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STATE-OF-THE-ART REVIEW

The emerging frontier of plant immunity's core hubs

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The ever-growing world population, increasingly frequent extreme weather events and conditions, emergence of novel devastating crop pathogens and the social strive for quality food products represent a huge challenge for current and future agricultural production systems. To address these challenges and find realistic solutions, it is becoming more important by the day to understand the complex interactions between plants and the environment, mainly the associated organisms, but in particular pathogens. In the past several years, research in the fields of plant pathology and plant–microbe interactions has enabled tremendous progress in understanding how certain receptor-based plant innate immune systems function to successfully prevent infections and diseases. In this review, we highlight and discuss some of these new ground-breaking discoveries and point out strategies of how pathogens counteract the function of important core convergence hubs of the plant immune system. For practical reasons, we specifically place emphasis on potential applications that can be detracted by such discoveries and what challenges the future of agriculture has to face, but also how these challenges could be tackled.

Introduction

Food production must be doubled by 2050 to meet the global demand with current projections, which becomes even more challenging with the accelerated rate of climate change that is expected to severely affect food production cycles [1]. Historical precedents of pathogen-derived famines are well known, and

Abbreviations
CEA, controlled environment agriculture; D/PAMP, damage- or pathogen-associated pattern; ETI, effector-triggered immunity; ETS, effector-triggered susceptibility; MAPK, mitogen-activated protein kinase; NLR, nucleotide-binding Leucine-rich repeat receptor; PRR, pattern-recognition receptor; PTI, PAMP-triggered immunity; RLK, receptor-like kinases; RLP, receptor-like protein.

bound to happen again if there are no safety measures in place [2,3]. Droughts, high temperatures, frosts, floods and other extreme weather phenomena in agriculturally sensitive regions are expected to alter the dynamics of plant-pathogen interactions and pose serious new challenges for agriculture [4]. Despite the grim challenges ahead, recent discoveries hold a lot of promise, however, only if they are effectively utilized in the field and greenhouses. Thus, the real challenge in the coming years is finding the best way to translate fundamental plant pathology research into practical applications for agriculture in real field conditions. A focal point of recent discoveries is the intersection of different types of plant immune responses and addressing some of them in this review on a wider context may hold one of the main keys for developing useful agricultural applications for the future. However, it is becoming an increasing necessity for scientists to reach out to as many specialists and non-specialists, so that they can utilize effectively and quickly new knowledge and concepts. Towards this end, this review touches on a wider range of concepts and references, without analysing them, which are necessary to place this new knowledge on a wider context for the non-specialists.

Plant pathogens use a large repertoire of molecules for inducing a successful infection and proliferation through their host plant [5]. Simultaneously, these molecules can also enable the host plant to recognize the invading pathogen and activate various levels of immune responses that have been eloquently defined in the 'Zig-Zag' model, which is a dynamic interplay between plant pathogens and their host plants, driving the evolution of both pathogenicity and defence response [6]. Typically, plants activate their first level of receptor-based defence through recognition of pathogen- or damage-associated molecular patterns (PAMPs or DAMPs, respectively) by pattern-recognition receptors (PRRs; Fig. 1) [7,8]. Pattern-recognition receptor activation triggers an immune response, which is generally referred to as PAMP-Triggered Immunity (PTI) [6]. Although PTI can restrict most pathogen invasions, adapted pathogens have evolved virulence proteins, called effectors, which can successfully suppress PTI and induce Effector-Triggered Susceptibility (ETS) [9,10]. In response, plants evolved a second level of defence that relies primarily on direct or indirect recognition of effectors by intracellular Nucleotide-binding Leucine-rich repeat Receptors (NLRs) and activate a stronger, more robust immune response, known as Effector-Triggered Immunity (ETI; Fig. 1) [6].

Both PRRs and NLRs activate a series of signalling events, which were often regarded as systems that functioned separately from one another, but an ever-growing number of recent studies shows that they share common cellular components and defence mechanisms, such as production of reactive oxygen species (ROS), initiation of calcium ion (Ca^{2+}) influx, mitogen-activated protein kinase (MAPK) activation and transcriptional reprogramming among others (Fig. 1) [11,12]. Mutual interdependencies between PRR- and NLR-mediated immunity, as well as the notion that ETI is potentiating an already activated PTI, have been shown in recent studies [11,13]. Pinpointing and analysing the critical intersections in this plant immunity crosstalk is vital for future development of agricultural applications such as the (a) designing of artificial resistance (*R*) genes [14], (b) selection of *R* genes with an optimal cost-to-fitness balance [15,16], (c) targeting susceptibility host genes via CRISPR-Cas9 technology [17], (d) creating enhanced molecular diagnostic tools [18,19], (e) developing advanced crop protection applications [20], (f) delivering the right genomic sequences of host- and pathogen-specific defence-related genes into cells without transforming them [21] and (g) breeding or engineering crops/microbes for manipulating the natural microbiome to ward off pathogens [22,23].

In this review, we would like to highlight the latest developments in plant immunity with an emphasis on the similarity between PRR- and NLR- mediated defence responses, their core convergence hubs that are being exploited by pathogens and discuss which factors will influence the possible strategies and emerging applications that can be extrapolated from such knowledge in the future to stave off crop losses and ensure global food security.

PRR-mediated immunity—resistance initiated at the cell surface

Recognition of extracellular non-self or damage-associated molecules is mediated by PRRs: multi-domain proteins with an N-terminal extracellular ligand-binding domain, a central single-pass transmembrane domain, and either an intracellular kinase domain, in the case of Receptor-Like Kinases (RLKs), or a short cytosolic tail, as found in Receptor-Like Proteins (RLPs; Fig. 2) [7,8]. The extracellular domain of PRRs determines the ligand-binding specificity and can be a leucine-rich repeat (LRR) domain, a lysin motif (LysM), or a lectin-like motif among others [7]. LRR-containing PRRs typically bind peptides or proteins, such as the *Arabidopsis thaliana* (hereafter Arabidopsis) LRR-RLKs Flagellin Sensitive 2 (FLS2) and EF-TU Receptor (EFR) that perceive conserved

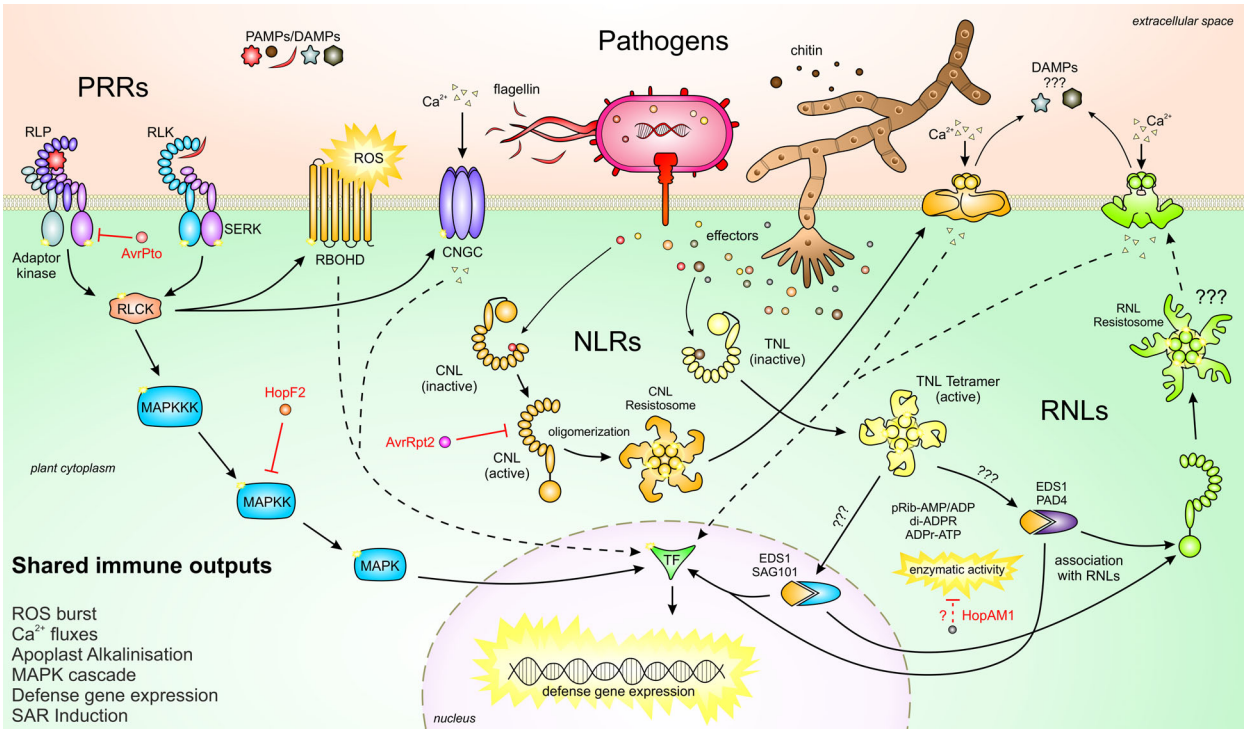

Fig. 1. Principles of plant receptor-based innate immune signalling and effector-mediated inhibition of signalling components. Pathogen-recognition receptors (PRRs)-mediated immunity (PTI): Receptor-Like-Kinases (RLK) and -proteins (RLP) are bind Pathogen-Associated-Molecular- or Danger-Associated-Molecular-Patterns (PAMPs/DAMPs) present in the extracellular space during pathogen infections. Ligand (PAMP/DAMP) binding enables recruitment of the SERK co-receptor, followed by trans- and auto-phosphorylations (yellow stars) of the receptors kinase domains, which leads to the initiation of the PRR-triggered-immune signalling cascade: Phosphorylation of Receptor-Like-Cytoplasmic-Kinases (RLCKs), activation of RBOHD and CNGCs to induce the Reactive-oxygen-species (ROS) burst and calcium influx, phosphorylation of the MAP kinase signalling pathway, and finally initiation of the transcriptional reprograming through the activation of transcription factors (TF) to induce defence gene expression. Pathogen-derived effector proteins (in red letters) can target the PRR-mediated immune response at different components. AvrPto inhibits PRR signalling directly at the LRR-RLK kinase domains and HopF2 can block MAPK activity. Nucleotide-binding leucine-rich repeat (NLRs)-mediated immunity (ETI): sensor NLRs of the coiled-coil NLR (CNL) and Toll-/Interleukin-1 receptor NLR (TNL) family perceive the presence or activity of pathogen-derived intracellular effectors, which enables their oligomerization and activation. CNLs form a wheel-like pentameric resistosome that translocate to the plasma membrane to facilitate calcium influx, required for cell death and resistance induction. TNL tetramerization results in the activation of the N-terminal TIR domain embedded enzymatic NADase and ADPR polymerase-like activity. The TNL catalysed products pRib-AMP/ADP, di-ADPR and ADPR-ATP initiate association of the EDS1-PAD4/SAG101 heterodimers with RNLs. Formation of this signalling hub is required for activation of defence gene expression and resistance. If association of RNLs with EDS1-PAD4/SAG101 heterodimers is required for RNL cell death activity is currently unclear. However, RNL activation leads to self-association and the formation of oligomeric complexes, potentially resistosomes (exact number of monomers in there is unknown) at the plasma membrane, which is required for calcium influx and cell death initiation. NLR function is also inhibited by pathogen effector activity. The bacterial effector AvrRpt2 was shown to indirectly block activation of a specific CNL and bacterial HopAM1 interferes with downstream enzymatic processes of TNLs to promote virulence. Immune responses initiated by both PRRs and NLRs are indicated by 'shared immune outputs' on the lower left corner. Solid lines/arrows indicate experimentally demonstrated signalling pathways and events, whereas dashed lines indicate not experimentally proven processes.

regions of bacterial flagellin or elongation factor EF-Tu, respectively [24–26]. LysM-type RLKs like the co-receptor Chitin Elicitor Receptor Kinase 1 (CERK1) can bind carbohydrate-based ligands, such as fungal chitin or bacterial peptidoglycan [27,28]. An example of a lectin-like PRR is Lipooligosaccheride-Specific Reduced Elicitation (LORE) that can perceive bacterial 3-hydroxy fatty acids [29]. Given the huge number of RLKs and RLPs in plants and their highly variable ligand-binding domains [30], PRRs can recognize a diverse range of PAMPs and DAMPs, effectively combating most non- or maladapted pathogens [6,7]. Intriguingly, these receptors can also be easily transferred between different species and demonstrated

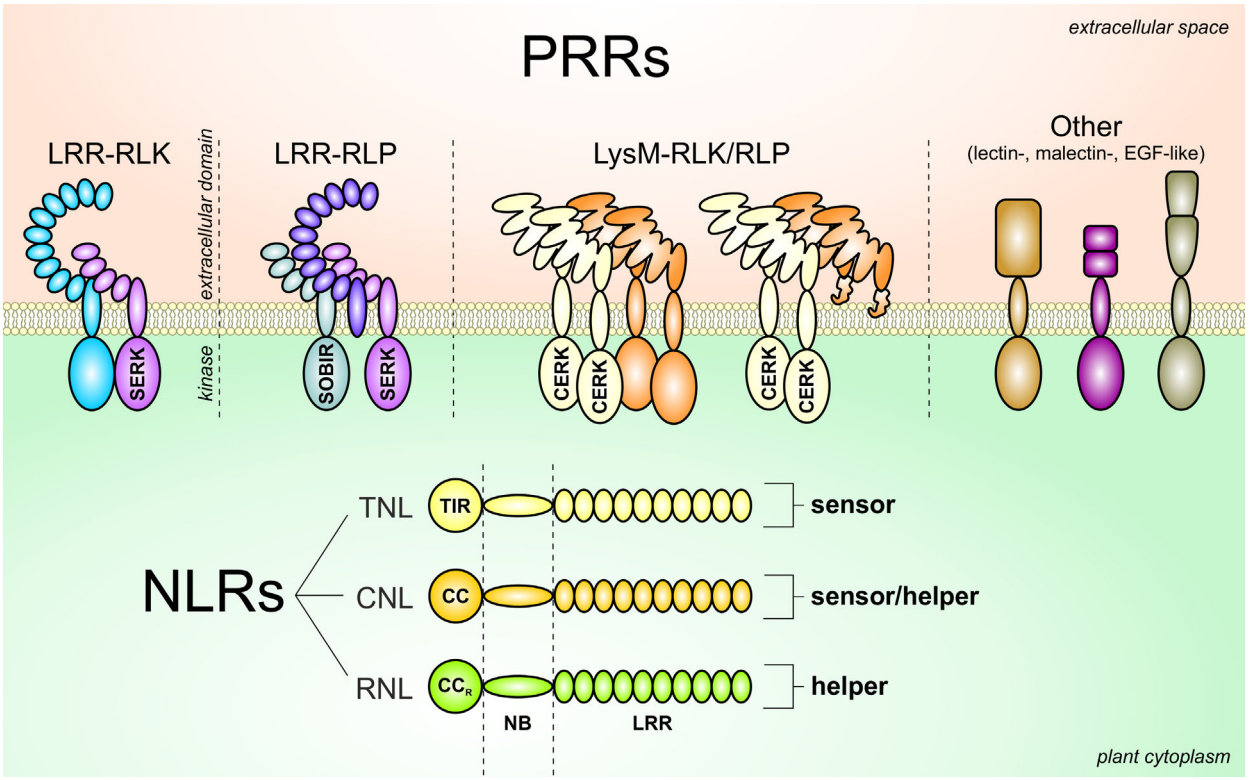

Fig. 2. Domain structure of plant extracellular and intracellular immune receptors. Pattern-recognition receptors (PRRs) are either Receptor-like kinases (RLKs) or Receptor-like proteins (RLPs) and can have various extracellular ligand-binding domains: leucin-rich-repeat (LRR), lysin motif (LysM), lectin-, malectin- or epidermal-growth-factor-like domain. RLKs have an intracellular kinase domain that is missing in RLPs. Most LRR-RLKs and LRR-RLPs associate in a ligand-dependent manner with a LRR-RLK co-receptor of the SERK family. LysM-RLKs and -RLPs signalling require the ligand-binding induced association with another LysM-RLK type receptor CERK1. LysM-RLPs lack a single-pass transmembrane domain and are attached to the outer plasma membrane leaflet by a GPI-anchor. Nucleotide-binding-LRR receptors (NLRs) are multidomain proteins, with a C-terminal LRR domain, a central nucleotide-binding domain and a varying N-terminal domain. TNLs have a Toll/Interleukin 1 receptor (TIR), CNLs a coiled-coil (CC) and RNLs a RPW8-like CC (CC-R) domain. Most TNLs and CNLs are effector sensors, whereas RNLs are required for sensor NLR-mediated immunity and considered as helper NLRs.

to be a promising strategy to engineer broad-spectrum and durable disease resistance in economically important crops [31,32]. The most famous example is the Arabidopsis EFR that can induce or enhance bacterial resistance in a range of plant species, which includes tomato, potato, apple, sweet orange, or even rice, if genetically engineered into these plants [33–38].

PRR activation—formation of heteromeric receptor signalling complexes

The activation and downstream signalling of different types of PRRs is thought to be governed by a similar (molecular) mechanism. So far, all characterized PRRs perceive their corresponding ligands through their extracellular ligand-binding domains [39,40], and upon ligand binding, these PRRs associate with co-receptors to initiate and activate PTI responses (Fig. 1). LRR-RLKs that belong to the Somatic-Embryogenesis Receptor-Like Kinase (SERK) family are common co-receptors shared by many LRR-type PRRs [41] and considered to act as common convergence points for multiple RLK-signalling networks, which are not only involved in plant immunity, but also in growth and development [41]. In Arabidopsis, Brassinosteroid Insensitive 1 (BRI1)-Associated Receptor Kinase 1 (BAK1/SERK3) and BAK1-Like 1 (BKK1/SERK4) are important members of this family [41–45]. BKK1 and its closest paralog BAK1 share common functions in (a) brassinosteroid signalling [46–48], (b) FLS2-, EFR-, and Perception of the Arabidopsis Danger Signal Peptide 1 or 2 (PEPR1/2)-mediated immune signalling [49], (c) Haesa- and Haesa-Like 2-mediated floral organ abscission [50], and (d) (auto-)immunity-associated cell death control [47,51]. Genetic data demonstrated *BAK1* as the major SERK in

brassinosteroid and immune signalling, as *bak1* mutants displayed impaired brassinosteroid and immune phenotypes that were not detectable in a *bkk1* mutant [47,49,52]. BKK1's contribution was only observed in the absence of BAK1, as *bak1 bkk1* mutants showed an enhanced phenotype compared to either single mutants. This suggests there is either a mechanistic regulation that prioritizes interaction of RLKs with BAK1 over BKK1 or that BAK1 and BKK1 have different specificities for the activated downstream signalling components.

BAK1 and BKK1 have also been described as redundant negative regulators of cell death, as simultaneous loss-of-function results in a cell death/lesion-mimicking phenotype reminiscent of NLR-mediated autoimmunity [47,51]. Interestingly, the *bak1 bkk1*-induced autoimmune phenotype was indeed linked to NLR-mediated signalling. Genetic loss of a certain NLR subfamily significantly suppressed the *bak1 bkk1* cell death phenotype [51], highlighting an interconnection of PRR- and NLR-mediated immune signalling pathways.

Formation of the PRR/co-receptor core complex leads to a series of auto- and/or trans-phosphorylation events [40,53–55] that, in the case of RLPs, are mediated by a constitutively associated 'adaptor' kinase [56–58]. These RLP/adaptor kinase complexes are considered to act equivalently to ligand-binding RLKs [57], albeit they induce both overlapping and distinct immune outputs [59], which suggests that RLK- and RLP-mediated signalling may activate different downstream components, at least partially [12]. To translate ligand binding into downstream responses, PRR/co-receptor complexes phosphorylate receptor-like cytoplasmic kinases (RLCKs) [60–62]. The RLCK Botrytis-Induced Kinase 1 (BIK1) interacts with FLS2 and EFR, and promotes their triggered immune responses [60,63]. In FLS2-mediated immunity, it was shown that following ligand binding, BAK1 directly phosphorylates BIK1 and thereby causes dissociation of BIK1 from FLS2, activating downstream signalling [60,63,64]. Upon activation, BIK1 phosphorylates the NADPH oxidase Respiratory burst oxidase homologue protein D (RbohD), promoting ROS production [65,66]. ROS can function as a secondary messenger by inducing the expression of genes involved in defence and stomatal closure, whose role is to restrict pathogen growth and entry [67,68]. Activated BIK1 also phosphorylates and activates Ca^{2+}-permeable cyclic nucleotide-gated channels (CNGCs), ion channels of the reduced hyperosmolality-induced [Ca^{2+}] increase/Transmembrane Protein 63 (OSCA/TMEM63) family and also glutamate receptor-like channels (GLRs) to trigger Ca^{2+} (or other ion) influx upon pathogen perception [69–73]. Just like ROS, Ca^{2+} further induces immune responses, such as defence gene expression and stomatal closure [69,71]. There is also some evidence indicating a mutual interplay between Ca^{2+} and ROS signalling during FLS2-mediated responses [74]. A full Ca^{2+} response/signal is required for proper ROS production and ROS-signalling, whereas ROS production has only a partial effect on the Ca^{2+} signal, but is required for a substantial calcium signalling/response during PTI. RLCKs are also linked to the activation of MAPKs [61,62], which translate endogenous and exogenous signals perceived by PRRs via phosphorylation cascades into downstream responses, such as transcriptional defence gene activation, ethylene and phytoalexin biosynthesis, stomatal closure, and eventually pathogen resistance [75]. The importance of RLCK and MAPK signalling during plant immunity is emphasized by the fact that many of these proteins are targeted by a diverse set of pathogen-derived effectors, as discussed in more detail below [5,76,77].

Although many responses induced by RLPs are similar to those of LRR-RLKs', they can differ in timing, amplitude and output [59]. For example, activation of RLP23 results in the production of the phytoalexin camalexin, which is not produced upon activation of LRR-RLKs [69]. Functionally homologous RLPs that recognize the same fungal effector, such as the convergently evolved tomato *Cf*-Ecp5s, appear to induce different responses in terms of timing and strength of the immune response and expression induction of downstream genes required for defence [78]. BIK1 was shown to play a negative regulatory role in RLP-mediated immunity and a positive during RLK signalling [59]. In contrast, the RLCKs PBL31 and, to a lesser extent, PBL30 have been shown to be positive regulators of LRR-RLP immune signalling [12]. Thus, it is plausible that the differences in RLP versus RLK signal-outputs may result from recruiting specific RLCKs and activating different downstream signalling components by these RLCKs.

Suppression of PRR-mediated immunity by pathogen-derived intracellular effectors

To overcome PRR-mediated immune responses, pathogens utilize effector proteins that target critical components of the plant innate immune signalling cascade, including PRRs, RLCKs, and many other proteins [6]. Comprehensive studies have already elucidated the role of effector proteins in enhancing pathogen virulence, mainly in interactions between

plants and pathogenic bacteria [5,77,79]. The specialized secretion systems are vital determinants for the virulence of many Gram-negative phytopathogenic bacteria, and their type III secretion system (T3SS) facilitates pathogen colonization and proliferation in host plants [77]. Here, we mainly discuss the role of bacterial type III effectors that target signalling components of PTI, including PRRs, RLCKs and MAPKs.

Pseudomonas syringae type III effector AvrPto interacts with the cytoplasmic kinase domain of PRRs FLS2 and EFR, interfering with PTI by inhibiting phosphorylation of FLS2 and EFR (Fig. 1) [80–82]. *Pseudomonas syringae* type III effector HopAO1 functions as a phosphatase that reduces tyrosine phosphorylation at Y836 residue of EFR sufficient for immune activation upon recognizing bacterial elf18 peptide from EF-Tu. In addition, HopAO1 also targets the cytoplasmic kinase domain of FLS2, dampening flg22-triggered FLS2 activation. However, the detailed molecular mechanism is still elusive [83,84]. The co-receptor BAK1 is also a target of the structurally unrelated AvrPto and HopF2 bacterial effector proteins. *Pseudomonas syringae* AvrPtoB was shown to hinder FLS2-BAK1 complex formation, thereby inhibiting PTI activation upon flg22 recognition [82,85,86]. AvrPtoB suppression of PRR-triggered responses is mediated by the activity of its C-terminal E3 ligase domain, leading to degradation of FLS2 via the 26S proteasomal degradation pathway. AvrPtoB also binds to BAK1, inhibiting its kinase activity, and thereby suppressing BAK1 function [80,87,88].

Many bacterial type III effectors have been described to directly associate with RLCKs and modify their essential function during an immune response [60,61]. The spatio-temporal protein dynamics of the well-studied RLCK BIK1 in the ligand-triggered FLS2-BAK1 protein complexes is critical to facilitate FLS2-induced PTI signalling [59,63,65]. Two bacterial type III effectors, AvrPphB from *P. syringae* and AvrAC from *Xanthomonas campestris* pv. *campestris* (*Xcc*), are known to target and dampen BIK1 function. AvrPphB, a cysteine protease, interacts with BIK1 and cleaves it, thereby leading to the interference of RLK-mediated immune responses [60,89]. Additional RLCK VII subfamily proteins PBS1 and PBS1-like (PBL) proteins are also cleaved by AvrPphB, including RIPK, a key-component required for the phosphorylation of the small immune regulatory protein RIN4 [60,90–92]. The uridylyl-transferase AvrAC uridylates BIK1 by UMP modification at conserved S236 and S237 phosphorylation sites of the activation loop. AvrAC also interacts and uridylates other RLCK VII subfamily members including RIPK and PBL2 [93,94], known to be also involved in NLR-mediated immunity [95,96].

Type III effector proteins can also repress PTI responses by specific biochemical modulation of PTI-associated MAPKs. The ADP-ribosyl-transferase HopF2 of *P. syringae* inhibits PTI activation by interacting with MPK6, MKK5 and other MAP2Ks (Fig. 1) [86,97]. HopAI1 interacts with MAPKs such as MPK3, MPK4 and MPK6, suppressing their kinase activities with a putative phosphothreonine lyase activity that leads to dephosphorylation of phosphothreonine residues in MPK3, MPK4 and MPK6 [98–100]. Different from the dephosphorylation activity of HopAI1, *P. syringae* type III effector AvrB induces phosphorylation of MPK4 and RIN4, thereby increasing negative regulation of immunity (PTI) and thus the susceptibility of host plants [91,101,102].

Taken together, bacterial type III effectors have evolved to diminish host PRR-mediated responses by modulating PRR-induced signalling cascades by directly targeting PRRs, RLCKs and MAPKs and thereby promoting pathogen virulence activity. Thus, understanding the function and mode of action of effector proteins is necessary for sustainable plant/crop protection.

NLR-mediated resistance—an intracellular triggered augmentation of immunity

Pathogens use their rapidly evolving effectors to cause disease, facilitate pathogen proliferation and dispersion in susceptible hosts. However, in resistant hosts effectors or effector function can be recognized, often inducing a stronger immune response than PRR-induced immunity. The countervailing assumption is that during a natural infection, ETI is a potentiation of the, albeit effector-suppressed, already initiated PRR-induced immune response. Historically, when defence signalling pathways were analysed, the immune outputs triggered by NLRs were often thought to be qualitatively distinct and separated from PRR-mediated immunity, but mostly only for the sake of simplicity. However, recent findings confirmed that there is extensive crosstalk between the two systems, leading to a mutual potentiation and interdependency [13,103–105], which reveal the inseparable nature of these two systems.

Perception of intracellular pathogen effectors is mainly driven by immune receptors of the NLR protein family. NLR-mediated immune responses are often associated with a localized cell death, the

hypersensitive response (HR) at infection sites [106], and historically termed as ETI (Fig. 1) [6,107]. *NLR* genes, and also LRR-RLP encoding genes, are evolutionary very dynamic with complex genomic variations, including presence/absence polymorphisms or sequence and copy number variations and they are often located in variably sized clusters and regions of balancing selection throughout the genome [12,108]. This grants an evolutionary advantage, ensuring that the plant immune system keeps up with the rapidly evolving pathogenic effectors. NLRs are modular proteins consisting of a variable N-terminal domain, followed by a central nucleotide-binding (NB) domain and a C-terminal LRR domain (Fig. 2) [107]. Plant NLRs can be sub-grouped into three classes based on their N-terminal domains: (a) Toll-like/Interleukin 1 receptor (TIR)-type NLRs (TNLs), (b) coiled-coil (CC)-type NLRs (CNLs) and (c) Resistance to Powdery Mildew 8 (RPW8) coiled-coil (CC-R)-type NLRs (RNLs) [109], and functionally into effector sensing NLRs (sensor NLRs) and helper NLRs, required downstream of sensor NLRs.

Helper NLRs—PRR and NLR signalling nodes

While all characterized TNLs and most CNLs function as effector sensors, a small, conserved, and phylogenetically distinct RNL subclass is required downstream of many effector-perceiving snensor NLRs (Fig. 1) [109–116]. RNLs are thus also referred to as helper NLRs [110], and are represented by two subgroups: the Activated Disease Resistance 1 (ADR1) and N Required Gene 1 (NRG1) families that have been demonstrated to function in an unequal redundant manner in Arabidopsis and *Nicotiana benthamiana* [116–118]. An important and predominant role of ADR1s is the activation of pathogen-induced salicylic acid (SA) biosynthesis (a phytohormone produced upon infection of and required for defence against biotrophic and hemibiotrophic pathogens), initiation of SA-related pathways and transcriptional reprogramming of defence genes in basal immunity and upon effector recognition by TNLs, and to some extent CNLs [110,118]. NRG1s, however, are essential for cell death induction downstream of most TNLs in Arabidopsis and all tested TNLs in *N. benthamiana*, but they can take over ADR1s' function in an Arabidopsis *adr1s* null mutant [118]. These findings and the conservation of *ADR1s* in all seed plants (*NRG1s* are either absent or appear to have been lost in monocot genomes) suggest a broader function for ADR1s during plant immunity and not only downstream of sensor NLRs [109,119]. Furthermore, recent data demonstrated that the two RNL subgroups operate separately from each other, in complex with important regulators of basal and TNL-mediated immunity—the plant-specific lipase-like proteins Enhanced Disease Susceptibility 1 (EDS1), Phytoalexin Deficient 4 (PAD4) and Senescence-Associated Gene 101 (SAG101) [120,121]. Effector-activated TNLs induce the association of ADR1s and NRG1s into specific complexes with EDS1 and PAD4 or EDS1 and SAG101 to trigger disease resistance and to activate the HR-like cell death, respectively [122,123]. PAD4 and SAG101 form mutually exclusive complexes with EDS1. Thus, the RNL-EDS1-PAD4/SAG101 immune modules are functionally not interchangeable, as shown by elegant genetic analysis of combinatorial mutants of *EDS1* and *RNL* family members [120,121]. A potential molecular mechanism regulating and determining the formation of the specific modules during ETI has recently been suggested. Small signalling molecules, produced by activated TIR-domains or TNLs (see below and Figs 1 and 3), determine which EDS1-heteromere will be triggered and thus, which RNL subgroup will be recruited and potentially activated [124,125].

The EDS1-PAD4-ADR1s immune module was recently demonstrated to be also required for LRR-RLP-triggered immune responses in Arabidopsis (Fig. 4) [12,126]. A ligand-independent association of RLP23 with the EDS1-PAD4-ADR1 module components, mediated by the adapter kinase Suppressor Of BAK1-Interacting Receptor-like Kinase 1 (SOBIR1), was required for full PTI. This PTI function of RNLs and the EDS1 complexe is potentially specific to Arabidopsis or *Brassicaceae*, as CRISPR/Cas-generated *EDS1* and *RNL* family mutants of *N. benthamiana* were not significantly impaired in PRR signalling [127]. Here, another helper NLR family, the NLR Required for Cell Death (NRC) proteins, identified in all solanaceous plant species, could mediate such a function. NRCs are canonical CNLs and are also required for immune signalling downstream of multiple sensor CNLs, which are phylogenetically related to NRCs [128–130]. NRCs form an NLR immune network with redundant signalling nodes, but also some degree of specificity towards their sensor NLRs [129,131]. Interestingly, NRCs have indeed been reported to be required for immune and cell death signalling downstream of some PRR receptors (Fig. 4). Thus, helper NLRs seem to have evolved or co-opted a function to connect cell surface and intracellular immune receptor networks also in solanaceous plants [128,132–134]. This is supported by the finding that the well-conserved NRC3 helper NLR was shown to be required for the LRR-RLP *Cf*-4-mediated cell death [133].

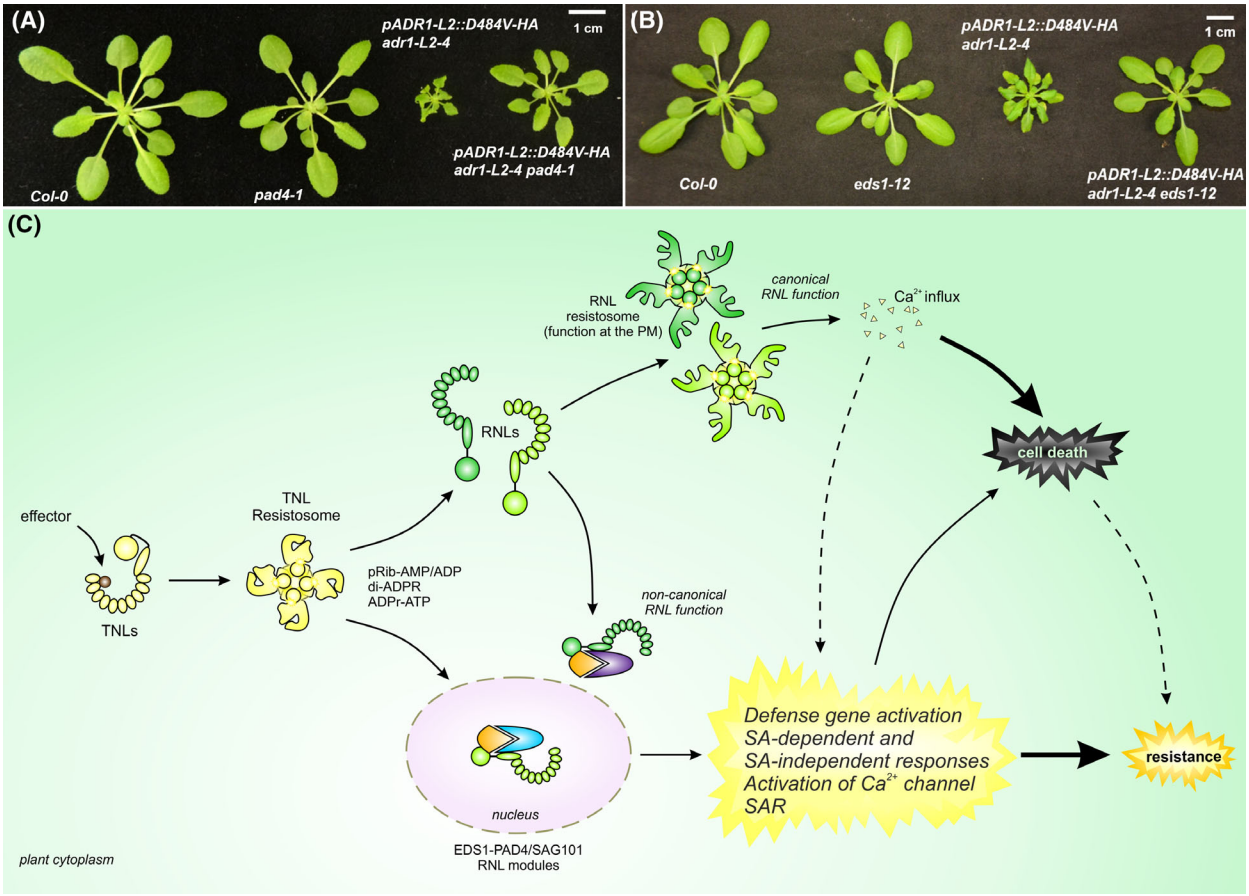

Fig. 3. Discrepancies of the dependency of autoactive and TNL-mediated activation of RNLs on the EDS1-PAD4 heterodimer may indicate an alternative TNL-mediated immunity activation model. (A) and (B) The autoimmune phenotype of *Arabidopsis thaliana* plants expressing an autoactive mutant ADR1-L2 (D484V) helper NLR (RNL) is strongly suppressed in *pad4-1* and *eds1-12* mutants. This suggests that activated Arabidopsis RNLs, at least ADR1-L2, require ESD1-PAD4-heterodimers for proper (auto-) immune signalling. (C) Hypothetical model of TNL-mediated RNL and EDS1-PAD4/SAG101 activation. TNL resistosome enzymatic activity (NADase, ADPR polymerase-like) induces monomeric RNLs to oligomerize into RNL resistosomes that mediate calcium (Ca^{2+}) influx to initiate a cell death response (canonical RNL function). Simultaneously, the TNL catalysed signalling moleculs induces association of the EDS1-PAD4/SAG101 heterodimers with monomeric RNLs to activate various defence responses that are also required for full cell death initiation and proper resistance (non-canonical RNL function).

The most obvious advantage of such a redundant (NLR) immune signalling network is its ability to maintain robustness and competence to adequately respond to rapidly evolving pathogens. Thus, it is not surprising that convergently evolved pathogen effectors have been identified to suppress NRC activities through different mechanisms [135], while others can potentially target the central key protein EDS1 [136–138], counteracting central nodes of both NLR- and PRR-mediated immunity.

Oligomerization into resistosomes—a prerequisite for NLR activity

Direct effector binding to NLRs, sensing of effector-mediated modifications or hetero-incompatibility-induced alterations of NLR guarded proteins, and mutations in the NLR NB domain, result in intramolecular conformational changes that can all trigger NLR oligomerization and eventually activation, thereby initiating (auto-)immune signalling [139–144]. NLR activation is also linked to the exchange of ADP by (d)ATP in their NB domain [141]. However, not all NLRs may require ATP binding for their immune function [110,143]. NLR oligomerization leads to the self-association of their N-terminal domains, which are considered to be the 'signalling domains', as overexpression of several TIR, CC and CC-R domains has been shown to be sufficient to trigger cell death [145,146]. Recently, ground-breaking cryo-EM structural studies of four full-length plant NLRs revealed the formation of the so-called resistosomes, following

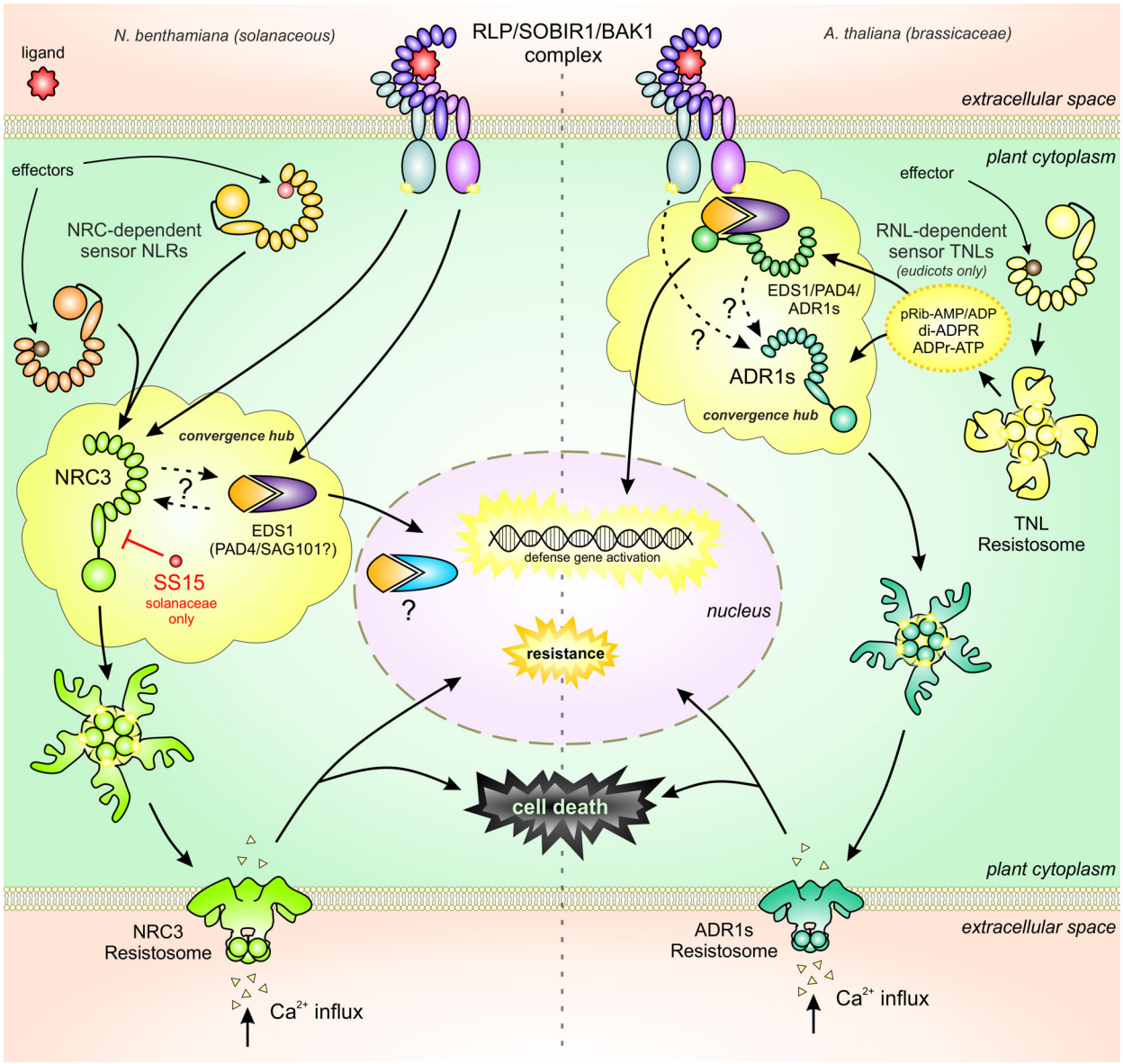

Fig. 4. Convergence hubs of PRR- and NLR-mediated immune signalling. Recognition of extracellular effectors or infection associated molecules (ligands) by RLPs requires the SOBIR1 and BAK1 co-receptors, core components of PRR-mediated immunity, in both *N. benthamiana* and Arabidopsis. Immune activation (cell death and resistance) by the RLP/SOBIR1/BAK1 complex is mediated by an intracellular core convergent hub consisting of the helper NLR NRC3 and EDS1 in *N. benthamiana* (left) and the EDS1/PAD4-heterodimer and associated RNLs of the ADR1 family in Arabidopsis (right). Both helper NLRs, the NRCs and the ADR1s are also required for sensor NLR-mediated immunity – NRC-dependent sensor NLRs and RNL-dependent sensor NLRs in *N. benthamiana* and Arabidopsis, respectively. If the other two lipase-like proteins PAD4 and SAG101 are also involved in RLP signalling in *N. benthamiana* and whether there is cooperation between NRCs and EDS1 proteins occurring is not known. NRC function in solanaceous plants is inhibited by the presence of the cyst nematode effector SPRYSEC15 (SS15). RNL-dependent sensor TNLs are only found in eudicots.

effector recognition [141–143,147,148]. The Arabidopsis CNL HopZ-Activated Resistance 1 (ZAR1) interacts with the RLCK Resistance-Related Kinase 1 (RSK1) and this ZAR1-RSK1 complex recognizes and binds the effector-uridylated RLCK PBL2 to form a pentameric wheel-like structure, the ZAR1 resistosome. In this resistosome, the very N-terminal α-helices of the five CC domains are exposed and fold into a funnel-shaped structure that is required for membrane association, cell death induction, and resistance against *Xcc* [141]. A follow-up study, with a strong focus on elucidating the molecular mechanism

of the ZAR1 resistosome function, convincingly demonstrated the formation of a cation-selective and Ca^{2+}-permeable channel at the plasma membrane, essential for the activation of plant immune responses (Fig. 1) [149].

In contrast to the Arabidopsis CNL ZAR1, the *N. benthamiana* TNL Recognition of XopQ 1 (Roq1) and the Arabidopsis TNL Recognition of *Peronospora parasitica 1* (RPP1), both lacking a CC domain, form a tetrameric resistosome when activated by their cognate effectors Xanthomonas outer protein Q (XopQ) and *Hyaloperonospora arabidopsidis* ATR1, respectively [142,143]. TNL tetramerization brings the TIR domains into close proximity and results in the formation of a holoenzyme capable of catalysing small molecules, which can act as ligands for the preformed EDS1/SAG101 or EDS1/PAD4 immune regulators. Binding of these specific ligands to either EDS1/SAG101 or EDS1/PAD4 induces conformational changes in SAG101 or PAD4 and results in the recruitment of NRG1s or ADR1s, respectively (Fig. 1) [124,125].

But how is the activity of TNLs or their TIR domains inducing cell death? A recently published study presented structural evidence that the CC-R domain shares similarity with the N-terminal 4-helix bundle of the mammalian and plant Mixed Lineage-Kinase domain-Like (MLKL) protein and the ZAR1 CC domain [113,144,150]. Through a structure–function analysis and cell biology experiments of autoactivated RNLs (mainly NRG1.1 and ADR1), an oligomerization and also cation-selective channel function of RNLs at the plasma membrane was demonstrated (Fig. 1) [144,151]. Expression of activated RNLs leads to Ca^{2+} influx in a human cell line, as *in planta*, suggesting that RNL-mediated Ca^{2+} influx is a prerequisite for cell death induction and independent of any other plant proteins. So most likely the TNL-triggered recruitment of RNLs to the preformed EDS1/PAD4 or EDS1/SAG101 complexes activates the RNL and leads to formation of RNL resistosomes initiating cell death and resistance. Thus, regulation of ion homeostasis could be a conserved mechanism among NLRs (CNLs and TNLs activating RNLs) to induce defence responses.

Cell death and resistance signalling of TIR domains or full-length activated TNLs requires the presence of EDS1-PAD4/SAG101 heterodimers and RNLs. However, cell death initiated by CC-R domains or autoactive Arabidopsis RNLs in *N. benthamiana* does not appear to require *NbEDS1* [116,144,152,153]. Thus, EDS1 function can be placed downstream of TNLs and upstream of RNLs (Fig. 1). Interestingly, the autoimmune phenotype of Arabidopsis plants, stably expressing an autoactive mutant ADR1-L2 protein, is strongly suppressed in *pad4* or *eds1* mutants (Fig. 3A, B) [114,154]. This result suggests that the EDS1-PAD4/SAG101 heterodimers operate in complex with RNLs as a functional module during (auto-)immunity and supports the findings that TIR-domain and full-length TNL enzymatic activity promotes the association of RNLs with the EDS1-PAD4/SAG101 heterodimers [120,121,123–125]. However, in an alternative model, the catalytic products generated by TNLs may directly or indirectly and EDS1-independently activate RNLs to oligomerize into the cation channel-forming resistosome required for TNL-induced cell death, and simultaneously these products/signals initiate the association of (monomeric?) RNLs with the EDS1-PAD4/SAG101 heterodimers to activate defence gene expression and SA-related immune pathways, which in turn would bolster or further activate the cell death response (Fig. 3C). Both pathways would be required for full resistance initiated by effector-triggered TNL activation and a fully established autoimmune phenotype.

Suppression of NLR-mediated immunity

Given the important function of NLRs and specifically of helper NLRs in plant innate immunity, it may well be assumed that plant pathogens have evolved effectors that target NLR proteins to interfere with plant immunity. However, it is interesting that thus far only a few examples are reported where effectors directly target NLRs or NLR function. Some of these examples are from pathogens that have a necrotrophic lifestyle, during which, the necrotrophic effector molecule (often considered a toxin) rather activates the NLR, to kill the infected cell/tissue ensuing cell death for pathogen proliferation, then disabling it [155,156]. Thus, these molecules can also be considered as elicitors hijacking the plant's biotroph immune system. Three necrotrophic effectors/elicitors, ToxA, victorin and PC-toxin, produced by pathogenic fungi have been demonstrated to activate NLR proteins inducing a disease response and cell death, which would normally lead to resistance against biotrophic pathogens, but susceptibility to necrotrophic ones [156]. ToxA is recognized by Tsn1, an NLR-like protein having an N-terminal serine/threonine protein kinase (S/TPK) domain, and sensitivity to PC-toxin and victorin is conferred by members of the CNL family [157–160]. In all three cases, the activation of the NLR is most likely facilitated by binding of the necrotrophic

effector/elicitor to a potential guardee of the NLR and not to the NLR directly [161]. Thus, these host gene-necrotrophic effector interactions function opposite of the classic gene-for-gene interaction, and are therefore also called 'inverse gene-for-gene interactions' [156].

In the past, identification of direct effector targets was mainly made by performing huge effector-host protein-interaction screens, such as the systematic yeast-2-hybrid screens presented in Mukhtar et al. and Weßling et al. [162,163]. However, only 2 NLRs have been identified as potential direct effector interactors, the biological relevance of these interactions has not yet been studied or proofed *in planta*. A recently published alternative approach to identify effectors potentially targeting NLRs or NLR function screened 165 bacterial, oomycete, nematode and aphid effectors for their ability to suppress cell death initiated by two NRC-dependent sensor NLRs, Prf and Rpiblb2, in *N. benthamiana* [135]. The authors identified five effectors suppressing cell death mediated by the NRC immune network, with two of them—the oomycete effector AVRcap1b and the cyst nematode effector SPRYSEC15 (SS15)—being also able to specifically suppress cell death triggered by autoactive mutant NRCs, indicating that these two effectors directly oppose NRC activity independently of sensor NLRs. Indeed, further analysis to understand the molecular mechanisms of the suppression of these five effectors revealed that: (a) three effectors suppressed the function of the sensor NLR Rpi-blb2 upstream of the NRC helpers, (b) AVRcap1b interferes with a trafficking related protein important for NRC2 and NRC3 function, and (c) SS15 directly binds the nucleotide-binding domain of NRC2 and NRC3, thereby inhibiting their activity [133].

The bacterial effector protein HopAM1 is another example of an effector potentially interfering with sensor NLR (in this case TNL) function and/or helper NLR activation. Infection of plants with *P. syringae* pathovars carrying HopAM1 can induce multiple symptoms and phenotypes of quantitative nature (cell death and/or meristem chlorosis, resistance against bacterial infections or bacterial growth restriction etc.,) depending on the plant haplotype (ranging from fully responsive to non-responsive) [164,165]. The interference of plant immunity by HopAM1 is mediated by its non-canonical TIR domain, which possesses *in planta* NADase activity and produces nicotinamide and probably a unique small signalling molecule, distinct from the once produced by animal, plant or other bacterial TIR domains [166]. It is plausible that this molecule beside its virulence function could interfere with effector-triggered TNL-produced signalling molecules to inhibit the immune function of the EDS1-PAD4/SAG101-RNL modules during PRR and NLR-mediated immune responses (Fig. 1). This hypothesis is also supported by the observation that the effect of HopAM1 is dramatically enhanced in *eds1* mutants [165].

There is also a number of effectors from different phytopathogens suppressing immunity triggered by the recognition of other effectors, or interfering with downstream components of NLR signalling [167–170]. However, the exact mechanisms are often unknown and, in most cases, NLR activity or function appears indirectly inhibited. A good example is AvrRpt2, a *P. syringae* effector targeting the Arabidopsis NLR- and PRR-associated protein RIN4 [171–173]. AvrRpt2-mediated cleavage of RIN4 withdraws it from being modified by other *P. syringae* effectors, including AvRpm1, and thus prevents the activation of the RIN4-interacting CNL RPM1, which responds to AvrRpm1-induced modifications of RIN4 [91,92,167,174,175]. However, these two effectors were insofar absent from the same *P. syringae* pathovar [176], suggesting it is unlikely that AvrRpt2 evolved to suppress RPM1 (NLR) mediated immunity.

In summary, the constant armsrace between plants and their pathogens led to the evolution of immunity-suppressing effectors that either directly target NLRs to inhibit their activity, or interfere with NLR downstream components playing key roles during plant immunity. It is interesting that only a couple of NLR-targeting effectors have been identified in plant pathogens thus far. However, the mutual relationship between NLR- and PRR-mediated immunity and the assumption that NLR activation feeds into and potentiates PRR-mediated, effector-inhibited immune responses in a natural infection [12,13,105,126], suggest that successful pathogens have evolved effectors that rather suppress these PRR-triggered and NLR-amplified pathways to establish virulence, than attack rapidly evolving NLRs directly.

Core convergence hubs required for PRR- and NLR-mediated immune responses

Co-infections represent the vast majority of diseases in agriculture, and interactions among host plants and different pathogens determine how detrimental the resulting disease will be [177,178]. Identifying key differences, and more importantly, commonalities between PRR- and NLR-mediated immunities is critical in discovering core convergence hubs that are utilized by most pathogens to hijack defences directly and indirectly [178]. Such core convergence hubs,

although potential targets of pathogens, can be selected or engineered to benefit the plant and mount an effective response, without perturbing the host's fitness or symbiotic/mutualistic microbes that exist on or inside the host and inhibit pathogen ingress [179–181]. One of the major discoveries of the recent years was that there is no strict separation of extracellular induced PRR-mediated (PTI) and intracellular-induced NLR-mediated immunity (ETI) [182]. The concept of a two-tiered, separately operating, innate immune system definitely helped to tackle major research questions of plant-pathogen/microbe interactions, but it also affected how we looked at these very interlinked interactions. In the following segments we describe some notable examples of important hubs that link PRRs and NLRs.

The RLP-NRC connection—extracellular effector-recognition requires intracellular NLRs to initiate a cell death response

An important signalling node is formed by the PRR co-receptors SOBIR1 and BAK1, which constitutively or ligand-induced interact with RLPs, respectively, and are required for RLP function [52,183,184]. The RLP/SOBIR1/BAK1-containing complexes mediate immune responses that to date include defence against *Cladosporium fulvum* [185], *Fusarium oxysporum f. sp. lycopersici* [186], *Leptosphaeria maculans* [187], *Magnaporthe oryzae* [188], *Phytophthora parasitica* [189] and *Verticillium dahlia* [190]. Interestingly, RLPs can be engineered to recognize different pathogen effectors, but using the same defence signalling apparatus. One example is the engineered chimeric EFR-*Cf*-9 receptor that can recognize elf18 and trigger a *Cf*-9/Avr9-like HR [191]. An intracellular bacterial pathogen effector that blocks many PRR-mediated defences by inhibiting BAK1 function, such as the *P. syringae* effector AvrPto, can suppress the *Cf*-4/Avr4-triggered HR in tomato, and thus paves the way for a variety of secondary or co-infections by *C. fulvum* strains [192]. Therefore, a successful bacterial infection opens the door for a fungal infection to also take place, compounding the biotic stress on the plant. How cool is evolution! Considering that only in the case of *C. fulvum* there is a multitude of novel and unknown effectors across its strains [193], it raises interesting questions about how microbes might have coevolved along with their effector repertoires in a mutualistic relationship by knocking down different host defence mechanisms.

Perception of the apoplastic fungal effector Avr4 by the SOBIR1/*Cf*-4 complex leads to the association with BAK1 to initiate the effector-triggered hypersensitive response (Fig. 4). Avr4-triggered immune responses require signalling-competent kinase activity for both SOBIR1 and BAK1 [56], which phosphorylate downstream RLCKs. Recently, it was shown that the cell death triggered by Avr4 recognition through *Cf*-4 in *N. benthamiana* and tomato also requires the helper NLR NRC3 [132,133]. NRC3 triggers cell death probably through the formation of an active ZAR1-like resistosome (Fig. 4). The *Cf*-4/Avr4-triggered cell death response also requires EDS1 in *N. benthamiana* [132]. How NRC3 and EDS1 are activated by the *Cf*-4/SOBIR1/BAK1 complex is not known, but given that the kinase activities of SOBIR1 and BAK1 are required for Avr4-triggered cell death, a phosphorylation-dependent activation could be possible. It is also not clear whether the NRCs cooperate with EDS1 (−heterodimers) during RLP-induced immunity or whether they function independent of each other or in a synergistic manner (Fig. 4).

The helper NRCs are convergence nodes for plant immune responses during infections. Therefore, it is also not surprising that they are targeted by effectors of at least two different types of pathogens [135]. This is another indication of pathogen convergent evolution or coevolution, which probably drove NLR diversification during co-infection events. NRC3 appears to be mediating cell death for a variety of RLPs and swapping domains with other NRCs could lead to a more efficient immune response, while avoiding targeting by pathogen effectors.

The EDS1-PAD4-ADR1s module is a signalling hub for cell surface and intracellular receptor signalling

The plant-specific EDS1 family is an important component of immunity in many but not all plants, regulating the activation of basal defence, SA-dependent and -independent immune pathways, and NLR-mediated immunity [194]. Specifically, the EDS1-PAD4 heterodimers seem to play a more important role during immunity, as they have been demonstrated to be the major regulators of transcriptional reprogramming and initiation of systemic defences. Most of the immune functions of the ESD1-PAD4 heterodimers are executed in cooperation with the ADR1 helper NLR family—at least in Arabidopsis [122]. Here, the EDS1-PAD4-ADR1 immunity node is required for: (a) basal immunity against host-adapted pathogens [110], (b) TNL-triggered resistance and cell death, (c) for the timely cell death induction and transcriptional reprogramming during CNL-triggered

immune responses [118] and (d) for RLP-triggered (RLP23 and LecRK-1.8) PTI outputs [12,195,196]. The requirement for EDS1 in RLP-triggered immune outputs was also demonstrated for the tomato RLPs Ve1 and *Cf*-4 [132,197]. However, no involvement of the ADR1s (or PAD4) could be demonstrated for *Cf*-4 triggered immune responses in *N. benthamiana* [133]. Thus, the central immune function of the EDS1-PAD4-ADR1 module may be restricted to *Brassicaceae* species or lost in the *Solanaceae* linages. The involvement of the NRC helper NLR NRC3 in *Cf*-4 triggered immune responses may indicate that in solanaceous plants this helper NLR family fulfils the same function as the RNL helper NLRs in this important cell surface and intracellular immune receptor convergent point (Fig. 4). It will be interesting to see whether there is also an inducible or steady-state interaction observable for the EDS1-heterodimers with members of the NRC family, as it is seen for the RNL helper NLRs [120,121]. Similar to the lack of mechanistical insights into the activation of NRC3 in *Cf*-4-triggered cell death, it is not known how the ADR1s are activated, or whether canonical activity is required for RLP-triggered immunity in Arabidopsis. It is interesting that a potential constitutive interaction between the cell surface receptor complex (RLP23-SOBIR1) and the EDS1-PAD4-ADR1 module was reported [12], whereas during TNL-triggered immunity, the EDS1-PAD4 heterodimer inducibly associates with the ADR1s [121]. Is the association of ESD1-PAD4 and the ADR1s mediated during ETI mechanistically different than during PTI? This still needs to be clarified. The enhanced TNL expression and the functional requirement of TNLs for proper PRR responses suggest that TIR enzymatic activity might also trigger the tight ADR1 association with the EDS1-PAD4 heterodimer during PTI. It is also possible that the observed pre-immunity triggered association of these important key-immune components is reflecting a constitutive formation of a super-complex at the plant plasma membrane functioning as a convergence point for defence signalling.

These two examples of core convergence hubs are the result of many years of research, whose notion of a unified plant immunity system has just started to pick up traction in plant pathology. The studies that will follow in the future undoubtedly will shed more light to these two and other core hubs, as there is an astronomical number of plant pathosystems out there, of which we can only study the most important ones based on our current needs as a society. Major discoveries will result in applications destined to become the next norm for our crop production systems and ensure global food security.

Conclusions

Plants encounter a massive variety of hostile and non-hostile microbial organisms throughout their life cycle. However, plants cannot actively evade these encounters by just getting out of the way or changing their habitat. Like other eukaryotes, plants evolved a wide range of defence strategies on several levels to ward off most infections. Apart from physical barriers, such as bark or plant cell walls, plants rely on their interconnected receptor-based immune system. PRRs form protein complexes at the cell surface, consisting of co-receptors, negative regulators, scaffold proteins, and, at least in some cases, their immune activation also relies on proteins important for NLR-mediated immunity [12,103]. This suggests that the recognition of pathogens and probably also beneficial microbes by the two immune receptor classes converges on evolutionary quite conserved signalling hubs (convergence points) for the appropriate induction of immunity. Various pathogen-secreted effector proteins target and modify these core immune (PRR) components to suppress PRR-mediated immune responses and subsequently lead to pathogen proliferation in the plant host. While most PRR-activated immune responses are shared between the different classes of PRRs, there are also some responses specific for certain types of PRRs [59]. It will be interesting to see what influences the 'decision' for a specific output. Furthermore, it still is unclear how RLCK VII subfamily, such as BIK1 for example, differentially regulate PRR-mediated signalling, or how they are recruited and activated [59]. The signalling hubs of PRRs and NLRs are partially shared, forming spatially defined or connected supramolecular protein complexes that can detect a pathogen and respond effectively. In the case, of a full (PTI plus ETI) immune response, there is a potential amplification of the first PRR-induced immune response, which is beneficial evolutionarily, skipping the need to evolve something completely new, and just revamping an existing mechanism. However, this carries obvious drawbacks as pathogens can easily evolve to manipulate these complexes by attacking them in a multifaceted way, to which the plants have a countermeasure: the plurality of NLRs and RLPs that can be easily adjusted to defend against new or unknown effectors at the population level, and not just individually. Other interesting open questions are as follows: (a) whether and how PTI activates or triggers TNL activation, thus producing signalling molecules that trigger EDS1/PAD4/SAG101-RNL associations that could prime other NLRs for porper ETI; (b) do activated EDS1/PAD4/SAG101 complexes interact with

monomeric RNLs or RNLs in a preformed, but not activated oligomeric state?; (c) How do Ca^{2+} influx and ROS burst during PTI and ETI activate or regulate cell death and/or resistance? (d) Does interplay between PTI and ETI at the local immune response contribute to prime systemic immune responses? These questions will be a focal point of the following years' research endeavours to discover more convergence hubs and how they relate to each other on a mutually exclusive or overlapping manner.

Perspectives

While new knowledge is always useful, to truly envision designing durable crop resistance and effective crop protection applications, in an ever-changing environment, is actually a very challenging task and several factors need to be considered (Fig. 5). First, extreme weather climate change is expected to alter crop pathogen distribution geographically, and spread established diseases into new regions [4,198,199]. Furthermore, in real field conditions, gene-for-gene interactions are the exception and not the rule. Plants are usually co-infected by multiple pathogens during the same growing season in a synchronous or asynchronous manner [178,200]. These co-infections are complex interactions, which take place within a large plant-associated microbial diversity at the rhizosphere, phyllosphere and endophytic compartments that can be antagonistic [201], coexisting [202], mutualistic [203] or synergistic [204]. Furthermore, pathogens should not be addressed as a single individual threat, but alongside insects and weeds, which both can negatively affect crops, directly or indirectly [205]. These interactions can dramatically alter the response of the plant or the direction of the disease, rendering unilateral approaches (genetic, chemical or agronomic) ineffective. Against such a multifaceted threat, plants could be equipped with a multitude of natural or engineered PRRs and NLRs that can preemptively activate both PTI and ETI, relying on the presence of common microbes or insects, for effective broad-spectrum resistance, taking into account the cost to fitness of such activations and the existence of abiotic stresses, due to extreme climate and antagonism with weeds [13,14,205]. Alternatively, a common multi-pathogen host target could be removed or edited by CRISPR-Cas9 approaches [17].

Second, effective resistance against pathogens through the utilization of master regulatory immune elements has frequently resulted into substantial costs to fitness, rendering such strategies inapplicable in agriculture [205–207]. This can be overcome partially by deploying stringent control in transcription and translation of key defence proteins, through editing of upstream open reading frames, modifying transcription factors, or hormone-based control of primary and specialized metabolite production (i.e. jasmonate), which all appear to minimize cost to fitness or decouple growth from defence altogether [15,16,208,209]. However, our general understanding of the signal transduction network for each pathosystem is still limited and there is a need to discover or engineer optimal defence-associated genes that have minimal cost to fitness on a broad-spectrum for agriculture. Towards this end, future studies need to focus on: (a) the effect of different types of pathogen-induced cell death in plants (Apoptosis-like, Necroptosis, Hypersensitive Response) and define them more accurately, for example as in animals [210–212], (b) the presence of hyperactive defence alleles [213], (c) role of ageing-induced cell death genes [214], (d) metabolic pathways and energy consumption during PTI-ETI activation [177,215], (e) cytotoxic thresholds of pathogen-derived byproducts during infection [216] and (f) possible epigenetic growth limitation in future generations after a successful defence response [217].

Third, in the coming decades, climate change, declining fisheries, soil degradation and higher production costs are expected to disrupt agriculture to such a degree that controlled environment agriculture (CEA) systems will become a necessity to meet urban food demand for delicate crops, such as vegetables, legumes, or low-altitude arboriculture (i.e. kiwifruit); especially if fusion energy becomes available on an industrial scale by 2050, which will drastically decrease the cost of construction, shipping lanes, and make ocean desalination financially viable globally [218–224]. Controlled environment agricultures can limit pathogen proliferation compared to rural farming, and in combination with strict hygienic practices, remote-sensing technologies and robotics, can severely restrict or eliminate diseases altogether [219]. In such settings, co-infections could be extremely rare and a more conservative approach can be sought by introducing NLR genes that function in a gene-for-gene manner, which should be sufficient to protect crops from a small set of CEA-specific pathogen strains. The advent of recent custom-made plant disease resistance technologies, such as Pikobodies, can successfully address CEAs crop protection by designing a core set of different NLRs that recognize a collection of common pathogen core effectors, while considering the cost to fitness in preventing these infections [14,206,209].

Fourth, effective crop defence does not include only engineering or breeding resistance genes into a crop,

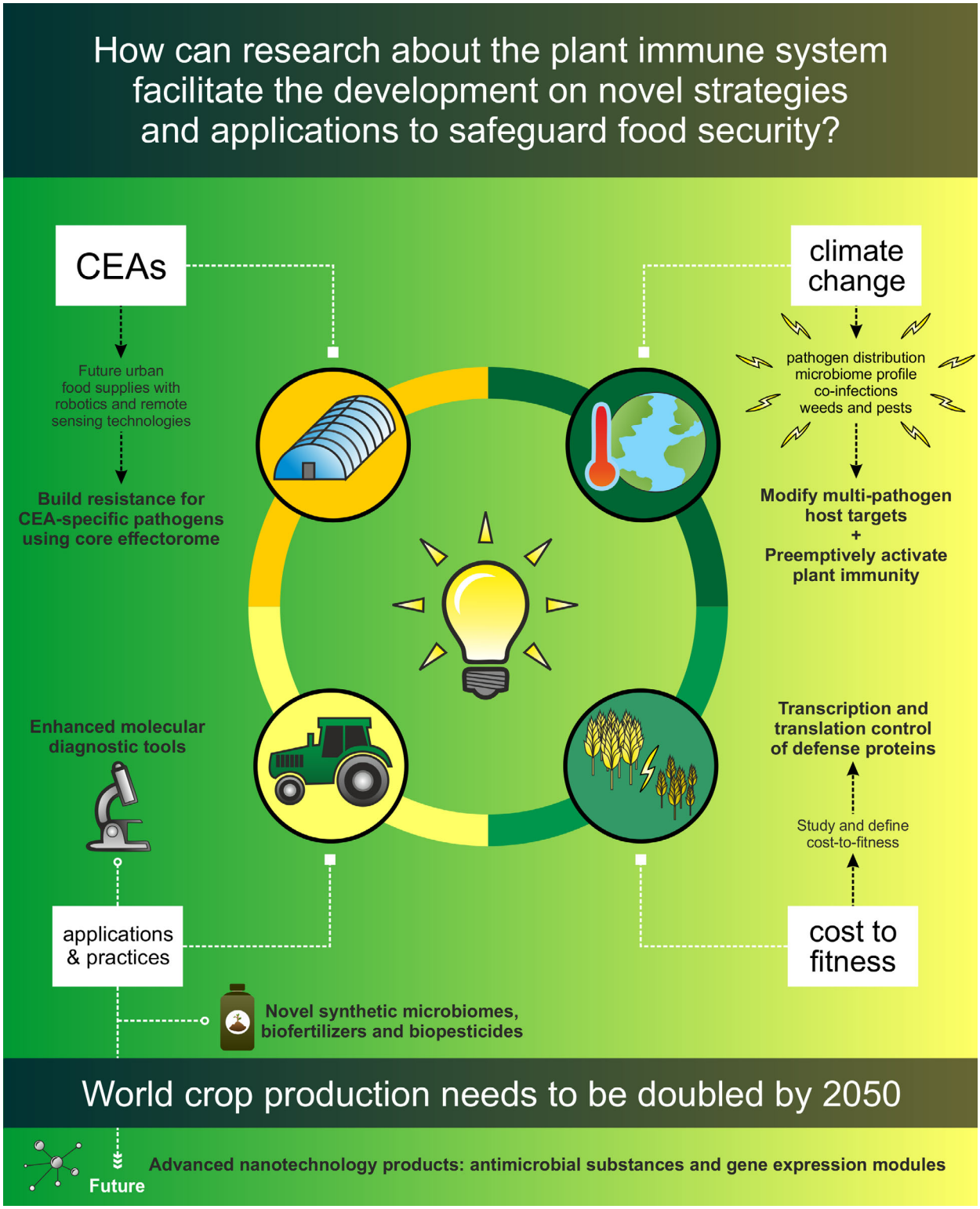

Fig. 5. Main factors influencing future crop protection. Infographic summarizing the four main factors that will influence the future of crop protection in agriculture, along with possible strategies and applications that will be derived from each one (in bold script).

but it can also include environment-friendly agricultural practices that can protect crops to a large or small extent, by complementing or enhancing existing crop defence mechanisms [20,22,225]. This has become an increasingly urgent target recently, as the world seeks also to eliminate its dependence on non-renewable fossil fuel-based agricultural products [226]. By elucidating the commonalities of PRR- and NLR-mediated immunity, novel synthetic cultures of beneficial bacteria (i.e. biofertilizers and biological control agents) could be selected or engineered that would provide a positive plant–soil feedback [227], which is a wide range of beneficial traits for both the crop and the local microbiome, without triggering a strong immune response and simultaneously, warding off pathogenic strains, pests, or even weeds [23,228–232]. Furthermore, knowledge about what type of defence host genes are activated during broad- or narrow-spectrum host infections can lead to: (a) improvement or development of enhanced molecular diagnostic tools, such as immunodetection, loop-mediated amplification, aptamer-based diagnosis, nanoanalytical biosensors, or portable nanopore sequencing, among others [18–20,228]; (b) optimization of selection or engineering of biopesticides in a custom manner that is crop- or pathogen-specific [225,229,230]; (c) development of advanced nanotechnology crop protection products that can deliver antimicrobial substances or genetic material, such as non-transgenic nanoparticle-based *NLR* gene expression strategies, nanoscale metalloids, carbon nanomaterials, liposomes, dendrimers and many others that are still in their infancy in terms of being deployed in agriculture, but hold tremendous potential [20,21,231–233]. In general, nanotechnology is slowly becoming a very promising tool in the hands of plant scientists and agronomists, which can soon become the next norm in disease management and diagnostics in open field and CEAs [20].

Preparing for the future is challenging, but not as challenging as it is for plant scientists to breed or design the crops of tomorrow. To tackle effectively this next monumental task, we have to think broadly, decisively, and collectively which path to take. The clock is ticking and countless lives are on the balance, just as they were before the Green Revolution in the 1960s [234]. Let's get on to it—the future is now!

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

MI, E-HC, SCS and FEK wrote, edited and revised the text. MI created the figures with input by FEK. FEK performed and characterized the crosses with help of ES.

Data availability statement

The data that support the findings presented in figure 3 are available from the corresponding author [farid.el-kasmi@zmbp.uni-tuebingen.de] upon reasonable request.

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