation of these expanded recognition phenotypes to disease resistance has remained limited (246-249). Recently, improved knowledge of how effectors, or effector activities, are directly perceived has inspired new methods of engineering.

**Decoy engineering**

Understanding how NLRs that guard host targets are activated can allow engineering of recognition specificity. The Arabidopsis NLR RPS5 perceives cleavage of the decoy kinase PBS1 by the *P. syringae* effector AvrPphB at a specific recognition sequence (250). Mutation of the recognition site in PBS1 to cleavage sequences recognised by other translocated pathogen proteases, including a second *Pseudomonas syringae* effector, AvrRpt2, and the Nla protease from tobacco etch virus, switched the RPS5 recognition specificity (251). It is of special note that the latter switched RPS5 perception from bacteria to viruses. Although this approach is limited to pathogens that translocate proteases into the host, the widespread conservation of this protease recognition systems in crop plants (252,253) has recently allowed engineering of disease resistance in soybean (250).

**Integrated domains: new possibilities to engineer disease resistance**

The discovery of integrated domains in plant NLRs opened new opportunities to understand and manipulate mechanisms of pathogen perception by intracellular immune receptors (164,211,254,255) (Fig. 6). These domains have become a promising avenue for engineering disease resistance conferred by NLRs (195,254,255). As previously introduced, the allelic rice NLRs Pik perceive variants of the rice blast pathogen effector AVR-Pik by direct binding via an HMA domain (12,177). Some natural effector variants are able to escape recognition by certain Pik NLR alleles, while other variants completely evade detection (177,192,256). Further, the binding of AVR-Pik effectors to the HMA is not in itself sufficient to activate immune signalling, and a threshold of binding needs to be reached to trigger immune responses (177) (Fig. 7A). An understanding of the biochemical and structural basis of different AVR-Pik/HMA interactions (177) has allowed design of specific mutations that increase the binding affinity to effector alleles, expanding the recognition capability of the Pikp NLR (195) (Fig. 7B). This proof-of-concept demonstrated that NLR binding to effectors, and the subsequent responses, can be manipulated by rational design. Additional HMA domain engineering could now focus on extending perception of sequence-
divergent rice blast effectors that also interact with HMAs, but at a different interface (178,179,257).

Looking to the future, combining mutations in NLRs to both sensitize and lower the threshold to trigger immune responses, as discussed above (Fig. 7C), and directly increase binding affinity to effectors (Fig. 7D), is an exciting long-term goal for the field.

**Other approaches: controlled expression of auto-active NLRs**

A further possibility for engineering disease resistance is to manipulate expression of NLRs. For example, the discovery of a mechanism controlling defence responses at transcriptional and translational level allowed the design of a pathogen-responsive expression cassette (258). Placing an autoactive NLR under control of this cassette generated an NLR-mediated plant defence system that does not rely on effector recognition. This conferred broad-spectrum resistance without a fitness cost (259), a defence-yield trade-off that can occur when engineering immunity (260).

**Concluding Statement**

Plant disease has shaped the natural and agricultural world. Crop losses due to disease, and the emergence of resistant cultivars, have been key events that have facilitated the way we breed and farm our food. Consequently, an understanding of the plant immune system is essential, as we attempt to develop new methods for disease control against a background of the climate emergency. Despite extensive studies, which we have reviewed here, further research is required to fully understand how the plant system works holistically to deliver disease resistance. Of the hundreds of cell-surface RLKs and RLPs identified, many of the biological functions and ligands of these receptors remain unknown. Furthermore, it is important to understand how plants distinguish between the MAMPs of pathogens/pests from the MAMPs of the beneficial mutualist microbes. Determining the function of more of these cell-surface receptors will lead to new avenues for engineering resistance in crops. Similarly, advances in understanding NLR biology will help to better arm plants against pathogens and pests that evolve to circumvent cell-surface immunity. As we generate a better understanding of the complex interactions between plants and pathogens and pests, we can assemble the pieces to inform engineering of disease resistance, to produce more durable crops and help battle the food security problems of the future.
Acknowledgements

Research in the Banfield Lab is supported by UKRI BBSRC, UK [grants BB/P012574, BB/M02198X]; the European Research Council [ERC; proposals 743165, 669926]; the John Innes Foundation; the UKRI Biotechnology and Biological Sciences Research Council (BBSRC) Norwich Research Park Biosciences Doctoral Training Partnership, UK [grant BB/M011216/1]. We thank Ruby O’Grady for the artwork and design inspiration for Fig. 1. The authors declare that they have no conflicts of interest with the contents of this article.

References

1. Savary, S., Willocquet, L., Pethybridge, S. J., Esker, P., McRoberts, N., and Nelson, A. (2019) The global burden of pathogens and pests on major food crops. *Nature Ecology & Evolution* 3, 430-439
2. Bebber, D. P., and Gurr, S. J. (2015) Crop-destroying fungal and oomycete pathogens challenge food security. *Fungal Genetics and Biology* 74, 62-64
3. Fisher, M. C., Henk, D. A., Briggs, C. J., Brownstein, J. S., Madoff, L. C., McCraw, S. L., and Gurr, S. J. (2012) Emerging fungal threats to animal, plant and ecosystem health. *Nature* 484, 186-194
4. TURNER, R. S. (2005) After the famine: Plant pathology, Phytophthora infestans, and the late blight of potatoes, 1845—1960. *Historical Studies in the Physical and Biological Sciences* 35, 341-370
5. Dean, R., Van Kan, J. A., Pretorius, Z. A., Hammond-Kosack, K. E., Di Pietro, A., Spanu, P. D., Rudd, J. J., Dickman, M., Kahmann, R., Ellis, J., and Foster, G. D. (2012) The Top 10 fungal pathogens in molecular plant pathology. *Mol Plant Pathol* 13, 414-430
6. Kamoun, S., Furzer, O., Jones, J. D., Judelson, H. S., Ali, G. S., Dalio, R. J., Roy, S. G., Schena, L., Zambounis, A., Panabieres, F., Cahill, D., Ruocco, M., Figueiredo, A., Chen, X. R., Hulvey, J., Stam, R., Lamour, K., Gijsen, M., Tyler, B. M., Grunwald, N. J., Mukhtar, M. S., Tome, D. F., Tor, M., Van Den Ackerveken, G., McDowell, J., Daayf, F., Fry, W. E., Lindqvist-Kreuzer, H., Meijer, H. J., Petre, B., Ristaino, J., Yoshida, K., Birch, P. R., and Govers, F. (2015) The Top 10 oomycete pathogens in molecular plant pathology. *Mol Plant Pathol* 16, 413-434
7. Mansfield, J., Genin, S., Magori, S., Citovsky, V., Siriariyanum, M., Ronald, P., Dow, M., Verdier, V., Beer, S. V., Machado, M. A., Toth, I., Salmond, G., and Foster, G. D. (2012) Top 10 plant pathogenic bacteria in molecular plant pathology. *Mol Plant Pathol* 13, 614-629
8. Scholthof, K. B., Adkins, S., Czosnek, H., Palukaitis, P., Jacquot, E., Hohn, T., Hohn, B., Saunders, K., Candresse, T., Ahlquist, P., Hemenway, C., and Foster, G. D. (2011) Top 10 plant viruses in molecular plant pathology. *Mol Plant Pathol* 12, 938-954
9. Savary, S., Willocquet, L., Pethybridge, S. J., Esker, P., McRoberts, N., and Nelson, A. (2019) The global burden of pathogens and pests on major food crops. *Nat Ecol Evol* 3, 430-439
10. van Esse, H. P., Reuber, T. L., and van der Does, D. (2020) Genetic modification to improve disease resistance in crops. *New Phytol* 225, 70-86
11. Liu, T., Liu, Z., Song, C., Hu, Y., Han, Z., She, J., Fan, F., Wang, J., Jin, C., Chang, J., Zhou, J.-M., and Chai, J. (2012) Chitin-Induced Dimerization Activates a Plant Immune Receptor. *Science* 336, 1160
12. Maqbool, A., Saitoh, H., Franceschetti, M., Stevenson, C. E. M., Uemura, A., Kanzaki, H., Kamoun, S., Terauchi, R., and Banfield, M. J. (2015) Structural basis of
pathogen recognition by an integrated HMA domain in a plant NLR immune receptor. *Elife* **4**, e08709

13. Sun, Y., Li, L., Macho, A. P., Han, Z., Hu, Z., Zipfel, C., Zhou, J.-M., and Chai, J. (2013) Structural Basis for flg22-Induced Activation of the *Arabidopsis* FLS2-BAK1 Immune Complex. *Science* **342**, 624

14. Tang, J., Han, Z., Sun, Y., Zhang, H., Gong, X., and Chai, J. (2015) Structural basis for recognition of an endogenous peptide by the plant receptor kinase PEPR1. *Cell Res* **25**, 110-120

15. Wang, J., Hu, M., Wang, J., Qi, J., Han, Z., Wang, G., Qi, Y., Wang, H.-W., Zhou, J.-M., and Chai, J. (2019) Reconstitution and structure of a plant NLR resistosome conferring immunity. *Science* **364**, eaav5870

16. Wang, J., Wang, J., Hu, M., Wu, S., Qi, J., Wang, G., Han, Z., Qi, Y., Gao, N., Wang, H.-W., Zhou, J.-M., and Chai, J. (2019) Ligand-triggered allosteric ADP release primes a plant NLR complex. *Science* **364**, eaav5868

17. Williams, S. J., Sohn, K. H., Wan, L., Bernoux, M., Sarris, P. F., Segonzac, C., Ve, T., Ma, Y., Sauzet, S. B., Ericsson, D. J., Casey, L. W., Lonhienne, T., Winzor, D. J., Zhang, X., Coerdt, A., Parker, J. E., Dodds, P. N., Kobe, B., and Jones, J. D. (2014) Structural basis for assembly and function of a heterodimeric plant immune receptor. *Science* **344**, 299-303

18. Zhang, Z.-M., Ma, K.-W., Gao, L., Hu, Z., Schwizer, S., Ma, W., and Song, J. (2017) Mechanism of host substrate acetylation by a YopJ family effector. *Nature Plants* **3**, 17115

19. Hao, W., Collier, S. M., Moffett, P., and Chai, J. (2013) Structural basis for the interaction between the potato virus X resistance protein (Rx) and its cofactor Ran GTPase-activating protein 2 (RanGAP2). *J Biol Chem* **288**, 35868-35876

20. Hohmann, U., and Hothorn, M. (2019) Crystal structure of the leucine-rich repeat ectodomain of the plant immune receptor kinase SOBIR1. *Acta Crystallogr D Struct Biol* **75**, 488-497

21. Bentham, A., Burdett, H., Anderson, P. A., Williams, S. J., and Kobe, B. (2016) Animal NLRs provide structural insights into plant NLR function. *Annals of Botany* **119**, 698-702

22. Jones, J. D. G., Vance, R. E., and Dangl, J. L. (2016) Intracellular innate immune surveillance devices in plants and animals. *Science* **354**, aaf6395

23. Meunier, E., and Broz, P. (2017) Evolutionary Convergence and Divergence in NLR Function and Structure. *Trends Immunol* **38**, 744-757

24. Wang, W., Feng, B., Zhou, J.-M., and Tang, D. (2020) Plant immune signaling: Advancing on two frontiers. *Journal of Integrative Plant Biology* **62**, 2-24

25. Kanyuka, K., and Rudd, J. J. (2019) Cell surface immune receptors: the guardians of the plant’s extracellular spaces. *Current Opinion in Plant Biology* **50**, 1-8

26. van Wersch, S., Tian, L., Hoy, R., and Li, X. (2020) Plant NLRs: The Whistleblowers of Plant Immunity. *Plant Communications* **1**, 100016

27. Snelders, N. C., Rovenich, H., Petti, G. C., Rocafort, M., Vorholt, J. A., Mesters, J. R., Seidl, M. F., Nijland, R., and Thomma, B. P. H. J. (2020) A plant pathogen utilizes effector proteins for microbiome manipulation. *bioRxiv*, 2020.2001.2030.926725

28. Varden, F. A., De la Concepcion, J. C., Maidment, J. H. R., and Banfield, M. J. (2017) Taking the stage: effectors in the spotlight. *Current Opinion in Plant Biology* **38**, 25-33
29. Ngou, B. P. M., Ahn, H.-K., Ding, P., and Jones, J. D. (2020) Mutual Potentiation of Plant Immunity by Cell-surface and Intracellular Receptors. bioRxiv, 2020.2004.2010.034173
30. Yuan, M., Jiang, Z., Bi, G., Nomura, K., Liu, M., He, S. Y., Zhou, J.-M., and Xin, X.-F. (2020) Pattern-recognition receptors are required for NLR-mediated plant immunity. bioRxiv, 2020.2004.2010.031294
31. Jones, J. D. G., and Dangl, J. L. (2006) The plant immune system. Nature 444, 323-329
32. Chisholm, S. T., Coaker, G., Day, B., and Staskawicz, B. J. (2006) Host-microbe interactions: Shaping the evolution of the plant immune response. Cell 124, 803-814
33. Takken, F. L. W., Albrecht, M., and Tameling, W. I. L. (2006) Resistance proteins: molecular switches of plant defence. Current Opinion in Plant Biology 9, 383-390
34. Takken, F. L. W., and Goverse, A. (2012) How to build a pathogen detector: structural basis of NB-LRR function. Current Opinion in Plant Biology 15, 375-384
35. Wirthmueller, L., Maqbool, A., and Banfield, M. J. (2013) On the front line: structural insights into plant-pathogen interactions. Nat. Rev. Microbiol. 11, 761-776
36. Schellenberger, R., Touchard, M., Clément, C., Baillieu, F., Cordelier, S., Crouzet, J., and Dorey, S. (2019) Apoplastic invasion patterns triggering plant immunity: plasma membrane sensing at the frontline. Molecular Plant Pathology 20, 1602-1616
37. Kourelas, I., and van der Hoorn, R. A. L. (2018) Defended to the Nines: 25 Years of Resistance Gene Cloning Identifies Nine Mechanisms for R Protein Function. Plant Cell 30, 285-299
38. Tamborski, J., and Krasileva, K. V. (2020) Evolution of Plant NLRs: From Natural History to Precise Modifications. Annu Rev Plant Biol
39. Hogenhout, S. A., Van der Hoorn, R. A. L., Terauchi, R., and Kamoun, S. (2009) Emerging concepts in effector biology of plant-associated organisms. Molecular Plant-Microbe Interactions 22, 115-122
40. Dong, S., Raffaele, S., and Kamoun, S. (2015) The two-speed genomes of filamentous pathogens: waltz with plants. Curr Opin Genet Dev 35, 57-65
41. Raffaele, S., Farrer, R. A., Cano, L. M., Studholme, D. J., MacLean, D., Thines, M., Jiang, R. H., Zody, M. C., Kunjeti, S. G., Donofrio, N. M., Meyers, B. C., Nusbaum, C., and Kamoun, S. (2010) Genome evolution following host jumps in the Irish potato famine pathogen lineage. Science 330, 1540-1543
42. Allen, R. L., Bittner-Eddy, P. D., Grenville-Briggs, L. J., Meitz, J. C., Rehmany, A. P., Rose, L. E., and Beynon, J. L. (2004) Host-Parasite Coevolutionary Conflict Between <em>Arabidopsis</em></a> and Downy Mildew. Science 306, 1957-1960
43. Sperschneider, J. Machine learning in plant–pathogen interactions: empowering biological predictions from field scale to genome scale. New Phytologist n/a
44. Franceschetti, M., Maqbool, A., Jimenez-Dalmaroni, M. J., Pennington, H. G., Kamoun, S., and Banfield, M. J. (2017) Effectors of Filamentous Plant Pathogens: Commonalities amid Diversity. Microbiol Mol Biol Rev 81
45. Wølfling, R., Epple, P., Altman, S., He, Y., Yang, L., Henz, Stefan R., McDonald, N., Wiley, K., Bader, Kai C., Glässer, C., Mukhtar, M. S., Haigis, S., Ghamsari, L., Stephens, Amber E., Ecker, Joseph R., Vidal, M., Jones, Jonathan D. G., Mayer, Klaus F. X., Ver Loren van Themaat, E., Weigel, D., Schulze-Lefert, P., Dangl, Jeffery L., Panstruga, R., and Braun, P. (2014) Convergent Targeting of a Common Host Protein-Network by Pathogen Effectors from Three Kingdoms of Life. Cell Host & Microbe 16, 364-375
46. Mukhtar, M. S., Carvunis, A. R., Dreze, M., Epple, P., Steinbrenner, J., Moore, J., Tasan, M., Galli, M., Hao, T., Nishimura, M. T., Pevzner, S. J., Donovan, S. E.,
Ghamsari, L., Santhanam, B., Romero, V., Poulin, M. M., Gebreab, F., Gutierrez, B. J., Tam, S., Monachello, D., Boxem, M., Harbort, C. J., McDonald, N., Gai, L., Chen, H., He, Y., Vandenhaute, J., Roth, F. P., Hill, D. E., Ecker, J. R., Vidal, M., Beynon, J., Braun, P., and Dangl, J. L. (2011) Independently evolved virulence effectors converge onto hubs in a plant immune system network. *Science* **333**, 596-601

47. Sanabria, N., Goring, D., Nürnberger, T., and Dubery, I. (2008) Self/nonself perception and recognition mechanisms in plants: a comparison of self-incompatibility and innate immunity. *New Phytologist* **178**, 503-514

48. Antolín-Llovera, M., Petutsching, E. K., Ried, M. K., Lipka, V., Nürnberger, T., Robatzek, S., and Parniske, M. (2014) Knowing your friends and foes – plant receptor-like kinases as initiators of symbiosis or defence. *New Phytologist* **204**, 791-802

49. Jamieson, P. A., Shan, L., and He, P. (2018) Plant cell surface molecular cypher: Receptor-like proteins and their roles in immunity and development. *Plant Sci* **274**, 242-251

50. Boller, T., and Felix, G. (2009) A Renaissance of Elicitors: Perception of Microbe-Associated Molecular Patterns and Danger Signals by Pattern-Recognition Receptors. *Annual Review of Plant Biology* **60**, 379-406

51. Saijo, Y., Loo, E. P.-i., and Yasuda, S. (2018) Pattern recognition receptors and signaling in plant–microbe interactions. *The Plant Journal* **93**, 592-613

52. Böhm, H., Albert, I., Fan, L., Reinhard, A., and Nürnberger, T. (2014) Immune receptor complexes at the plant cell surface. *Current Opinion in Plant Biology* **20**, 47-54

53. Macho, Alberto P., and Zipfel, C. (2014) Plant PRRs and the Activation of Innate Immune Signaling. *Molecular Cell* **54**, 263-272

54. Dodds, P. N., and Rathjen, J. P. (2010) Plant immunity: towards an integrated view of plant–pathogen interactions. *Nature Reviews Genetics* **11**, 539-548

55. Boutrot, F., and Zipfel, C. (2017) Function, Discovery, and Exploitation of Plant Pattern Recognition Receptors for Broad-Spectrum Disease Resistance. *Annual Review of Phytopathology* **55**, 257-286

56. Lamb, C., and Dixon, R. A. (1997) THE OXIDATIVE BURST IN PLANT DISEASE RESISTANCE. *Annual Review of Plant Physiology and Plant Molecular Biology* **48**, 251-275

57. Balint-Kurti, P. (2019) The plant hypersensitive response: concepts, control and consequences. *Mol Plant Pathol* **20**, 1163-1178

58. Greenberg, J. T. (1997) PROGRAMMED CELL DEATH IN PLANT-PATHOGEN INTERACTIONS. *Annu Rev Plant Physiol Plant Mol Biol* **48**, 525-545

59. Zipfel, C., and Oldroyd, G. E. (2017) Plant signalling in symbiosis and immunity. *Nature* **543**, 328-336

60. Wang, J., and Chai, J. (2020) Structural Insights into the Plant Immune Receptors PRRs and NLRs. *Plant Physiology* **182**, 1566

61. Dardick, C., Schwessinger, B., and Ronald, P. (2012) Non-arginine-aspartate (non-RD) kinases are associated with innate immune receptors that recognize conserved microbial signatures. *Current Opinion in Plant Biology* **15**, 358-366

62. Ma, X., Xu, G., He, P., and Shan, L. (2016) SERKIng Coreceptors for Receptors. *Trends in Plant Science* **21**, 1017-1033

63. Gao, X., Ruan, X., Sun, Y., Wang, X., and Feng, B. (2019) BAKing up to Survive a Battle: Functional Dynamics of BAK1 in Plant Programmed Cell Death. *Frontiers in Plant Science* **9**, 1913
64. Burkart, R. C., and Stahl, Y. (2017) Dynamic complexity: plant receptor complexes at the plasma membrane. *Current Opinion in Plant Biology* **40**, 15-21

65. Wu, Y., and Zhou, J.-M. (2013) Receptor-Like Kinases in Plant Innate Immunity. *Journal of Integrative Plant Biology* **55**, 1271-1286

66. Zipfel, C. (2014) Plant pattern-recognition receptors. *Trends in Immunology* **35**, 345-351

67. Kunze, G., Zipfel, C., Robatzek, S., Niehaus, K., Boller, T., and Felix, G. (2004) The N Terminus of Bacterial Elongation Factor Tu Elicits Innate Immunity in Arabidopsis Plants. *The Plant Cell* **16**, 3496

68. Chinchilla, D., Zipfel, C., Robatzek, S., Kemmerling, B., Nürnberger, T., Jones, J. D. G., Felix, G., and Boller, T. (2007) A flagellin-induced complex of the receptor FLS2 and BAK1 initiates plant defence. *Nature* **448**, 497-500

69. Miya, A., Albert, P., Shinya, T., Ichimura, K., Shirasu, K., Narusaka, Y., Kawakami, N., Kaku, H., and Shibuya, N. (2007) CERK1, a LysM receptor kinase, is essential for chitin elicitor signaling in *Arabidopsis*. *Proceedings of the National Academy of Sciences* **104**, 19613

70. Cao, Y., Liang, Y., Tanaka, K., Nguyen, C. T., Jedrzejczak, R. P., Joachimiak, A., and Stacey, G. (2014) The kinase LYK5 is a major chitin receptor in Arabidopsis and forms a chitin-induced complex with related kinase CERK1. *Elife* **3**, e03766

71. Zipfel, C., Kunze, G., Chinchilla, D., Caniard, A., Jones, J. D. G., Boller, T., and Felix, G. (2006) Perception of the Bacterial PAMP EF-Tu by the Receptor EFR Restricts *Agrobacterium*-Mediated Transformation. *Cell* **125**, 749-760

72. Albert, M. (2013) Peptides as triggers of plant defence. *Journal of Experimental Botany* **64**, 5269-5279

73. Mott, G. A., Middleton, M. A., Desveaux, D., and Guttmann, D. S. (2014) Peptides and small molecules of the plant-pathogen apoplastic arena. *Frontiers in plant science* **5**, 677-677

74. Smakowska-Luzan, E., Mott, G. A., Parys, K., Stegmann, M., Howton, T. C., Layeghfard, M., Neuhold, J., Lehner, A., Kong, J., Grünwald, K., Weinberger, N., Satbhai, S. B., Mayer, D., Busch, W., Madalinski, M., Stolt-Bergner, P., Provartrt, N. J., Mukhtar, M. S., Zipfel, C., Desveaux, D., Guttmann, D. S., and Belkhadir, Y. (2018) An extracellular network of Arabidopsis leucine-rich repeat receptor kinases. *Nature* **553**, 342-346

75. Pruitt, R. N., Schwessinger, B., Joe, A., Thomas, N., Liu, F., Albert, M., Robinson, M. R., Chan, L. J. G., Luu, D. D., Chen, H., Bahar, O., Daudi, A., De Vleesschauwer, D., Caddell, D., Zhang, W., Zhao, X., Li, X., Heazlewood, J. L., Ruan, D., Majumder, D., Chern, M., Kalbacher, H., Midha, S., Patil, P. B., Sonti, R. V., Petzold, C. J., Liu, C. C., Brodbelt, J. S., Felix, G., and Ronald, P. C. (2015) The rice immune receptor XA21 recognizes a tyrosine-sulfated protein from a Gram-negative bacterium. *Sci Adv* **1**, e1500245-e1500245

76. Felix, G., and Boller, T. (2003) Molecular Sensing of Bacteria in Plants: THE HIGHLY CONSERVED RNA-BINDING MOTIF RNP-1 OF BACTERIAL COLD SHOCK PROTEINS IS RECOGNIZED AS AN ELICITOR SIGNAL IN TOBACCO. *Journal of Biological Chemistry* **278**, 6201-6208

77. Wang, L., Albert, M., Einig, E., Fürst, U., Krust, D., and Felix, G. (2016) The pattern-recognition receptor CORE of Solanaceae detects bacterial cold-shock protein. *Nature Plants* **2**, 16185

78. Wei, Y., Caceres-Moreno, C., Jimenez-Gongora, T., Wang, K., Sang, Y., Lozano-Duran, R., and Macho, A. P. (2018) The Ralstonia solanacearum csp22 peptide, but
not flagellin-derived peptides, is perceived by plants from the Solanaceae family. Plant Biotechnology Journal 16, 1349-1362

79. Albert, I., Böhm, H., Albert, M., Feiler, C. E., Imkampe, J., Wallmeroth, N., Brancato, C., Raaymakers, T. M., Oome, S., Zhang, H., Krol, E., Grefen, C., Gust, A. A., Chai, J., Hedrich, R., Van den Ackerveken, G., and Nürnberger, T. (2015) An RLP23–SOBIR1–BAK1 complex mediates NLP-triggered immunity. Nature Plants 1, 15140

80. Haruta, M., Sabat, G., Stecker, K., Minkoff, B. B., and Sussman, M. R. (2014) A peptide hormone and its receptor protein kinase regulate plant cell expansion. Science (New York, N.Y.) 343, 408-411

81. Xiao, Y., Stegmann, M., Han, Z., DeFalco, T. A., Parys, K., Xu, L., Belkhadir, Y., Zipfel, C., and Chai, J. (2019) Mechanisms of RALF peptide perception by a heterotypic receptor complex. Nature 572, 270-274

82. Thynne, E., Saur, I. M. L., Simbaqueba, J., Ogilvie, H. A., Gonzalez-Cendales, Y., Mead, O., Taranto, A., Catanzariti, A.-M., McDonald, M. C., Schwessinger, B., Jones, D. A., Rathjen, J. P., and Solomon, P. S. (2017) Fungal phytopathogens encode functional homologues of plant rapid alkalization factor (RALF) peptides. Molecular Plant Pathology 18, 811-824

83. Krol, E., Mentzel, T., Chinchilla, D., Boller, T., Felix, G., Kemmerling, B., Postel, S., Arents, M., Jeworutzki, E., Al-Rasheid, K. A. S., Becker, D., and Hedrich, R. (2010) Perception of the Arabidopsis danger signal peptide 1 involves the pattern recognition receptor AtPEPR1 and its close homologue AtPEPR2. The Journal of biological chemistry 285, 13471-13479

84. Yamaguchi, Y., Huffaker, A., Bryan, A. C., Tax, F. E., and Ryan, C. A. (2010) PEPR2 Is a Second Receptor for the Pep1 and Pep2 Peptides and Contributes to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidopsis&lt;/em&gt; and Contributing to Defense Responses in &lt;em&gt;Arabidop
92. Wan, J., Zhang, X.-C., Neece, D., Ramonell, K. M., Clough, S., Kim, S.-Y., Stacey, M. G., and Stacey, G. (2008) A LysM receptor-like kinase plays a critical role in chitin signaling and fungal resistance in Arabidopsis. *The Plant cell* **20**, 471-481

93. Ranf, S., Gisch, N., Schäffer, M., Illig, T., Westphal, L., Knirel, Y. A., Sánchez-Carbello, P. M., Zähringer, U., Hückelhoven, R., Lee, J., and Scheel, D. (2015) A lectin S-domain receptor kinase mediates lipopolysaccharide sensing in Arabidopsis thaliana. *Nature Immunology* **16**, 426-433

94. Verica, J. A., and He, Z.-H. (2002) The cell wall-associated kinase (WAK) and WAK-like kinase gene family. *Plant physiology* **129**, 455-459

95. Brutus, A., Sicilia, F., Macone, A., Cervone, F., and De Lorenzo, G. (2010) A domain swap approach reveals a role of the plant wall-associated kinase 1 (WAK1) as a receptor of oligogalacturonides. *Proceedings of the National Academy of Sciences* **107**, 9452

96. Kohorn, B. D. (2015) Cell wall-associated kinases and pectin perception. *Journal of Experimental Botany* **67**, 489-494

97. Souza, C. d. A., Li, S., Lin, A. Z., Boutrot, F., Grossmann, G., Zipfel, C., and Somerville, S. C. (2017) Cellulose-Derived Oligomers Act as Damage-Associated Molecular Patterns and Trigger Defense-Like Responses. *Plant Physiology* **173**, 2383

98. Kohorn, B. D., and Kohorn, S. L. (2012) The cell wall-associated kinases, WAKs, as pectin receptors. *Frontiers in plant science* **3**, 88-88

99. Choi, J., Tanaka, K., Cao, Y., Qi, Y., Qiu, J., Liang, Y., Lee, S. Y., and Stacey, G. (2014) Identification of a Plant Receptor for Extracellular ATP. *Science* **343**, 290

100. Tanaka, K., Choi, J., Cao, Y., and Stacey, G. (2014) Extracellular ATP acts as a damage-associated molecular pattern (DAMP) signal in plants. *Frontiers in Plant Science* **5**, 446

101. Yasuda, S., Okada, K., and Saijo, Y. (2017) A look at plant immunity through the window of the multitasking coreceptor BAK1. *Current Opinion in Plant Biology* **38**, 10-18

102. Chinchilla, D., Shan, L., He, P., de Vries, S., and Kemmerling, B. (2009) One for all: the receptor-associated kinase BAK1. *Trends in plant science* **14**, 535-541

103. Schulze, B., Mentzel, T., Jehle, A. K., Mueller, K., Beeher, S., Boller, T., Felix, G., and Chinchilla, D. (2010) Rapid Heteromerization and Phosphorylation of Ligand-activated Plant Transmembrane Receptors and Their Associated Kinase BAK1. *Journal of Biological Chemistry* **285**, 9444-9451

104. Gust, A. A., and Felix, G. (2014) Receptor-like proteins associate with SOBIR1-type of adaptors to form bimolecular receptor kinases. *Current Opinion in Plant Biology* **21**, 104-111

105. Liebrand, T. W. H., van den Burg, H. A., and Joosten, M. H. A. J. (2014) Two for all: receptor-associated kinases SOBIR1 and BAK1. *Trends in Plant Science* **19**, 123-132

106. van der Burgh, A. M., Postma, J., Robatzek, S., and Joosten, M. H. A. J. (2019) Kinase activity of SOBIR1 and BAK1 is required for immune signalling. *Molecular plant pathology* **20**, 410-422

107. Tör, M., Lotze, M. T., and Holton, N. (2009) Receptor-mediated signalling in plants: molecular patterns and programmes. *Journal of experimental botany* **60**, 3645-3654

108. Postma, J., Liebrand, T. W. H., Bi, G., Evrard, A., Bye, R. R., Mbengue, M., Kuhn, H., Joosten, M. H. A. J., and Robatzek, S. (2016) Avr4 promotes Cf-4 receptor-like protein association with the BAK1/SERK3 receptor-like kinase to initiate receptor endocytosis and plant immunity. *New Phytologist* **210**, 627-642

109. Domazakis, E., Wouters, D., Visser, R. G. F., Kamoun, S., Joosten, M. H. A. J., and Vleeshouwers, V. G. A. A. (2018) The ELR-SOBIR1 Complex Functions as a Two-
Component Receptor-Like Kinase to Mount Defense Against Phytophthora infestans. *Molecular Plant-Microbe Interactions* **31**, 795-802

10. Shimizu, T., Nakano, T., Takamizawa, D., Desaki, Y., Ishii-Minami, N., Nishizawa, Y., Minami, E., Okada, K., Yamane, H., Kaku, H., and Shibuya, N. (2010) Two LysM receptor molecules, CEBiP and OsCERK1, cooperatively regulate chitin elicitor signaling in rice. *Plant J* **64**, 204-214

11. Squegglia, F., Berisio, R., Shibuya, N., and Kaku, H. (2017) Defense Against Pathogens: Structural Insights into the Mechanism of Chitin Induced Activation of Innate Immunity. *Curr Med Chem* **24**, 3980-3986

12. Kaku, H., Nishizawa, Y., Ishii-Minami, N., Akimoto-Tomiyama, C., Dohmae, N., Takio, K., Minami, E., and Shibuya, N. (2006) Plant cells recognize chitin fragments for defense signaling through a plasma membrane receptor. *Proc Natl Acad Sci U S A* **103**, 11086-11091

13. Lu, D., Wu, S., Gao, X., Zhang, Y., Shan, L., and He, P. (2010) A receptor-like cytoplasmic kinase, BIK1, associates with a flagellin receptor complex to initiate plant innate immunity. *Proceedings of the National Academy of Sciences* **107**, 496

14. Lin, W., Ma, X., Shan, L., and He, P. (2013) Big roles of small kinases: the complex functions of receptor-like cytoplasmic kinases in plant immunity and development. *Journal of integrative plant biology* **55**, 1188-1197

15. Liang, X., and Zhou, J.-M. (2018) Receptor-Like Cytoplasmic Kinases: Central Players in Plant Receptor Kinase–Mediated Signaling. *Annual Review of Plant Biology* **69**, 267-299

16. Veronese, P., Nakagami, H., Bluhm, B., AbuQamar, S., Chen, X., Salmeron, J., Dietrich, R. A., Hirt, H., and Mengiste, T. (2006) The Membrane-Anchored BOTRYTIS-INDUCED KINASE1 Plays Distinct Roles in Arabidopsis and Resistance to Necrotrophic and Biotrophic Pathogens. *The Plant Cell* **18**, 257

17. Zhang, J., Li, W., Xiang, T., Liu, Z., Laluk, K., Ding, X., Zou, Y., Gao, M., Zhang, X., Chen, S., Mengiste, T., Zhang, Y., and Zhou, J.-M. (2010) Receptor-like Cytoplasmic Kinases Integrate Signaling from Multiple Plant Immune Receptors and Are Targeted by a Pseudomonas syringae Effector. *Cell Host & Microbe* **7**, 290-301

18. Ranf, S., Eschen-Lippold, L., Fröhlich, K., Westphal, L., Scheel, D., and Lee, J. (2014) Microbe-associated molecular pattern-induced calcium signaling requires the receptor-like cytoplasmic kinases, PBL1 and BIK1. *BMC Plant Biology* **14**, 374

19. Kadowa, Y., Shirasu, K., and Zipfel, C. (2015) Regulation of the NADPH Oxidase RBOHD During Plant Immunity. *Plant and Cell Physiology* **56**, 1472-1480

20. Monaghan, J., Matschi, S., Romeis, T., and Zipfel, C. (2015) The calcium-dependent protein kinase CPK28 negatively regulates the BIK1-mediated PAMP-induced calcium burst. *Plant Signaling & Behavior* **10**, e1018497

21. Li, L., Li, M., Yu, L., Zhou, Z., Liang, X., Liu, Z., Cai, G., Gao, L., Zhang, X., Wang, Y., Chen, S., and Zhou, J.-M. (2014) The FLS2-Associated Kinase BIK1 Directly Phosphorylates the NADPH Oxidase RbohD to Control Plant Immunity. *Cell Host & Microbe* **15**, 329-338

22. Qi, J., Wang, J., Gong, Z., and Zhou, J.-M. (2017) Apoplastic ROS signaling in plant immunity. *Current Opinion in Plant Biology* **38**, 92-100

23. Lal, N. K., Nagalakshmi, U., Hurlburt, N. K., Flores, R., Bak, A., Sone, P., Ma, X., Song, G., Walley, J., Shan, L., He, P., Casteel, C., Fisher, A. J., and Dinesh-Kumar, S. P. (2018) The Receptor-like Cytoplasmic Kinase BIK1 Localizes to the Nucleus and Regulates Defense Hormone Expression during Plant Innate Immunity. *Cell Host & Microbe* **23**, 485-497.e485
124. Couto, D., and Zipfel, C. (2016) Regulation of pattern recognition receptor signalling in plants. *Nature Reviews Immunology* **16**, 537-552

125. Gómez-Gómez, L., Bauer, Z., and Boller, T. (2001) Both the Extracellular Leucine-Rich Repeat Domain and the Kinase Activity of FLS2 Are Required for Flagellin Binding and Signaling in Arabidopsis. *The Plant Cell* **13**, 1155

126. Ding, Z., Wang, H., Liang, X., Morris, E. R., Gallazzi, F., Pandit, S., Skolnick, J., Walker, J. C., and Van Doren, S. R. (2007) Phosphoprotein and Phosphopeptide Interactions with the FHA Domain from Arabidopsis Kinase-Associated Protein Phosphatase. *Biochemistry* **46**, 2684-2696

127. Park, C.-J., Caddell, D. F., and Ronald, P. C. (2012) Protein phosphorylation in plant immunity: insights into the regulation of pattern recognition receptor-mediated signaling. *Frontiers in plant science* **3**, 177-177

128. Segonzac, C., Macho, A. P., Sanmartín, M., Ntoukakis, V., Sánchez-Serrano, J. J., and Zipfel, C. (2014) Negative control of BAK1 by protein phosphatase 2A during plant innate immunity. *EMBO J* **33**, 2069-2079

129. Durian, G., Rahikainen, M., Alegre, S., Brosché, M., and Kangasjärvi, S. (2016) Protein Phosphatase 2A in the Regulatory Network Underlying Biotic Stress Resistance in Plants. *Frontiers in Plant Science* **7**, 812

130. Halter, T., Imkampe, J., Blaum, B. S., Stehle, T., and Kemmerling, B. (2014) BIR2 affects complex formation of BAK1 with ligand binding receptors in plant defense. *Plant Signaling & Behavior* **9**, e28944

131. Halter, T., Imkampe, J., Mazzotta, S., Wierzbka, M., Postel, S., Bücherl, C., Kiefer, C., Stahl, M., Chinchilla, D., Wang, X., Nürnberg, T., Zipfel, C., Clouse, S., Borst, Jan W., Boeren, S., de Vries, Sacco C., Tax, F., and Kemmerling, B. (2014) The Leucine-Rich Repeat Receptor Kinase BIR2 Is a Negative Regulator of BAK1 in Plant Immunity. *Current Biology* **24**, 134-143

132. Liu, Y., Huang, X., Li, M., He, P., and Zhang, Y. (2016) Loss-of-function of Arabidopsis receptor-like kinase BIR1 activates cell death and defense responses mediated by BAK1 and SOBIR1. *New Phytologist* **212**, 637-645

133. Wang, J., Grubb, L. E., Wang, J., Liang, X., Li, L., Gao, C., Ma, M., Feng, F., Li, M., Li, L., Zhang, X., Yu, F., Xie, Q., Chen, S., Zipfel, C., Monaghan, J., and Zhou, J.-M. (2018) A Regulatory Module Controlling Homeostasis of a Plant Immune Kinase. *Molecular Cell* **69**, 493-504.e496

134. Robatzek, S., Chinchilla, D., and Boller, T. (2006) Ligand-induced endocytosis of the pattern recognition receptor FLS2 in Arabidopsis. *Genes Dev* **20**, 537-542

135. Lu, D., Lin, W., Gao, X., Wu, S., Cheng, C., Avila, J., Heese, A., Devarenne, T. P., He, P., and Shan, L. (2011) Direct Ubiquitination of Pattern Recognition Receptor FLS2 Attenuates Plant Innate Immunity. *Science* **332**, 1439

136. Smith, J. M., Salamango, D. J., Leslie, M. E., Collins, C. A., and Heese, A. (2014) Sensitivity to Flg22 Is Modulated by Ligand-Induced Degradation and de Novo Synthesis of the Endogenous Flagellin-Receptor FLAGELLIN-SENSING2. *Plant Physiology* **164**, 440

137. Ma, X., Claus, L. A. N., Leslie, M. E., Tao, K., Wu, Z., Liu, J., Yu, X., Li, B., Zhou, J., Savatin, D. V., Peng, J., Tyler, B. M., Heese, A., Russinova, E., He, P., and Shan, L. (2020) Ligand-induced monoubiquitination of BIK1 regulates plant immunity. *Nature*

138. Korasick, D. A., McMichael, C., Walker, K. A., Anderson, J. C., Bednarek, S. Y., and Heese, A. (2010) Novel Functions of Stomatal Cytokinesis-Defective 1 (SCD1) in Innate Immune Responses against Bacteria. *Journal of Biological Chemistry* **285**, 23342-23350
139. McMichael, C. M., Reynolds, G. D., Koch, L. M., Wang, C., Jiang, N., Nadeau, J., Sack, F. D., Gelderman, M. B., Pan, J., and Bednarek, S. Y. (2013) Mediation of Clathrin-Dependent Trafficking during Cytokinesis and Cell Expansion by STOMATAL CYTOKINESIS DEFECTIVE Proteins. *The Plant Cell* **25**, 3910

140. Spallek, T., Beck, M., Ben Khaled, S., Salomon, S., Bourdais, G., Schellmann, S., and Robatzek, S. (2013) ESCRT-I Mediates FLS2 Endosomal Sorting and Plant Immunity. *PLOS Genetics* **9**, e1004035

141. Schuh, A. L., and Audhya, A. (2014) The ESCRT machinery: from the plasma membrane to endosomes and back again. *Crit Rev Biochem Mol Biol* **49**, 242-261

142. Ben Khaled, S., Postma, J., and Robatzek, S. (2015) A Moving View: Subcellular Trafficking Processes in Pattern Recognition Receptor–Triggered Plant Immunity. *Annual Review of Phytopathology* **53**, 379-402

143. Bücherl, C. A., Jarsch, I. K., Schudoma, C., Segonzac, C., Mbengue, M., Robatzek, S., MacLean, D., Ott, T., and Zipfel, C. (2017) Plant immune and growth receptors share common signalling components but localise to distinct plasma membrane nanodomains. *Elife* **6**, e25114

144. Dong, O. X., and Ronald, P. C. (2019) Genetic Engineering for Disease Resistance in Plants: Recent Progress and Future Perspectives. *Plant Physiology* **180**, 26

145. Rodriguez-Moreno, L., Song, Y., and Thomma, B. P. H. J. (2017) Transfer and engineering of immune receptors to improve recognition capacities in crops. *Current Opinion in Plant Biology* **38**, 42-49

146. Gómez-Gómez, L., and Boller, T. (2000) FLS2: An LRR Receptor–like Kinase Involved in the Perception of the Bacterial Elicitor Flagellin in Arabidopsis. *Molecular Cell* **5**, 1003-1011

147. Shiu, S.-H., and Bleecker, A. B. (2001) Receptor-like kinases from *Arabidopsis* form a monophyletic gene family related to animal receptor kinases. *Proceedings of the National Academy of Sciences* **98**, 10763

148. Hayashi, F., Smith, K. D., Ozinsky, A., Hawn, T. R., Yi, E. C., Goodlett, D. R., Eng, J. K., Akira, S., Underhill, D. M., and Aderem, A. (2001) The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. *Nature* **410**, 1099-1103

149. Heese, A., Hann, D. R., Gimenez-Ibanez, S., Jones, A. M. E., He, K., Li, J., Schroeder, J. I., Peck, S. C., and Rathjen, J. P. (2007) The receptor-like kinase SERK3/BAK1 is a central regulator of innate immunity in plants. *Proc Natl Acad Sci U S A* **104**, 12217-12222

150. Dangl, J. L., and Jones, J. D. G. (2001) Plant pathogens and integrated defence responses to infection. *Nature* **411**, 826-833

151. Flor, H. H. (1971) Current Status of the Gene-For-Gene Concept. *Annual Review of Phytopathology* **9**, 275-296

152. Takken, F. L. W., and Tameling, W. I. L. (2009) To Nibble at Plant Resistance Proteins. *Science* **324**, 744-746

153. Zou, H., Li, Y., Liu, X., and Wang, X. (1999) An APAF-1.cytchrome c multimeric complex is a functional apotosome that activates procaspase-9. *J Biol Chem* **274**, 11549-11556

154. Duncan, J. A., Bergstralh, D. T., Wang, Y., Willingham, S. B., Ye, Z., Zimmermann, A. G., and Ting, J. P.-Y. (2007) Cryopyrin/NALP3 binds ATP/dATP, is an ATPase, and requires ATP binding to mediate inflammatory signaling. *Proceedings of the National Academy of Sciences* **104**, 8041-8046
155. Poyet, J. L., Srinivasula, S. M., Tnani, M., Razmara, M., Fernandes-Alnemri, T., and Alnemri, E. S. (2001) Identification of Ipaf, a human caspase-1-activating protein related to Apaf-1. *J Biol Chem* **276**, 28309-28313

156. Sharif, H., Wang, L., Wang, W. L., Magupalli, V. G., Andreeva, L., Qiao, Q., Hauenstein, A. V., Wu, Z., Núñez, G., Mao, Y., and Wu, H. (2019) Structural mechanism for NEK7-licensed activation of NLRP3 inflammasome. *Nature* **570**, 338-343

157. Tenthorey, J. L., Haloupek, N., López-Blanco, J. R., Grob, P., Adamson, E., Hartenian, E., Lind, N. A., Bourgeois, N. M., Chacón, P., Nogales, E., and Vance, R. E. (2017) The structural basis of flagellin detection by NAIP5: A strategy to limit pathogen immune evasion. *Science* **358**, 888-893

158. Zhang, L., Chen, S., Ruan, J., Wu, J., Tong, A. B., Yin, Q., Li, Y., David, L., Lu, A., Wang, W. L., Marks, C., Ouyang, Q., Zhang, X., Mao, Y., and Wu, H. (2015) Cryo-EM structure of the activated NAIP2-NLRC4 inflammasome reveals nucleated polymerization. *Science* **350**, 404-409

159. Van der Biezen, E. A., and Jones, J. D. (1998) Plant disease-resistance proteins and the gene-for-gene concept. *Trends Biochem Sci* **23**, 454-456

160. Duxbury, Z., Ma, Y., Furzer, O. J., Huh, S. U., Cevik, V., Jones, J. D. G., and Sarris, P. F. (2016) Pathogen perception by NLRs in plants and animals: Parallel worlds. *BioEssays* **38**, 769-781

161. Dodds, P. N., Lawrence, G. J., Catanzariti, A.-M., Ayliffe, M. A., and Ellis, J. G. (2004) The *Melampsora lini* AvrL567 Avirulence Genes Are Expressed in Haustoria and Their Products Are Recognized inside Plant Cells. *The Plant Cell* **16**, 755-768

162. Faustin, B., Lartigue, L., Bruey, J. M., Luciano, F., Sergienko, E., Bailly-Maitre, B., Volkmann, N., Hanein, D., Rouiller, I., and Reed, J. C. (2007) Reconstituted NALP1 inflammasome reveals two-step mechanism of caspase-1 activation. *Mol Cell* **25**, 713-724

163. Zhang, X., Dodds, P. N., and Bernoux, M. (2017) What Do We Know About NOD-Like Receptors in Plant Immunity? *Annual Review of Phytopathology* **55**, 205-229

164. Cesari, S., Bernoux, M., Moncuquet, P., Kroj, T., and Dodds, P. N. (2014) A novel conserved mechanism for plant NLR protein pairs: the "integrated decoy" hypothesis. *Front Plant Sci* **5**, 606

165. Cesari, S., Thilliez, G., Ribot, C., Chalvon, V., Michel, C., Jauneau, A., Rivas, S., Alaix, L., Kanzaki, H., Okuyama, Y., Morel, J. B., Fournier, E., Tharreau, D., Terauchi, R., and Kroj, T. (2013) The rice resistance protein pair RGA4/RGA5 recognizes the *Magnaporthe oryzae* effectors AVR-Pia and AVR1-CO39 by direct binding. *Plant Cell* **25**, 1463-1481

166. Sarris, P. F., Duxbury, Z., Huh, S. U., Ma, Y., Segonzac, C., Sklenar, J., Derbyshire, P., Cevik, V., Rallapalli, G., Saucet, S. B., Wirthmueller, L., Menke, F. L. H., Sohn, K. H., and Jones, J. D. G. (2015) A Plant Immune Receptor Detects Pathogen Effectors that Target WRKY Transcription Factors. *Cell* **161**, 1089-1100

167. Le Roux, C., Huet, G., Jauneau, A., Camborde, L., Tremousaygue, D., Kraut, A., Zhou, B., Levaillant, M., Adachi, H., Yoshioka, H., Raffaele, S., Berthome, R., Coute, Y., Parker, J. E., and Deslandes, L. (2015) A receptor pair with an integrated decoy converts pathogen disabling of transcription factors to immunity. *Cell* **161**, 1074-1088

168. Cesari, S. (2018) Multiple strategies for pathogen perception by plant immune receptors. *New Phytologist* **219**, 17-24

169. Islam, M. R., and Mayo, G. M. E. (1990) A Compendium on Host Genes in Flax Conferring Resistance to Flax Rust. *Plant Breeding* **104**, 89-100
170. Ellis, J. G., Lawrence, G. J., Luck, J. E., and Dodds, P. N. (1999) Identification of Regions in Alleles of the Flax Rust Resistance Gene That Determine Differences in Gene-for-Gene Specificity. *The Plant Cell* **11**, 495-506

171. Dodds, P. N., Lawrence, G. J., and Ellis, J. G. (2001) Six Amino Acid Changes Confined to the Leucine-Rich Repeat β-Strand/β-Turn Motif Determine the Difference between the and Rust Resistance Specificities in Flax. *The Plant Cell* **13**, 163-178

172. Mackey, D., Holt, B. F., III, Wiig, A., and Dangl, J. L. (2002) RIN4 Interacts with Pseudomonas syringae Type III Effector Molecules and Is Required for RPM1-Mediated Resistance in Arabidopsis. *Cell* **108**, 743-754

173. Mackey, D., Belkhadir, Y., Alonso, J. M., Ecker, J. R., and Dangl, J. L. (2003) Arabidopsis RIN4 is a target of the type III virulence effector AvrRpt2 and modulates RPS2-mediated resistance. *Cell* **112**, 379-389

174. Mucyn, T. S., Clemente, A., Andriotis, V. M. E., Balmuth, A. L., Oldroyd, G. E. D., Staskawicz, B. J., and Rathjen, J. P. (2006) The Tomato NBARC-LRR Protein Prf Interacts with Pto Kinase in Vivo to Regulate Specific Plant Immunity. *The Plant Cell* **18**, 2792-2806

175. Mucyn, T. S., Wu, A.-J., Balmuth, A. L., Arasteh, J. M., and Rathjen, J. P. (2009) Regulation of Tomato Prf by Pto-like Protein Kinases. *Molecular Plant-Microbe Interactions* **22**, 391-401

176. Ntoukakis, V., Saur, I. M., Conlan, B., and Rathjen, J. P. (2014) The changing of the guard: the Pto/Prf receptor complex of tomato and pathogen recognition. *Curr Opin Plant Biol* **20**, 69-74

177. De la Concepcion, J. C., Franceschetti, M., Maqbool, A., Saitoh, H., Terauchi, R., Kamoun, S., and Banfield, M. J. (2018) Polymorphic residues in rice NLRs expand binding and response to effectors of the blast pathogen. *Nat Plants* **4**, 576-585

178. Ortiz, D., de Guillen, K., Cesari, S., Chalvon, V., Gracy, J., Padilla, A., and Kroj, T. (2017) Recognition of the Magnaporthe oryzae Effector AVR-Pia by the Decoy Domain of the Rice NLR Immune Receptor RGA5. *Plant Cell* **29**, 156-168

179. Guo, L., Cesari, S., de Guillen, K., Chalvon, V., Mammri, L., Ma, M., Meusnier, I., Bonnot, F., Padilla, A., Peng, Y.-L., Liu, J., and Kroj, T. (2018) Specific recognition of two MAX effectors by integrated HMA domains in plant immune receptors involves distinct binding surfaces. *Proceedings of the National Academy of Sciences* **115**, 11637-11642

180. Narusaka, M., Shirasu, K., Noutoshi, Y., Kubo, Y., Shiraishi, T., Iwabuchi, M., and Narusaka, Y. (2009) RRS1 and RPS4 provide a dual Resistance-gene system against fungal and bacterial pathogens. *Plant J* **60**, 218-226

181. Sohn, K. H., Hughes, R. K., Piquerez, S. J., Jones, J. D. G., and Banfield, M. J. (2012) Distinct regions of the Pseudomonas syringae coiled-coil effector AvrRps4 are required for activation of immunity. *Proceedings of the National Academy of Sciences* **109**, 16371-16376

182. Steuernagel, B., Witek, K., Krattinger, S. G., Ramirez-Gonzalez, R. H., Schoonbeek, H.-j., Yu, G., Baggs, E., Witek, A., Yadav, I., Krasileva, K. V., Jones, J. D., Uauy, C., Keller, B., Ridout, C. J., and Wulff, B. B. (2020) The NLR-Annontator tool enables annotation of the intracellular immune receptor repertoire. *Plant Physiology*, pp.01273.02019

183. Bailey, P. C., Schudoma, C., Jackson, W., Baggs, E., Dagdas, G., Haerty, W., Moscou, M., and Krasileva, K. V. (2018) Dominant integration locus drives continuous diversification of plant immune receptors with exogenous domain fusions. *Genome Biol* **19**, 23

25
184. Sarris, P. F., Cevik, V., Dagdas, G., Jones, J. D. G., and Krasileva, K. V. (2016) Comparative analysis of plant immune receptor architectures uncovers host proteins likely targeted by pathogens. BMC Biology 14, 8
185. Kroj, T., Chanclud, E., Michel-Romiti, C., Grand, X., and Morel, J. B. (2016) Integration of decoy domains derived from protein targets of pathogen effectors into plant immune receptors is widespread. New Phytol 210, 618-626
186. Wang, L., Zhao, L., Zhang, X., Zhang, Q., Jia, Y., Wang, G., Li, S., Tian, D., Li, W.-H., and Yang, S. (2019) Large-scale identification and functional analysis of NLR genes in blast resistance in the Tetep rice genome sequence. Proceedings of the National Academy of Sciences 116, 18479-18487
187. de Abreu-Neto, J. B., Turchetto-Zolet, A. C., de Oliveira, L. F. V., Bodanese Zanettini, M. H., and Margis-Pinheiro, M. (2013) Heavy metal-associated isoprenylated plant protein (HIPP): characterization of a family of proteins exclusive to plants. The FEBS Journal 280, 1604-1616
188. Cowan, G. H., Roberts, A. G., Jones, S., Kumar, P., Kalyandurg, P. B., Gil, J. F., Savenkov, E. I., Hemsley, P. A., and Torrance, L. (2018) Potato Mop-Top Virus Co-opts the Stress Sensor HIPP26 for Long-Distance Movement. Plant Physiology 176, 2052-2070
189. Radakovic, Z. S., Anjam, M. S., Escobar, E., Chopra, D., Cabrera, J., Silva, A. C., Escobar, C., Sobczak, M., Grundler, F. M. W., and Siddique, S. (2018) Arabidopsis HIPP27 is a host susceptibility gene for the beet cyst nematode Heterodera schachtii. Mol Plant Pathol
190. Fukuoka, S., Saka, N., Koga, H., Ono, K., Shimizu, T., Ebana, K., Hayashi, N., Takahashi, A., Hirochika, H., Okuno, K., and Yano, M. (2009) Loss of Function of a Proline-Containing Protein Confers Durable Disease Resistance in Rice. Science 325, 998-1001
191. Mukhtar, M. S., Carvunis, A.-R., Dreze, M., Epplen, P., Steinbrenner, J., Moore, J., Tasan, M., Galli, M., Hao, T., Nishimura, M. T., Pevzner, S. J., Donovan, S. E., Ghamsari, L., Santhanam, B., Romero, V., Poulin, M. M., Gebreab, F., Gutierrez, B. J., Tam, S., Monachello, D., Boxem, M., Harbert, C. J., McDonald, N., Gai, L., Chen, H., He, Y., Vandenhauwe, J., Roth, F. P., Hill, D. E., Ecker, J. R., Vidal, M., Beynon, J., Braun, P., and Dangl, J. L. (2011) Independently Evolved Virulence Effectors Converge onto Hubs in a Plant Immune System Network. Science 333, 596-601
192. Kanzaki, H., Yoshida, K., Saitoh, H., Fujisaki, K., Hirabuchi, A., Alaux, L., Fournier, E., Tharreau, D., and Terauchi, R. (2012) Arms race co-evolution of Magnaporthe oryzae AVR-Pik and rice Pik genes driven by their physical interactions. Plant J 72, 894-907
193. Yoshida, K., Saitoh, H., Fujisawa, S., Kanzaki, H., Matsumura, H., Yoshida, K., Tosa, Y., Chuma, I., Takano, Y., Win, J., Kamoun, S., and Terauchi, R. (2009) Association genetics reveals three novel avirulence genes from the rice blast fungal pathogen Magnaporthe oryzae. Plant Cell 21, 1573-1591
194. Costanzo, S., and Jia, Y. (2010) Sequence variation at the rice blast resistance gene Pi-km locus: Implications for the development of allele specific markers. Plant Science 178, 523-530
195. De la Concepcion, J. C., Franceschetti, M., MacLean, D., Terauchi, R., Kamoun, S., and Banfield, M. J. (2019) Protein engineering expands the effector recognition profile of a rice NLR immune receptor. Elife 8
196. Williams, S. J., Sornaraj, P., deCourcy-Ireland, E., Menz, R. I., Kobe, B., Ellis, J. G., Dodds, P. N., and Anderson, P. A. (2011) An Autoactive Mutant of the M Flax Rust
Resistance Protein Has a Preference for Binding ATP, Whereas Wild-Type M Protein Binds ADP. Molecular Plant-Microbe Interactions® 24, 897-906

197. Tameling, W. I. L., Vossen, J. H., Albrecht, M., Lengauer, T., Berden, J. A., Haring, M. A., Cornelissen, B. J. C., and Takken, F. L. W. (2006) Mutations in the NB-ARC domain of I-2 that impair ATP hydrolysis cause autoactivation. Plant physiology 140, 1233-1245

198. Adachi, H., Contreras, M. P., Harant, A., Wu, C. H., Derevnina, L., Sakai, T., Duggan, C., Moratto, E., Bozkurt, T. O., Maqbool, A., Win, J., and Kamoun, S. (2019) An N-terminal motif in NLR immune receptors is functionally conserved across distantly related plant species. Elife 8

199. Bernoux, M., Ve, T., Williams, S., Warren, C., Hatters, D., Valkov, E., Zhang, X., Ellis, J. G., Kobe, B., and Dodds, P. N. (2011) Structural and functional analysis of a plant resistance protein TIR domain reveals interfaces for self-association, signaling, and autoregulation. Cell Host Microbe 9, 200-211

200. Williams, S., Yin, L., Foley, G., Casey, L., Outram, M., Ericsson, D., Lu, J., Boden, M., Dry, I., and Kobe, B. (2016) Structure and function of the TIR domain from the grape NLR protein RPV1. Frontiers in Plant Science 7

201. Horsefield, S., Burdett, H., Zhang, X., Manik, M. K., Shi, Y., Chen, J., Qi, T., Gilley, J., Lai, J.-S., Rank, M. X., Casey, L. W., Gu, W., Ericsson, D. J., Foley, G., Hughes, R. O., Bosanac, T., von Itzstein, M., Rathjen, J. P., Nanson, J. D., Boden, M., Dry, I. B., Williams, S. J., Staskawicz, B. J., Coleman, M. P., Ve, T., Dodds, P. N., and Kobe, B. (2019) NAD+ cleavage activity by animal and plant TIR domains in cell death pathways. Science 365, 793-799

202. Zhang, X., Bernoux, M., Bentham, A. R., Newman, T. E., Ve, T., Casey, L. W., Raaymakers, T. M., Hu, J., Croll, T. I., Schreiber, K. J., Staskawicz, B. J., Anderson, P. A., Sohn, K. H., Williams, S. J., Dodds, P. N., and Kobe, B. (2017) Multiple functional self-association interfaces in plant TIR domains. Proceedings of the National Academy of Sciences 114, E2046-E2052

203. Ve, T., Williams, S. J., and Kobe, B. (2015) Structure and function of Toll/interleukin-1 receptor/resistance protein (TIR) domains. Apoptosis 20, 250-261

204. Wan, L., Essuman, K., Anderson, R. G., Sasaki, Y., Monteiro, F., Chung, E.-H., Osborne Nishimura, E., DiAntonio, A., Milbrandt, J., Dangl, J. L., and Nishimura, M. T. (2019) TIR domains of plant immune receptors are NAD+cleaving enzymes that promote cell death. Science 365, 799-803

205. Martin, R., Qi, T., Zhang, H., Liu, F., King, M., Toth, C., Nogales, E., and Staskawicz, B. J. (2020) Structure of the activated Roq1 resistosome directly recognizing the pathogen effector XopQ. bioRxiv, 2020.2008.2013.246413

206. Wu, C. H., Derevnina, L., and Kamoun, S. (2018) Receptor networks underpin plant immunity. Science 360, 1300-1301

207. Adachi, H., Derevnina, L., and Kamoun, S. (2019) NLR singletons, pairs, and networks: evolution, assembly, and regulation of the intracellular immunoreceptor circuitry of plants. Curr Opin Plant Biol 50, 121-131

208. Jubic, L. M., Saile, S., Furzer, O. J., El Kasmi, F., and Dangl, J. L. (2019) Help wanted: helper NLRs and plant immune responses. Curr Opin Plant Biol 50, 82-94

209. van der Biezen, E. A., Freddie, C. T., Kahn, K., Parker, J. E., and Jones, J. D. (2002) Arabidopsis RPP4 is a member of the RPP5 multigene family of TIR-NB-LRR genes and confers downy mildew resistance through multiple signalling components. Plant J 29, 439-451

210. Bialas, A., Zess, E. K., De la Concepcion, J. C., Franceschetti, M., Pennington, H. G., Yoshida, K., Upson, J. L., Chanclud, E., Wu, C. H., Langner, T., Maqbool, A.,
Varden, F. A., Derevnina, L., Belhaj, K., Fujisaki, K., Saitoh, H., Terauchi, R., Banfield, M. J., and Kamoun, S. (2018) Lessons in Effector and NLR Biology of Plant-Microbe Systems. *Mol Plant Microbe Interact* **31**, 34-45

211. Cesari, S., Kanzaki, H., Fujiwara, T., Bernoux, M., Chalvon, V., Kawano, Y., Shimamoto, K., Dodds, P., Terauchi, R., and Kroj, T. (2014) The NB-LRR proteins RGA4 and RGA5 interact functionally and physically to confer disease resistance. *EMBO J* **33**, 1941-1959

212. Zdrzałek, R., Kamoun, S., Terauchi, R., Saitoh, H., and Banfield, M. J. (2020) The rice NLR pair Pikp-1/Pikp-2 initiates cell death through receptor cooperation rather than negative regulation. *bioRxiv*, 2020.2006.2020.162834

213. Peart, J. R., Mestre, P., Lu, R., Malcuit, I., and Baulcombe, D. C. (2005) NRG1, a CC-NB-LRR Protein, together with N, a TIR-NB-LRR Protein, Mediates Resistance against Tobacco Mosaic Virus. *Current Biology* **15**, 968-973

214. Castel, B., Ngou, P. M., Cevik, V., Redkar, A., Kim, D. S., Yang, Y., Ding, P., and Jones, J. D. G. (2019) Diverse NLR immune receptors activate defence via the RPW8-NLR NRG1. *New Phytol* **222**, 966-980

215. Feehan, J. M., Castel, B., Bentham, A. R., and Jones, J. D. G. (2020) Plant NLRs get by with a little help from their friends. *Current Opinion in Plant Biology* **56**, 99-108

216. Wu, C.-H., Abd-El-Haliem, A., Bozkurt, T. O., Belhaj, K., Terauchi, R., Vossen, J. H., and Kamoun, S. (2017) NLR network mediates immunity to diverse plant pathogens. *Proceedings of the National Academy of Sciences* **114**, 8113-8118

217. Burdett, H., Bentham, A. R., Williams, S. J., Dodds, P. N., Anderson, P. A., Banfield, M. J., and Kobe, B. (2019) The Plant Resistosome: Structural Insights into Immune Signaling. *Cell Host & Microbe* **26**, 193-201

218. Monteiro, F., and Nishimura, M. T. (2018) Structural, Functional, and Genomic Diversity of Plant NLR Proteins: An Evolved Resource for Rational Engineering of Plant Immunity. *Annu Rev Phytopathol* **56**, 243-267

219. Ahmar, S., Gill, R. A., Jung, K. H., Faheem, A., Qasim, M. U., Mubeen, M., and Zhou, W. (2020) Conventional and Molecular Techniques from Simple Breeding to Speed Breeding in Crop Plants: Recent Advances and Future Outlook. *Int J Mol Sci* **21**

220. Rodriguez-Moreno, L., Song, Y., and Thomma, B. P. (2017) Transfer and engineering of immune receptors to improve recognition capacities in crops. *Curr Opin Plant Biol* **38**, 42-49

221. Kumar, K., Gambhir, G., Dass, A., Tripathi, A. K., Singh, A., Jha, A. K., Yadava, P., Choudhary, M., and Rakshit, S. (2020) Genetically modified crops: current status and future prospects. *Planta* **251**, 91

222. Hickey, L. T., Robinson, H., Jackson, S. A., Leal-Bertioli, S. C. M., Tester, M., Gao, C., Godwin, I. D., Hayes, B. J., and Wulff, B. B. H. (2019) Breeding crops to feed 10 billion. *Nat Biotechnol* **37**, 744-754

223. Chakraborty, J., Ghosh, P., and Das, S. (2018) Autoimmunity in plants. *Planta* **248**, 751-767

224. Lacombe, S., Rougon-Cardoso, A., Sherwood, E., Peeters, N., Dahlbeck, D., van Esse, H. P., Smoker, M., Rallapalli, G., Thomma, B. P. H. J., Staskawicz, B., Jones, J. D. G., and Zipfel, C. (2010) Interfamily transfer of a plant pattern-recognition receptor confers broad-spectrum bacterial resistance. *Nature Biotechnology* **28**, 365-369

225. Kunwar, S., Iriarte, F., Fan, Q., Evaristo da Silva, E., Ritchie, L., Nguyen, N. S., Freeman, J. H., Stall, R. E., Jones, J. B., Minsavage, G. V., Colee, J., Scott, J. W., Vallad, G. E., Zipfel, C., Horvath, D., Westwood, J., Hutton, S. F., and Paret, M. L.
Transgenic Expression of EFR and Bs2 Genes for Field Management of Bacterial Wilt and Bacterial Spot of Tomato. *Phytopathology* **108**, 1402-1411

Schoonbeek, H. J., Wang, H. H., Stefanato, F. L., Craze, M., Bowden, S., Wallington, E., Zipfel, C., and Ridout, C. J. (2015) Arabidopsis EF-Tu receptor enhances bacterial disease resistance in transgenic wheat. *New Phytol* **206**, 606-613

Tripathi, J. N., Lorenzen, J., Bahar, O., Ronald, P., and Tripathi, L. (2014) Transgenic expression of the rice Xa21 pattern-recognition receptor in banana (Musa sp.) confers resistance to Xanthomonas campestris pv. musacearum. *Plant Biotechnol J* **12**, 663-673

Mendes, B. M. J., Cardoso, S. C., Boscarel-Camargo, R. L., Cruz, R. B., Filho, F. A. A. M., and Filho, A. B. (2010) Reduction in susceptibility to Xanthomonas axonopodis pv. citri in transgenic Citrus sinensis expressing the rice Xa21 gene. *Plant Pathology* **59**, 68-75

Afroz, A., Chaudhry, Z., Rashid, U., Muhammad Ali, G., Nazir, F., Iqbal, J., and Rashid Khan, M. (2011) Enhanced resistance against bacterial wilt in transgenic tomato (Lycopersicon esculentum) lines expressing the Xa21 gene. *Plant Cell, Tissue and Organ Culture* **104**, 227-237

Furst, U., Zeng, Y., Albert, M., Witte, A. K., Fliegmann, J., and Felix, G. (2020) Perception of Agrobacterium tumefaciens flagellin by FLS2(XL) confers resistance to crown gall disease. *Nat Plants* **6**, 22-27

Piquerez, S. J. M., Harvey, S. E., Beynon, J. L., and Ntoukakis, V. (2014) Improving crop disease resistance: lessons from research on Arabidopsis and tomato. *Frontiers in Plant Science* **5**, 671

Tian, J., Xu, G., and Yuan, M. (2020) Towards Engineering Broad-Spectrum Disease-Resistant Crops. *Trends in Plant Science* **25**, 424-427

Arora, S., Steuernagel, B., Gaurav, K., Chandramohan, S., Long, Y., Matny, O., Johnson, R., Enk, J., Periyannan, S., Singh, N., Asyraf Md Hatta, M., Athiyannan, N., Cheema, J., Yu, G., Kangara, N., Ghosh, S., Szabo, L. J., Poland, J., Bariana, H., Jones, J. D. G., Bentely, A. R., Ayliffe, M., Olson, E., Xu, S. S., Steffenson, B. J., Lagudah, E., and Wulff, B. B. H. (2019) Resistance gene cloning from a wild crop relative by sequence capture and association genetics. *Nat Biotechnol* **37**, 139-143

Steuernagel, B., Periyannan, S. K., Hernandez-Pinzon, I., Witek, K., Rouse, M. N., Yu, G., Hatta, A., Ayliffe, M., Bariana, H., Jones, J. D., Lagudah, E. S., and Wulff, B. B. (2016) Rapid cloning of disease-resistance genes in plants using mutagenesis and sequence capture. *Nat Biotechnol* **34**, 652-655

Bevan, M. W., Uauy, C., Wulff, B. B. H., Zhou, J., Krasileva, K., and Clark, M. D. (2017) Genomic innovation for crop improvement. *Nature* **543**, 346-354

Jupe, F., Witek, K., Verweij, W., Sliwka, J., Pritchard, L., Etherington, G. J., Maclean, D., Cock, P. J., Leggett, R. M., Bryan, G. J., Cardle, L., Hein, I., and Jones, J. D. (2013) Resistance gene enrichment sequencing (RenSeq) enables reannotation of the NB-LRR gene family from sequenced plant genomes and rapid mapping of resistance loci in segregating populations. *Plant J* **76**, 530-544

Kawashima, C. G., Guimarães, G. A., Nogueira, S. R., MacLean, D., Cook, D. R., Steuernagel, B., Baek, J., Bouyioukos, C., Melo, B. d. V. A., Tristão, G., de Oliveira, J. C., Rauscher, G., Mittal, S., Panichelli, L., Bacot, K., Johnson, E., Iyer, G., Tabor, G., Wulff, B. B. H., Ward, E., Rairdan, G. J., Broglie, K. E., Wu, G., van Esse, H. P., Jones, J. D. G., and Brommonschenkel, S. H. (2016) A pigeonpea gene confers resistance to Asian soybean rust in soybean. *Nature Biotechnology* **34**, 661

Ghislain, M., Byarugaba, A. A., Magembe, E., Njorge, A., Rivera, C., Roman, M. L., Tovar, J. C., Gamboa, S., Forbes, G. A., Kreuze, J. F., Barekye, A., and Kiggundu,
A. (2019) Stacking three late blight resistance genes from wild species directly into African highland potato varieties confers complete field resistance to local blight races. *Plant Biotechnol J* **17**, 1119-1129

239. Witek, K., Jupe, F., Witek, A. I., Baker, D., Clark, M. D., and Jones, J. D. (2016) Accelerated cloning of a potato late blight-resistance gene using RenSeq and SMRT sequencing. *Nat Biotechnol* **34**, 656-660

240. Meyers, B. C., Kozik, A., Griego, A., Kuang, H. H., and Michelmore, R. W. (2003) Genome-wide analysis of NBS-LRR-encoding genes in Arabidopsis. *Plant Cell* **15**, 809-834

241. Cao, F. Y., Yoshioka, K., and Desveaux, D. (2011) The roles of ABA in plant-pathogen interactions. *J Plant Res* **124**, 489-499

242. Van de Weyer, A.-L., Monteiro, F., Furzer, O. J., Nishimura, M. T., Cevik, V., Witek, K., Jones, J. D. G., Dangl, J. L., Weigel, D., and Bemm, F. (2019) A Species-Wide Inventory of NLR Genes and Alleles in Arabidopsis thaliana. *Cell* **178**, 1260-1272.e1214

243. Hurni, S., Brunner, S., Stirnweis, D., Herren, G., Peditto, D., McIntosh, R. A., and Keller, B. (2014) The powdery mildew resistance gene Pm8 derived from rye is suppressed by its wheat ortholog Pm3. *The Plant Journal* **79**, 904-913

244. Stirnweis, D., Milani, S. D., Brunner, S., Herren, G., Buchmann, G., Peditto, D., Jordan, T., and Keller, B. (2014) Suppression among alleles encoding nucleotide-binding–leucine-rich repeat resistance proteins interferes with resistance in F1 hybrid and allele-pyramided wheat plants. *The Plant Journal* **79**, 893-903

245. Slootweg, E., Koropacka, K., Roosien, J., Dees, R., Overmars, H., Lankhorst, R. K., van Schaik, C., Pomp, R., Bouwman, L., Helder, J., Schots, A., Bakker, J., Smant, G., and Goverse, A. (2017) Sequence Exchange between Homologous NB-LRR Genes Converts Virus Resistance into Nematode Resistance, and Vice Versa. *Plant Physiology* **175**, 498-510

246. Farnham, G., and Baulcombe, D. C. (2006) Artificial evolution extends the spectrum of viruses that are targeted by a disease-resistance gene from potato. *Proc Natl Acad Sci U S A* **103**, 18828-18833

247. Harris, C. J., Slootweg, E. J., Goverse, A., and Baulcombe, D. C. (2013) Stepwise artificial evolution of a plant disease resistance gene. *Proc Natl Acad Sci U S A* **110**, 21189-21194

248. Giannakopoulou, A., Steele, J. F., Segretin, M. E., Bozkurt, T. O., Zhou, J., Robatzek, S., Banfield, M. J., Pais, M., and Kamoun, S. (2015) Tomato I2 Immune Receptor Can Be Engineered to Confer Partial Resistance to the Oomycete Phytophthora infestans in Addition to the Fungus Fusarium oxysporum. *Mol Plant Microbe Interact* **28**, 1316-1329

249. Segretin, M. E., Pais, M., Franceschetti, M., Chaparro-Garcia, A., Bos, J. I., Banfield, M. J., and Kamoun, S. (2014) Single amino acid mutations in the potato immune receptor R3a expand response to Phytophthora effectors. *Mol Plant Microbe Interact* **27**, 624-637

250. Pottinger, S. E., Bak, A., Margets, A., Helm, M., Tang, L., Casteel, C., and Innes, R. W. (2020) Optimizing the PBS1 Decoy System to Confer Resistance to Potyvirus Infection in Arabidopsis and Soybean. *Mol Plant Microbe Interact*

251. Kim, S. H., Qi, D., Ashfield, T., Helm, M., and Innes, R. W. (2016) Using decoys to expand the recognition specificity of a plant disease resistance protein. *Science* **351**, 684-687

252. Carter, M. E., Helm, M., Chapman, A. V. E., Wan, E., Restrepo Sierra, A. M., Innes, R. W., Bogdanove, A. J., and Wise, R. P. (2019) Convergent Evolution of Effector
Protease Recognition by Arabidopsis and Barley. *Mol Plant Microbe Interact* **32**, 550-565

253. Helm, M., Qi, M., Sarkar, S., Yu, H., Whitham, S. A., and Innes, R. W. (2019) Engineering a Decoy Substrate in Soybean to Enable Recognition of the Soybean Mosaic Virus Nla Protease. *Mol Plant Microbe Interact* **32**, 760-769

254. Ellis, J. G. (2016) Integrated decoys and effector traps: how to catch a plant pathogen. *BMC Biology* **14**, 13

255. Malik, S., and Van der Hoorn, R. A. (2016) Inspirational decoys: a new hunt for effector targets. *New Phytol* **210**, 53-63

256. Longya, A., Chaipanya, C., Franceschetti, M., Maidment, J. H. R., Banfield, M. J., and Jantasuriyarat, C. (2019) Gene Duplication and Mutation in the Emergence of a Novel Aggressive Allele of the AVR-Pik Effector in the Rice Blast Fungus. *Mol Plant Microbe Interact* **32**, 740-749

257. Varden, F. A., Saitoh, H., Yoshino, K., Franceschetti, M., Kamoun, S., Terauchi, R., and Banfield, M. J. (2019) Cross-reactivity of a rice NLR immune receptor to distinct effectors from the rice blast pathogen Magnaporthe oryzae provides partial disease resistance. *J Biol Chem* **261**, 12768-12778

258. Xu, G., Yuan, M., Ai, C., Liu, L., Zhuang, E., Karapetyan, S., Wang, S., and Dong, X. (2017) uORF-mediated translation allows engineered plant disease resistance without fitness costs. *Nature* **545**, 491

259. Xu, G., Greene, G. H., Yoo, H., Liu, L., Marqués, J., Motley, J., and Dong, X. (2017) Global translational reprogramming is a fundamental layer of immune regulation in plants. *Nature* **545**, 487-491

260. Huot, B., Yao, J., Montgomery, B. L., and He, S. Y. (2014) Growth-defense tradeoffs in plants: a balancing act to optimize fitness. *Mol Plant* **7**, 1267-1287

261. Sun, Y., Li, L., Macho, A. P., Han, Z., Hu, Z., Zipfel, C., Zhou, J.-M., and Chai, J. (2013) Structural Basis for flg22-Induced Activation of the **<em>Arabidopsis</em>** FLS2-BAK1 Immune Complex. *Science* **342**, 624-628

262. Hohmann, U., and Hothorn, M. (2019) Crystal structure of the leucine-rich repeat ectodomain of the plant immune receptor kinase SOBIR1. *Acta Crystallographica Section D* **75**, 488-497

263. Hohmann, U., Nicolet, J., Moretti, A., Hothorn, L. A., and Hothorn, M. (2018) The SERK3 elongated allele defines a role for BIR ectodomains in brassinosteroid signalling. *Nature Plants* **4**, 345-351

264. Liu, S., Wang, J., Han, Z., Gong, X., Zhang, H., and Chai, J. (2016) Molecular Mechanism for Fungal Cell Wall Recognition by Rice Chitin Receptor OsCEBiP. *Structure* **24**, 1192-1200

265. Maekawa, T., Cheng, W., Spiridon, L. N., Toller, A., Lukasik, E., Saijo, Y., Liu, P., Shen, Q. H., Michuta, M. A., Somssich, I. E., Takken, F. L. W., Petrescu, A. J., Chai, J., and Schulze-Lefert, P. (2011) Coiled-coil domain-dependent homodimerization of intracellular barley immune receptors defines a minimal functional module for triggering cell death. *Cell Host Microbe* **9**, 187-199

266. Casey, L. W., Lavrencic, P., Bentham, A. R., Cesari, S., Ericsson, D. J., Croll, T., Turk, D., Anderson, P. A., Mark, A. E., Dodds, P. N., Mobli, M., Kobe, B., and Williams, S. J. (2016) The CC domain structure from the wheat stem rust resistance protein Sr33 challenges paradigms for dimerization in plant NLR proteins. *Proc Natl Acad Sci USA* **113**, 12856-12861

267. Hyun, K.-g., Lee, Y., Yoon, J., Yi, H., and Song, J.-J. (2016) Crystal structure of Arabidopsis thaliana SNC1 TIR domain. *Biochemical and Biophysical Research Communications* **481**, 146-152
268. Casey, L. W., Lavrencic, P., Bentham, A. R., Cesari, S., Ericsson, D. J., Croll, T.,
Turk, D., Anderson, P. A., Mark, A. E., Dodds, P. N., Mobli, M., Kobe, B., and
Williams, S. J. (2016) The CC domain structure from the wheat stem rust resistance
protein Sr33 challenges paradigms for dimerization in plant NLR proteins. 
Proceedings of the National Academy of Sciences 113, 12856-12861

269. Steele, J. F. C., Hughes, R. K., and Banfield, M. J. (2019) Structural and biochemical
studies of an NB-ARC domain from a plant NLR immune receptor. PLOS ONE 14,
e0221226

270. Dong, J., Xiao, F., Fan, F., Gu, L., Cang, H., Martin, G. B., and Chai, J. (2009)
Crystal Structure of the Complex between <em>Pseudomonas</em> Effector
AvrPtoB and the Tomato Pto Kinase Reveals Both a Shared and a Unique Interface
Compared with AvrPto-Pto. The Plant Cell 21, 1846-1859

271. Baudin, M., Hassan, J. A., Schreiber, K. J., and Lewis, J. D. (2017) Analysis of the
ZAR1 Immune Complex Reveals Determinants for Immunity and Molecular
Interactions. Plant Physiol 174, 2038-2053

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| AVR          | Avirulence gene |
| ADR1         | Activated disease resistance 1 |
| BAK1         | BRASSINOSTEROID INSENSITIVE 1-associated receptor kinase 1 |
| BIK1         | Botrytis-induced kinase 1 |
| CC           | Coiled-coil |
| CEBIP        | Chitin elicitor binding protein |
| CERK1        | Chitin elicitor receptor kinase 1 |
| CORE         | Cold shock protein receptor |
| DAMP         | Damage-associated molecular pattern |
| DORN1        | Doesn’t respond to nucleotides |
| eATP         | extracellular ATP |
| ECD          | Extracellular domain |
| EF-Tu        | Elongation factor Tu |
| EFR          | Elongation factor Tu receptor |
| EGF          | Epidermal growth factor |
| Elf18        | N-acetylated peptide comprising the first 18 amino acids of bacterial elongation factor EF-
Tu |
| FER          | Feronia |
| Flg22        | A 22-amino acid epitope of bacterial flagellin |
| FLS2         | Flagellin-sensitive 2 |
| HIPPs        | Heavy metal-associated isoprenylated plant protein |
| HMA          | Heavy metal-associated (domain) |
| HPP          | Heavy metal-associated plant protein |
| ID           | Integrated domain |
| KD           | Kinase domain |
| LORE         | Lipooligosaccharide-specific reduced elicitation |
| LRR          | Leucine-rich repeat |
| Abbreviation | Description |
|--------------|-------------|
| **LPS**      | Lipopolysaccharide |
| **LYK5**     | Lysin motif receptor kinase 5 |
| **LysM**     | Lysine motif |
| **MADA motif** | A consensus MADAxVSFxVxKLxxLLxxEx sequence conserved at the N termini of NRC family proteins |
| **MAMP**     | Microbial-associated molecular pattern |
| **MAPK**     | Mitogen-activated protein kinase |
| **MHD motif** | A consensus sequence (methionine-histidine-aspartate) at the carboxy terminus of ARC2 |
| **MLA**      | Mildew resistance locus A |
| **NADPH**    | Nicotinamide adenine dinucleotide phosphate |
| **NB-ARC**   | Nucleotide-binding domain shared with APAF1, R gene products and CED4 |
| **NB-ARC**   | Nucleotide-binding domain |
| **NLP**      | Necrosis and ethylene-inducing peptide 1 (Nep1)-like proteins |
| **NLR**      | Nucleotide-binding leucine-rich repeat receptor |
| **NLRP3**    | NLR family CARD domain-containing protein 4 |
| **NLRP3**    | NLR family pyrin domain containing 3 |
| **NRG1**     | N requirement gene 1 |
| **NRC**      | NLR required for cell death |
| **OG**       | Oligosaccharides |
| **PBL**      | PBS1-like kinase |
| **PBS1/2**   | Arabidopsis AVRPPHB susceptible 1/2 |
| **PGN**      | Peptidoglycan |
| **PEP**      | Plant elicitor peptide |
| **PEPR1**    | Perception of the Arabidopsis danger signal peptide |
| **PIP**      | PAMP-induced secreted peptide |
| **PIK1**     | Pyricularia oryzae resistance-k |
| **PP2A**     | Protein phosphatase 2A |
| **PRR**      | Pattern recognition receptor |
| **RALF1**    | Rapid alkalization factor 1 |
| **RaxX21-sY** | A sulfated, 21–amino acid synthetic RaxX peptide |
| **RBOHD**    | Respiratory burst oxidase homolog protein D |
| **RG5**      | R-gene analog 5 |
| **RHA3A/B**  | E3 ubiquitin ligases RING-H2 FINGER A3A/B |
| **RIN4**     | RPM1 interacting protein 4 |
| **RKS1**     | Resistance related kinase 1 |
| **RLCK**     | Receptor-like cytoplasmic kinase |
| **RLK**      | Receptor-like kinase |
| **RLP**      | Receptor-like protein |
| **RPM1**     | Resistance to Pseudomonas syringae pv. maculicola 1 |
| **RPS2**     | Resistance to Pseudomonas syringae 2 |
| **RPP4**     | Recognition of Peronospora parasitica 4 |
| **RPS4**     | Resistance to Pseudomonas syringae 4 |
| **RPW8**     | Resistance to powdery mildew 8 |
| **RRS1**     | Resistance to Ralstonia solanacearum 1 |
| **ROS** | Reactive oxygen species |
|---------|-------------------------|
| **SERK** | Somatic embryogenesis receptor kinase |
| **SOBIR1** | Suppressor of Bir 1-1 |
| **STAND** | Signal transduction ATPases with numerous domains |
| **TIR** | Toll/Interleukin-1 receptor |
| **TLR5** | Toll like receptor 5 |
| **TMV** | Tobacco mosaic virus |
| **UMP** | Uridine monophosphate |
| **WAKs** | Cell wall-associated kinase |
| **ZARI** | HopZ-activated resistance 1 |
Table 1: Structures of plant immune receptors, or their domains, covered in this review

| Receptor | Type (Cell-surface) | Plant host | Ligand | Ligand type | Co-receptor | PDB code | References |
|----------|---------------------|------------|--------|-------------|-------------|-----------|------------|
| FLS2     | LRR-RLK             | Arabidopsis thaliana | flg22  | MAMP        | BAK1        | 4MN8      | (261)      |
| PEPR1    | LRR-RLK             | Arabidopsis thaliana | Atpep  | DAMP        | BAK1        | 5GR8      | (14)       |
| CERK1    | LysM-RLK            | Arabidopsis thaliana | PGN    | MAMP        | LYM3/1      | 4EBY      | (11)       |
| SOBIR1   | LRR-RLK             | Arabidopsis thaliana | N/A    | N/A         | LRR-RLP, BAK1 | 6R1H      | (262)      |
| BIR3     | Pseudokinase        | Arabidopsis thaliana | N/A    | N/A         | BRI1/SEK1   | 6FG8      | (263)      |
| BIK1     | RLCK                | Arabidopsis thaliana | N/A    | N/A         | BAK1, FLS2  | 5TOS      | (123)      |
| CEBIP    | LysM-RLP            | Oryza sativa | chitin | MAMP        | OsCERK1     | 5JCD, 5JCE | (264)      |

| Receptor | Type (Intracellular) | Plant host | Ligand(s) | Ligand type | Co-receptor | PDB code | References |
|----------|----------------------|------------|-----------|-------------|-------------|-----------|------------|
| MLA10 CC | CC-NLR               | Hordeum vulgare | N/A      | N/A         | N/A         | 3QFL, 5T1Y | (265,266) |
| Pikp-1 HMA| CC-NLR              | Oryza sativa | AVR-PikD, AVR-PikE, AVR-PikA, AVR-Pia | MAX effector | Pikp-2      | 5A6W, 5A6P, 6G11, 6G10, 6Q76 | (12,177,257) |
| Pikm-1 HMA| CC-NLR              | Oryza sativa | AVR-PikE, AVR-PikA, AVR-PikD | MAX effector | Pikm-2      | 6FUB, 6FUD, 6F9U | (177) |
| Pia HMA  | CC-NLR               | Oryza sativa | Avr1-CO39 | MAX effector | RGA4        | 5ZNG, 5ZNE | (179) |
| RRS1 WRKY| TIR-NLR              | Arabidopsis thaliana | PopP2   | T3SE        | RPS4        | 5W3X      | (18)       |
| ZAR1     | CC-NLR               | Arabidopsis thaliana | Avr-AC   | T3SE        | RKS1        | 6J5T, 6J6l, 6J5W, 6J5V | (15,16) |
| RPS4 TIR | TIR-NLR              | Arabidopsis thaliana | N/A      | N/A         | RRS1        | 4C6T, 4C6R | (17)       |
| RRS1 TIR | TIR-NLR              | Arabidopsis thaliana | N/A      | N/A         | RPS4        | 4C6T,4C6S | (17)       |
| SNC1 TIR | TIR-NLR              | Arabidopsis thaliana | N/A      | N/A         | N/A         | 5TEC      | (202)      |
| SNC1 TIR | TIR-NLR              | Arabidopsis thaliana | N/A      | N/A         | N/A         | 5H3C      | (267)      |
| Sr33 CC  | CC-NLR               | Aegilops tauschii | N/A      | N/A         | N/A         | 2NCG      | (268)      |
| RPP1 TIR | TIR-NLR              | Arabidopsis thaliana | N/A      | N/A         | N/A         | 5TEB      | (202)      |
| NRC1 NB-ARC| TIR-NLR         | Solanum lycopersicum | N/A      | N/A         | N/A         | 6SP2      | (269)      |
| RUN1 TIR | TIR-NLR              | Vitis rotundifolia | N/A      | N/A         | N/A         | 600W      | (201)      |
| Rx CC    | CC-NLR               | Solanum tuberosum | N/A      | N/A         | RamGAP2     | 4M70      | (19)       |
| RPV1 TIR | TIR-NLR              | Vitis rotundifolia | N/A      | N/A         | N/A         | 5K7U      | (200)      |
| L6 TIR   | TIR-NLR              | Linum usitatissimum | N/A      | N/A         | 3OZI       | (199)      |
| Pto      | Kinase               | Solanum pimpinellifolium | AvrPtoB | T3SE        | Prf         | 3HGK      | (270)      |
Figures:

Figure 1

**Figure 1. Plant Immunity at a glance.** Left: Plants are the target of a variety of pathogens and pests that cause disease, via both their over ground and underground structures. Right: Pathogens/pests shed microbe-associated molecular patterns (MAMPs) or generate damage-associated molecular patterns (DAMPs) that can be received by receptors to initiate cell-surface immunity. Pathogens/pests can deliver effectors to the outside (not shown here for simplicity) or inside of cells where they can act on host systems to their benefit, including the suppression of signalling pathways downstream of cell-surface receptors. Effectors, or their activities, can be sensed by intracellular immune receptors (NLRs) to initiate intracellular immunity.
**Figure 2. Diversity of cell-surface immune receptors.** A schematic representation depicting domain architecture of different classes of plant RLKs/RLPs. ECD = Extracellular ligand binding domain, KD = Intracellular kinase domain. Surface representations are shown for those ECDs for which crystal structures are available. LRR type – crystal structure of the ECD of Arabidopsis RLK FLS2, PDB: 4MNA (green), LysM – crystal structure of the ECD of Arabidopsis RLK – CERK1, PDB: 4EBY (purple), Lectin – representative crystal structure of lectin domain of Phytohemagglutinin from *Phaseolus vulgaris*, PDB: 3WCR (yellow).
Figure 3. A mechanistic view of flg22 sensing by FLS2. Flg22 (light green) stabilises the heterodimerization of FLS2 (dark green, PDB: 4NMA, 4NM8) with BAK1 (purple, PDB: 3ULZ, 4NM8) (68,103,149). Ligand perception leads to activation and phosphorylation of BIK1 (orange, PDB: 5TOS) by BAK1 (113,117). Following phosphorylation, BIK1 is monoubiquitinated by the E3 ligases RHA3A/B. Monoubiquitinated BIK1 is then released from the FLS2–BAK1 complex and initiates ROS production and Ca2+ signalling through phosphorylation of plasma membrane-localised NADPH oxidases and cyclic nucleotide gated channels (137). Bi-directional arrow indicates that both BIK1 and BAK1 can transphosphorylate each other.
Figure 4. NLRs perceive effectors via distinct mechanisms and induce immune responses through different mechanisms. (A) Effector (purple) perception induces activation of the NLR (orange) via Direct binding. NLRs can indirectly perceive and respond to effectors by monitoring modifications of a physiologically relevant host target (Guardee, grey) or a molecular mimic that likely resulted via gene duplication and is now only involved in immune signalling (Decoy, blue). NLRs can directly perceive and respond to effectors via NLR integrated domains (blue), which likely have their evolutionary origin in ancestral host targets of effectors. (B) NLR singletons are able to initiate immune responses upon effector perception. Several sensor NLRs require downstream helper NLRs (green) to transduce effector perception into immune responses. NLRs can function in pairs or as part of interconnected networks.
Figure 5. Incorporation of host targets in NLRs leads to the evolution of NLR with integrated domains. NLRs (orange) can sense changes in host proteins (grey) that are targeted by pathogen effector molecules (purple) and initiate defence signalling. Over time, some of these host proteins can be found integrated into the NLRs core structure (blue), acting as the effector recognition domains for the NLR. Binding of an effector to the integrated domain of an NLR leads to initiation of defence responses.
**Figure 6. The activation of the ZAR1 immune receptor.** ZAR1 (orange) is an Arabidopsis CC-NLR that forms complexes with pseudokinases, including ZED1 and RKS1 (green), to perceive effector activity (271). The ZAR1:RKS1 receptor complex guards the receptor-like cytoplasmic decoy kinase PBL2. Following uridylylation of PBL2 by the *Xanthomonas campestris* effector protein AvrAC, PBL2\(^{pUMP}\) (purple) binds to RKS1, activating ZAR1. Activate ZAR1 is then able to oligomerise into a pentameric wheel with the CC domains each contributing their H1 helix (yellow) to form a funnel-like structure.
Figure 7. Alternative strategies for immune receptor engineering. (A) Plant immune receptors (orange/grey) bind natural variants of effector and ligands (purple/cyan/yellow) with different binding affinities (schematically depicted by the height of the coloured bars). Only some binding events are of sufficient level to reach an activation threshold (represented by the dashed line), triggering immune responses. (B) Mutations in the receptor (grey to blue) can extend pathogen recognition by gaining or increasing binding to effectors and ligands, leading to immune responses to pathogens previously undetected. (C) Mutations in the immune receptors (orange to green) can lower the activation threshold, allowing for increased intensity of immune signalling. (D) The combination of both mutations (green/blue receptor) that enhance recognition and immune responses can lead to wider and increased immune responses to effectors and ligands.
A molecular roadmap to the plant immune system
Adam R Bentham, Juan Carlos De la Concepcion, Nitika Mukhi, Rafal Zdrzalek, Markus Draeger, Danylo Gorenkin, Richard K. Hughes and Mark J. Banfield

J. Biol. Chem. published online August 17, 2020

Access the most updated version of this article at doi: 10.1074/jbc.REV120.010852

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts