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# NLR we there yet? Nucleocytoplasmic coordination of NLR-mediated immunity

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## Summary

Plant intracellular nucleotide-binding leucine-rich repeat immune receptors (NLRs) perceive the activity of pathogen-secreted effector molecules that, when undetected, promote colonisation of hosts. Signalling from activated NLRs converges with and potentiates downstream responses from activated pattern recognition receptors (PRRs) that sense microbial signatures at the cell surface. Efficient signalling of both receptor branches relies on the host cell nucleus as an integration point for transcriptional reprogramming, and on the macromolecular transport processes that mediate the communication between cytoplasm and nucleoplasm. Studies on nuclear pore complexes (NPCs), the nucleoporin proteins (NUPs) that compose NPCs, and nuclear transport machinery constituents that control nucleocytoplasmic transport, have revealed that they play important roles in regulating plant immune responses. Here, we discuss the contributions of nucleoporins and nuclear transport receptor (NTR)-mediated signal transduction in plant immunity with an emphasis on NLR immune signalling across the nuclear compartment boundary and within the nucleus. We also highlight and discuss cytoplasmic and nuclear functions of NLRs and their signalling partners and further consider the potential implications of NLR activation and resistosome formation in both cellular compartments for mediating plant pathogen resistance and programmed host cell death.

## I. Introduction

Plants can sense microbial invaders using genome-encoded cell surface and intracellular immune receptors. Surface-associated pattern recognition receptors (PRRs) detect nonself microbe-associated molecular patterns (MAMPs), or modified-self damage-associated molecular patterns (DAMPs), which can be generated

during attempted pathogen invasion (Boutrot & Zipfel, 2017; Gust *et al.*, 2017; Albert *et al.*, 2019; Hou *et al.*, 2019; Kanyuka & Rudd, 2019). The activation of PRRs triggers immune responses known as pattern-triggered immunity (PTI) that can be sufficient to prevent colonisation by nonadapted microbes (Dangl *et al.*, 2013). To subvert PTI and manipulate host cell physiology, host-adapted pathogens secrete effector molecules into plant cells (Macho & Zipfel, 2015; Collemare *et al.*, 2019; Wang *et al.*, 2022). Intracellular nucleotide-binding leucine-rich repeat receptors (NLRs) can detect the presence of these pathogen effectors and trigger robust immune responses that often include a localised programmed cell death at attempted invasion sites, referred to as the hypersensitive response (HR; Jones & Dangl, 2006; Balint-Kurti, 2019). Therefore, NLR-mediated effector-triggered immunity (ETI) is particularly effective in restricting host invasion by biotrophic pathogens that require living host tissues to complete their life cycle (Glazebrook, 2005; Dangl *et al.*, 2013).

Cell surface and intracellular branches of defence work synergistically and share a conserved cellular signalling network that conveys signals of pathogen invasion into the nuclear envelope (NE)-enclosed nucleus. In the nucleus, the perceived stress signals trigger changes in gene expression that lead to the further induction of immune responses and immunity. Compared with responses mediated by surface receptors alone, ETI-triggered transcriptional changes are amplified and more sustained (Tao *et al.*, 2003; Tsuda *et al.*, 2009; Cui *et al.*, 2015; Mine *et al.*, 2018; Ngou *et al.*, 2021; Yuan *et al.*, 2021a). Embedded in the double lipid bilayer of the NE, nuclear pore complexes (NPCs) connect the nucleoplasm to the surrounding cytoplasm. Nuclear pore complexes function as macromolecular transportation hubs that facilitate the selective bidirectional exchange of information in form of proteins, RNAs and ribonucleoprotein particles (RNPs) in a signal-, nuclear transport receptor (NTR)- and energy-dependent manner (Lüdke *et al.*, 2021a).

Here, we discuss advances in our understanding of NLR-dependent immune responses in plants with a focus on the nuclear transport machinery in regulating cellular signal transduction between and within the cytoplasm and the nucleus. Whereas other excellent recent reviews have covered important mechanistic insights into plasma membrane-associated cell death signalling upon NLR complex formation (Saur *et al.*, 2020; Bi & Zhou, 2021; Maruta *et al.*, 2022; Parker *et al.*, 2022), we discuss nucleocytoplasmic signalling events that induce transcriptional changes and cell death upon NLR activation and resistosome formation. We further consider the contributions of the nuclear transport machinery in signal integration and crosstalk regulation of cell surface and intracellular defence branches.

## II. Macromolecular transport into and out of the nucleus: a regulatory hub and convergence point for defence signalling and gene expression

The nucleus is compartmentalised from the surrounding cytoplasm by the NE. Whereas imported proteins and small molecules mediate signal integration, exported proteins and several RNA species function as output responses towards stimuli that are perceived intracellularly or transduced from the cell surface (Ibarra & Hetzer, 2015; Ashkenazy-Titelman *et al.*, 2020; Lüdke *et al.*, 2021a). The gateways for the selective macromolecular exchange across the NE are NPCs, which are composed of proteins called nucleoporins (NUPs) that assemble in distinct subcomplexes within the supramolecular NPC (Tamura *et al.*, 2010; Tamura & Hara-Nishimura, 2013; Tang *et al.*, 2020). By fusing the two lipid bilayers of the NE, the inner and outer nuclear membrane (INM and ONM), NPCs form transport channels across the perinuclear space that is continuous with the lumen of the endoplasmic reticulum (ER). The channels formed by NPCs enable the passive diffusion of small soluble molecules below *c.* 40 kDa as well as the energy-dependent selective bidirectional transport of larger macromolecules and macromolecular complexes (Stewart, 2007; Wang & Brattain, 2007; Raveh *et al.*, 2016). Nucleoporins with intrinsically disordered domains containing phenylalanine-glycine (FG) repeats form a selectively permeable barrier within the NPC central transport channel that enables the regulation of macromolecular trafficking into and out of the nucleus (Grossman *et al.*, 2012; Tamura & Hara-Nishimura, 2013; Beck & Hurt, 2017). Soluble NTRs that mediate nuclear import (importins) or export (exportins) of macromolecular cargos can traverse the central channel by interacting with the FG-NUP permeability barrier (Fig. 1; Christie *et al.*, 2016; Schmidt & Görlich, 2016).

For canonical nuclear import of proteins, a cytoplasmic complex is formed between cargo proteins carrying nuclear localisation signals (NLSs), importin-α adapter proteins that directly interact with NLSs and importin-β transport receptors, which mediate the passage of the ternary complex through the NPC (Fig. 1; Kobe, 1999; Chang *et al.*, 2012; C-W. Chang *et al.*, 2013; Marfori *et al.*, 2012). The cargo binding to and release from the importin-α/β heterodimer is controlled by the bound nucleotide state of RAS-RELATED NUCLEAR PROTEIN (RAN), a small GTPase that exists in a GTP-bound nuclear and GDP-bound cytoplasmic state and energises nucleocytoplasmic protein transport (Fig. 1; Izaurralde *et al.*, 1997; Terry *et al.*, 2007; Nielsen, 2020). This compartmentalised asymmetric RAN·GDP-RAN·GTP distribution is generated by RAN GTPase-ACTIVATING PROTEIN (RanGAP) and its co-factor RAN·GTP BINDING PROTEIN1 (RanBP1) that impart GTP hydrolysis on RAN in the cytoplasm, whereas chromatin-associated RAN GUANINE NUCLEOTIDE EXCHANGE FACTOR (RanGEF) mediates nucleotide exchange on RAN in the nucleus (Fig. 1; Stewart, 2007; Nielsen, 2020). Binding of RAN·GTP to importin-β in the nucleoplasm triggers the dissociation of ternary import complexes and drives nuclear cargo release (Görlich *et al.*, 1996; Moroianu *et al.*, 1996). Some importin-β NTRs, however, can function independently of importin-α adapters to mediate nuclear cargo import or export (Fig. 1; Christie *et al.*, 2016).

Whereas Ran·GTP triggers the dissociation of cargos from the nuclear import receptor inside the nucleus, it imposes the association of export receptors with nuclear cargo substrates. For instance, protein export from the nucleus is mediated by the export receptor EXPORTIN1 (XPO1, also known as CRM1) that recognises leucine-rich nuclear export signals (NESs) on cargo

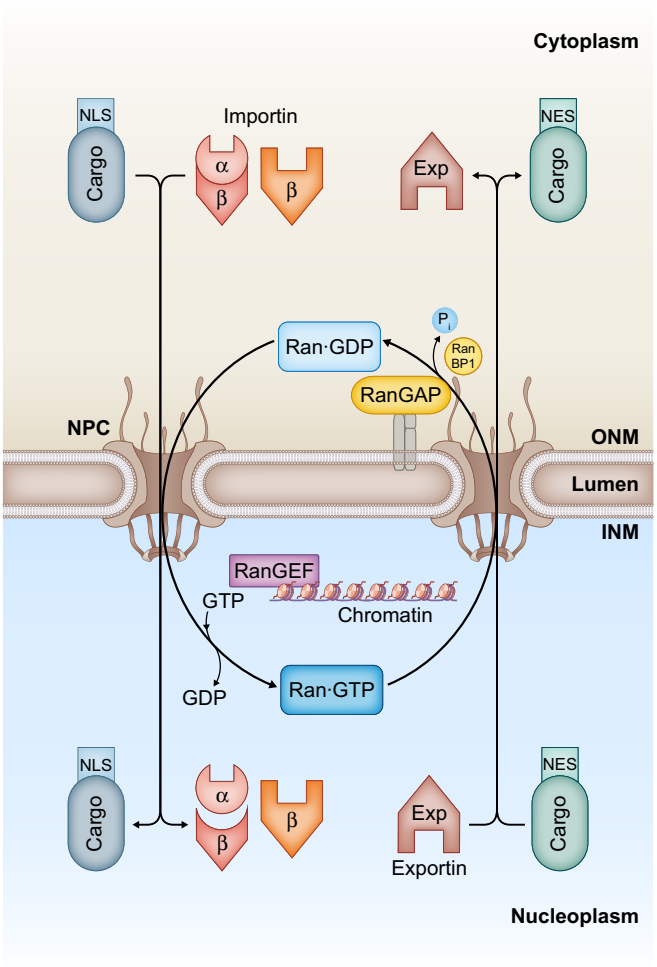


**Fig. 1** Nuclear transport receptor (NTR)-mediated nucleocytoplasmic protein transport. Importin-β or importin-α/β complexes associate with nuclear localisation signals (NLSs) of respective cargo proteins to mediate translocation across the inner and outer nuclear membrane (INM and ONM) through the nuclear pore complex (NPC). Transport directionality is imposed by the small GTPase RAS-RELATED NUCLEAR PROTEIN (RAN). Chromatin-associated RAN GUANINE NUCLEOTIDE EXCHANGE FACTOR (RanGEF) mediates GDP to GTP exchange on RAN, initiating dissociation of import complexes and cargo release inside the nucleoplasm. Nuclear Ran·GTP enables the association of export receptors (Exp) with respective nuclear cargo proteins containing nuclear export signals (NESs). After translocation through the NPC, the ternary cargo/Exp/Ran·GTP complex dissociates upon GTP hydrolysis on RAN, mediated by RAN GTPase-ACTIVATING PROTEIN (RanGAP) tethered to the cytoplasmic side of the ONM and its cofactor RAN BINDING PROTEIN1 (RanBP1).

proteins (Fig. 1; Fornerod *et al.*, 1997; Stade *et al.*, 1997; Fukuda *et al.*, 1997; la Cour *et al.*, 2004; Kosugi *et al.*, 2009). XPO1 directly binds to cargos cooperatively with Ran·GTP and facilitates the translocation of the ternary cargo/XPO1/Ran·GTP complex through the central pore into the cytoplasm, where the complex disassembles following GTP hydrolysis on RAN (Fig. 1; Hutten & Kehlenbach, 2007).

In addition to their roles in selective bidirectional exchange of macromolecules between the nucleoplasm and the cytoplasm, NPCs are also involved in regulating several other transport-independent cellular processes including chromatin organisation, DNA repair, gene expression and epigenetic gene regulation (Meier *et al.*, 2017; Groves *et al.*, 2020; Lüdke *et al.*, 2021a). In plants, several genes encoding NPC and nuclear transport machinery components were initially revealed in genetic screens for specific mutant phenotypes, including defects in or the suppression of, NLR-mediated (auto)immune responses, as detailed in Section VI.

## III. Plant immunity relies on nonself and modified-self recognition by cell surface and intracellular immune receptors

The perception of pathogens in the apoplastic space via PRRs is considered the first line of active defence. Plasma membrane-associated PRRs can recognise MAMPs or DAMPs via extracellular ligand recognition domains (Albert *et al.*, 2019). Elicitor binding by these receptors usually activates phosphorylation-based signalling cascades initiated by surface-receptors through associated co-receptor kinases and leads to responses including the generation of reactive oxygen species (ROS) at the cell surface (Kadota *et al.*, 2014; Kimura *et al.*, 2017; Lee *et al.*, 2020; Ngou *et al.*, 2021). Through protein kinase relay systems, these signals are also transmitted into the nucleus, where they converge on the transcriptional machinery to initiate defence responses towards perceived pathogen threats (Adachi *et al.*, 2015; Bi *et al.*, 2018; Bigeard & Hirt, 2018; Saijo & Loo, 2020).

In contrast with cell surface PRRs, plant NLRs function as intracellular receptors of effector molecules that are delivered by host-adapted pathogens to suppress immune responses and promote infection (Toruño *et al.*, 2016; Kourelis *et al.*, 2021b; Wang *et al.*, 2022). Nucleotide-binding leucine-rich repeat immune receptor activation occurs either through direct interaction with effectors or through indirect mechanisms, such as the surveillance of functional host effector targets ('guardees'), or nonfunctional target derivatives ('decoys'; van der Biezen & Jones, 1998; van der Hoorn & Kamoun, 2008). Nucleotide-binding leucine-rich repeat immune receptors across plant species can contain additional integrated domains (IDs) within their canonical protein structures, some of which directly interact with and/or are modified by cognate effector molecules. These IDs can often represent nonfunctional effector targets, which are likely to have evolved from ancient, functional targets and serve as integrated effector decoys (César *et al.*, 2014; Maqbool *et al.*, 2015; Saucet *et al.*, 2015; Le Roux *et al.*, 2016; Sarris *et al.*, 2016; Fujisaki *et al.*, 2017; Bailey *et al.*, 2018; De la Concepcion *et al.*, 2018; Oikawa *et al.*, 2020; Białas *et al.*, 2021; Maidment *et al.*, 2021; Kourelis *et al.*, 2021b)

To date, nearly 500 NLRs from over 30 different plant genera have been experimentally validated to function in immunity (Kourelis *et al.*, 2021b). Although NLRs use different molecular mechanisms for effector detection, they share a modular, tripartite domain architecture with a central NB-ARC (nucleotide-binding adaptor shared by APAF-1, certain *R* gene products and CED-4), C-terminal LRRs and either a Toll/interleukin-1 receptor (TIR) domain or a coiled-coil (CC) domain at the N-terminus. Distinct phylogenetic classes of NLRs can be determined through their NB-ARC domain. The N-terminal domain generally follows this

phylogeny, subdividing NLRs into TIR-type NLR (TNL) and CC-type NLR (CNL) clades (Jacob *et al.*, 2013; Bentham *et al.*, 2016; Shao *et al.*, 2016; Kourelis *et al.*, 2021b). Whereas some ancient CNLs, such as HOPZ ACTIVATED RESISTANCE1 (ZAR1), can function as multifunctional singletons that combine both effector detection and downstream signalling capacities and do not require additional NLRs, all characterised TNLs and several CNLs function as effector sensors that require helper NLRs for the induction of immunity (Fig. 2; Adachi *et al.*, 2019b, 2020). The two helper NLR families, ACTIVATED DISEASE RESISTANCE (ADRs) and N REQUIREMENT GENE (NRGs), can have specific and redundant functions in downstream signalling for sensor NLRs that perceive effector activities (Fig. 2; Peart *et al.*, 2005; Bonardi *et al.*, 2011; Castel *et al.*, 2019; Wu *et al.*, 2019; Saile *et al.*, 2020). The ADR/NRG helper NLR families are highly preserved in land plants and contain an N-terminal RESISTANCE TO POWDERY MILDEW8 (RPW8)-type coiled-coil ($CC_R$) domain (also termed RNLs; Collier *et al.*, 2011; Shao *et al.*, 2016). The $CC_R$ domain shares structural homology with animal and plant mixed-lineage kinase domain-like (MLKL), as well as HeLo and HeLo-like (HELL) domains found in fungi, which can form multi-helix bundles and induce cell death (Greenwald *et al.*, 2010; Seuring *et al.*, 2012; Bentham *et al.*, 2016; Daskalov *et al.*, 2016; Mahdi *et al.*, 2020; Tamborski & Krasileva, 2020; Jacob *et al.*, 2021).

Another helper family, the NLR-REQUIRED FOR CELL DEATH (NRC) superclade of CNLs, has been extensively described in Solanaceae plant species. NRCs form elaborate receptor networks with NRC-sensors relying on NRC-helpers for downstream signalling. NRC-helpers together with their sensor mates can function specifically or redundantly in conferring robust resistance against an array of pathogens, including viruses, bacteria, oomycetes, nematodes and insects (Wu *et al.*, 2016, 2017; Adachi *et al.*, 2019b). In contrast with $CC_R$-domain helpers, NRC-helpers, and some singleton CNLs (e.g. ZAR1), contain a MADA amino acid motif within the first alpha-helix of their CC domain that is required for downstream signalling function. Strikingly, a MADA motif is absent/degenerated in NRC-sensors, which is likely to be the result of a specialisation towards effector perception within the sensor clade. Therefore, the MADA motif appears to be an ancient signature of singleton NLRs that is maintained in the NRC-helper clade throughout evolution, substantiating a requirement of this motif for downstream signalling function (Adachi *et al.*, 2019a, 2020).

The molecular mechanisms underpinning activation of immunity and HR cell death by MADA containing CNLs came to light in structure-based studies of *Arabidopsis* (*At*) ZAR1 and wheat Sr35. The reconstruction of active ZAR1 and Sr35 resistosomes – pentameric wheel-like structure anchored to the plasma membrane – suggests that integration of the MADA motif containing α-helices disturbs membrane integrity, leading to the initiation of a cell death response (Fig. 2; Wang *et al.*, 2019a; Förderer *et al.*, 2022). Indeed, the ZAR1 and Sr35 resistosomes form membrane channels that allow for the influx of mono- and divalent cations including $Ca^{2+}$ (Bi *et al.*, 2021; Förderer *et al.*, 2022). Strikingly, activated *At*ADR1 and *At*NRG1 helper NLR complexes are also plasma membrane localised and can function as $Ca^{2+}$ influx channels (Fig. 2; Jacob *et al.*, 2021; Saile *et al.*, 2021). $Ca^{2+}$ plays important signalling roles in plant defence, and misregulation of $Ca^{2+}$ influx in plant cells can induce HR cell death and auto-immunity (Wang *et al.*, 2019b; Thor *et al.*, 2020; Tian *et al.*, 2020; Ren *et al.*, 2021; Kim *et al.*, 2022; Xu *et al.*, 2022). The activated *Nicotiana benthamiana* (*Nb*) helpers NRC2 and NRC4 also form homo-oligomers and dynamically reorganise into plasma-membrane localised punctate structures upon sensor activation (Adachi *et al.*, 2019a; Duggan *et al.*, 2021; Ahn *et al.*, 2022; Contreras *et al.*, 2022). This suggests that activated CC-type singleton/helper NLR resistosomes act as membrane channels that initiate downstream responses, likely to involve $Ca^{2+}$ signalling-mediated transcriptional changes and cell death (Fig. 2; Bi & Zhou, 2021). Whether this function is restricted to plasma membranes remains an important question to address, as other membrane-enclosed cell compartments, such as the endoplasmic reticulum (ER), can function as $Ca^{2+}$ reservoirs, and an ER localisation has previously been described for *Arabidopsis* NRG1A and NRG1B (Wu *et al.*, 2019). Considering that the ER is continuous with the NE, a perturbation of nuclear integrity through resistosome formation at the ONM or INM might be a potential function of singleton/helper NLRs to boost either cytoplasmic (when formed at the ONM) or nuclear (when formed at the INM) $Ca^{2+}$ influx (Fig. 3). Nuclear $Ca^{2+}$ influx pathways have previously been described to regulate transcriptional changes in other plant signalling pathways (Charpentier, 2018; Leitão *et al.*, 2019). To investigate this idea, the subcellular localisations of activated resistosome complexes requires more in-depth analyses. In addition, the exact mechanism of how $Ca^{2+}$ influx signals at the plasma membrane, or other membrane compartments, are translated into transcriptional changes inside the nucleus and HR cell-death that mediate immunity still requires characterisation.

Similar to resistosome-forming CNLs, (homo-)oligomerisation is also required for the function of TNLs (Zhang *et al.*, 2017; Wang *et al.*, 2019a; Horsefield *et al.*, 2019; Burdett *et al.*, 2021; Yu *et al.*, 2022). In contrast with CNL singletons or helper NLRs, the activation of TNL sensors, such as *At* RECOGNITION OF PERONOSPORA PARASITICA1 (RPP1) and *Nb* RECOGNITION OF XopQ1 (ROQ1), by their respective effectors, leads to the formation of tetrameric resistosomes that appear not to be membrane associated. The resistosome formation of TNLs induces an enzymatic function of the TIR domains that depends on structurally distinct oligomers and distinct TIR domain interfaces (Horsefield *et al.*, 2019; Wang *et al.*, 2019a; Ma *et al.*, 2020; Martin *et al.*, 2020; Burdett *et al.*, 2021; Yu *et al.*, 2022). The enzymatic activities of activated TNLs include the degradation of $NAD^+$/$NADP^+$, leading to the production of (cyclic-)ADP-ribose ((c)ADPR) isomer products, and the hydrolysis of DNA/RNA substrates, leading to the synthesis of 2′,3′-cAMP/cGMP (Fig. 2). Strikingly, the NADase function of plant NLR TIR domains is similar to the $NAD^+$/$NADP^+$ degrading function of human sterile alpha and Toll/interleukin-1 receptor motif containing1 (SARM1) but appears not to be aimed at $NAD^+$/NADP depletion but rather the generation of the small molecules (Essuman *et al.*, 2017; Horsefield *et al.*, 2019; Wan *et al.*, 2019). However, neither (c)

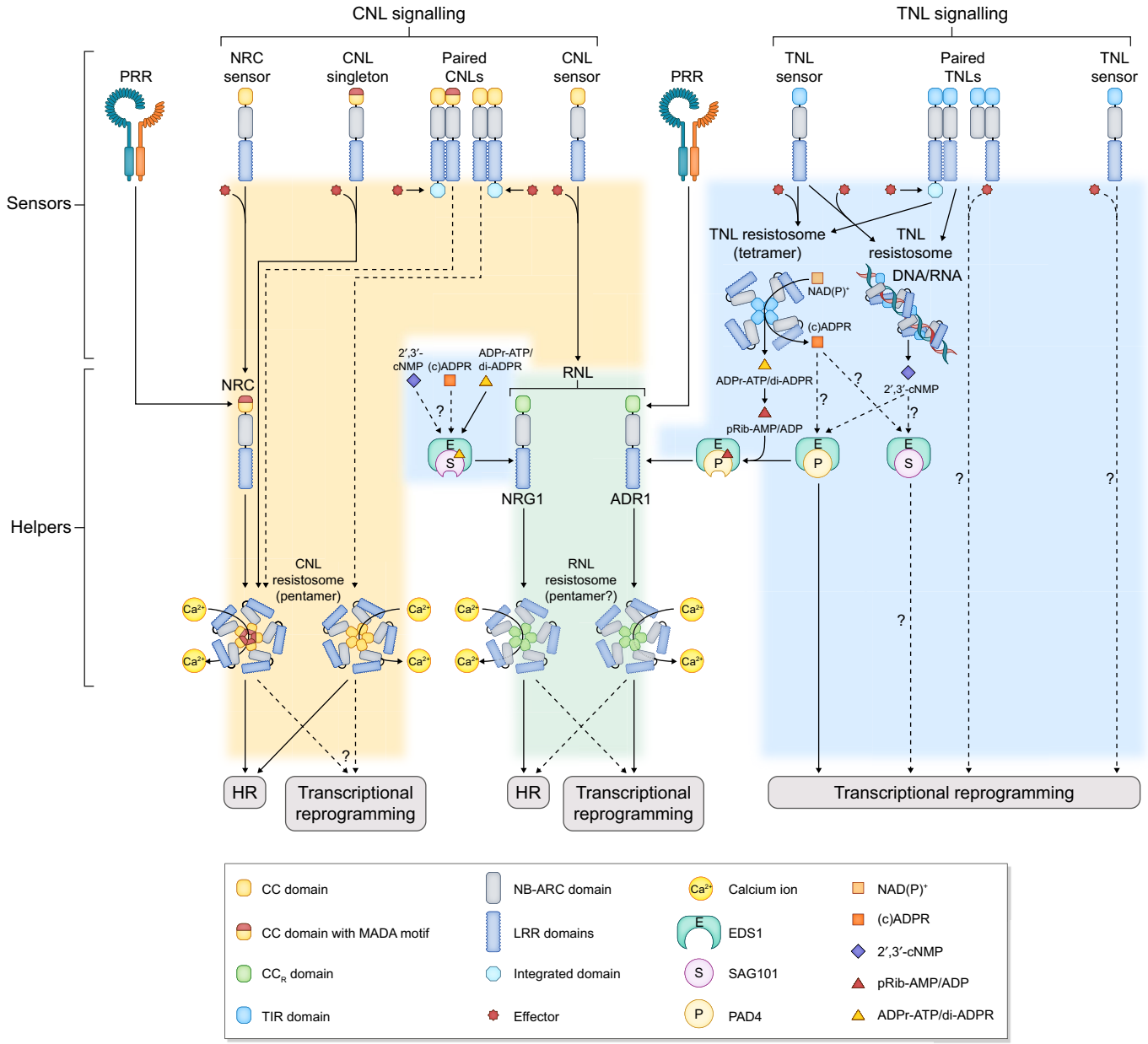


**Fig. 2** Nucleotide-binding leucine-rich repeat immune receptor (NLR)-mediated signalling pathways. Effector detecting coiled-coil (CC)-type NLR (CNL) sensors (and microbe-associated molecular pattern (MAMP) detecting pattern recognition receptors (PRRs)) rely on RESISTANCE TO POWDERY MILDEW8 (RPW8) coiled-coil domain ($CC_R$)-type (RNL) helper or MADA motif-containing NLR-REQUIRED FOR CELL DEATH (NRC) helper NLR families for downstream signalling and induction of a hypersensitive response (HR). CNL singletons combine effector sensing and downstream signalling/HR induction. Genetically linked CNL pairs can form steady-state complexes in which an integrated domain (ID) of the sensor interacts directly with an effector, triggering downstream signalling through activation of the associated helper. $CC_R$ and MADA motif-containing helpers form CNL 'resistosome' complexes upon activation, which are membrane associated and are likely to function as ion channels (e.g. for $Ca^{2+}$ ion influx). Membrane integration and ion influx lead to induction of transcriptional programming and/or HR, resulting in plant immunity. Effector activation of Toll/interleukin-1 receptor (TIR)-type NLR (TNL) sensors, genetically linked TNL pairs with IDs or TN/TNL pairs, leads to the formation of tetrameric TNL 'resistosomes'. Structurally distinct subpopulations of these resistosomes form a holoenzyme and induce an enzymatic function of the TIR domains that leads to the $NAD(P)^+$-derived production of either (cyclic-)ADP-ribose ((c)ADPR), 2′-(5″-phosphoribosyl)-5′-adenosine mono-/di-phosphate (pRib–AMP/ADP) and ADP-ribosylated ATP (ADPr–ATP)/ADP-ribosylated ADPR (di-ADPR). 2′,3′-cyclic nucleotide monophosphates (2′,3′-cNMP) can be produced from DNA/RNA as substrates. EDS1 (E) complexed with PAD4 (P) or SAG101 (S) is required for downstream signalling upon small molecule production by TNL resistosomes. The distinct EDS1 complexes further depend on the $CC_R$ helper families of NRG1 (i.e. E-S) and ADR1 (i.e. E-P). pRib-AMP/ADP induces a structural change in PAD4 allowing for the formation of the EDS1-PAD4-ADR1 complex, while ADPr-ATP/di-ADPR induces a structural change in SAG101 to allow the formation of EDS1-SAG101-NRG1. Whereas NRG1 is predominantly required for HR induction, ADR1 is mainly required for transcriptional programming. EDS1 and PAD4 also positively regulate transcriptional responses in systemic tissues. Some TNL and CNL sensors interact with transcription factors potentially influencing transcriptional outputs. Dashed arrows indicate speculation.

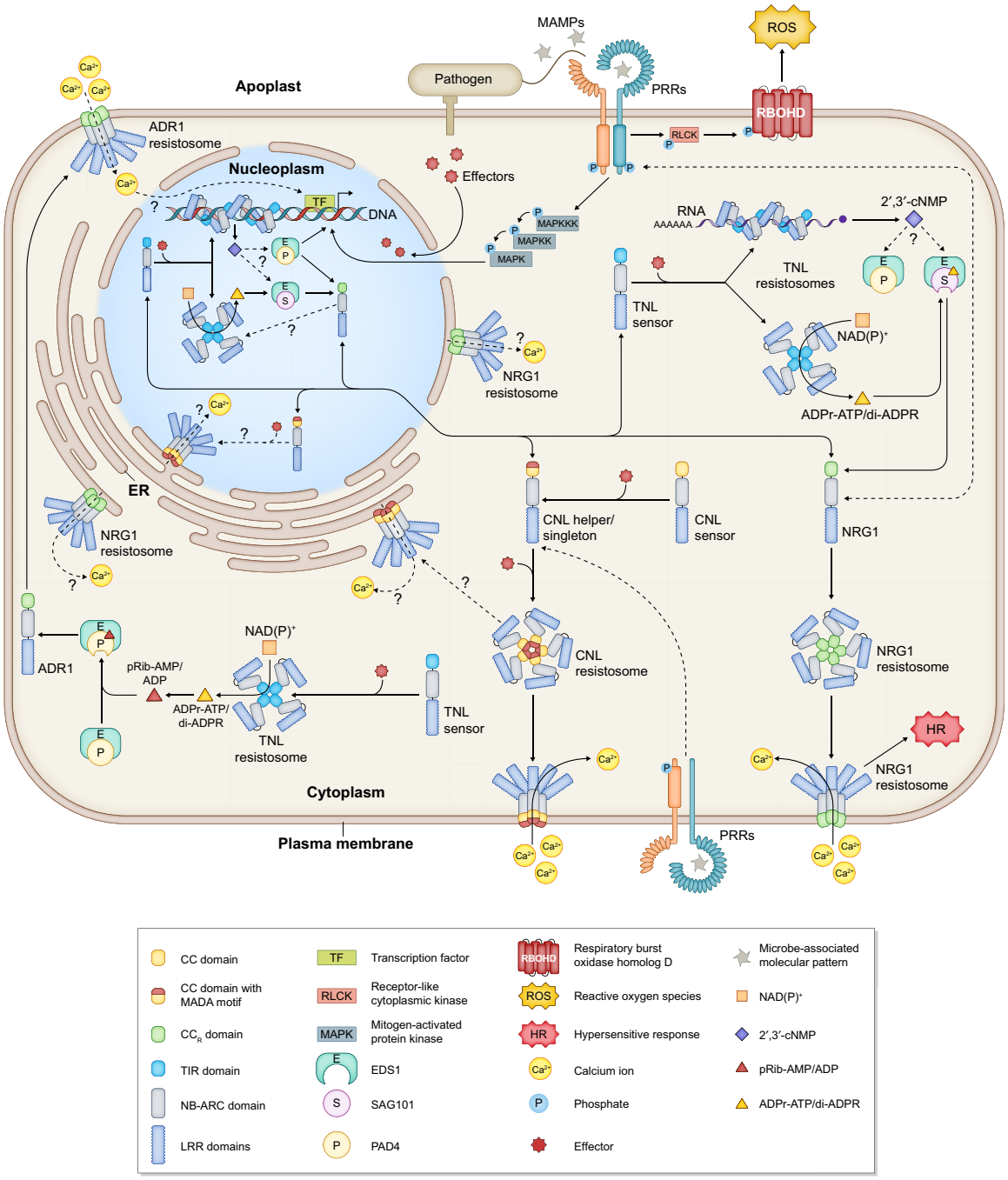


**Fig. 3** Nucleotide-binding leucine-rich repeat immune receptor (NLR)-mediated signalling across nucleocytoplasmic compartment boundaries. Microbe-associated molecular pattern (MAMP) detection by cell surface localised pattern recognition receptors (PRRs) leads to the production of reactive oxygen species (ROS). PRR activation is also followed by nuclear signal integration via mitogen activated protein (MAP) kinase cascades that converge on the transcriptional machinery. Signalling and defence output from activated cell surface PRRs is potentiated by N-terminal RESISTANCE TO POWDERY MILDEW8 (RPW8)-type coiled-coil domain ($CC_R$) and MADA motif-containing intracellular helper NLRs. Pathogens secrete effector proteins that interfere with immune signalling on various levels. Intracellular sensor NLRs or singleton NLRs detect the presence/activity of effectors and initiate downstream signalling via respective helper NLRs. Activated helper NLR 'resistosomes' localise to the plasma membrane where they function as ion influx channels. As a localisation to the endoplasmic reticulum (ER) has also been described for NRG1, activated coiled-coil (CC)-type NLR (CNL) resistosomes might also function as ion channels at other membrane-enclosed cellular compartments such as the nuclear membrane or the Golgi apparatus. Multiple Toll/interleukin-1 receptor (TIR)-type NLR (TNL) and CNL sensor NLRs show a nucleocytoplasmic distribution and some sensors require a nuclear localisation to detect effectors inside the nucleoplasm. TNL activation and resistosome formation in the nucleus and the cytoplasm lead to the production of small molecules ((c)ADPR, pRib-AMP/ADP, ADPr-ATP/di-ADPR and 2′,3′-cNMP). While nuclear TNL subpools could utilise DNA and RNA as substrate, cytoplasmic TNL pools probably use RNA for 2′,3′-cNMP production. EDS1 (E) together with either PAD4 (P) or SAG101 (S) is required for downstream signalling upon TNL-mediated production of small molecules. pRib-AMP/ADP induces a structural change in PAD4 allowing for the formation of the EDS1-PAD4-ADR1 complex while ADPr-ATP/di-ADPR induces a structural change in SAG101 to allow the formation of EDS1-SAG101-NRG1. Distinct subpopulations of EDS1 complexes exert transcriptional control inside the nucleus, but also associate with RESISTANCE TO POWDERY MILDEW8 (RPW8) coiled-coil domain ($CC_R$)-type helper NLRs (RNLs) during the induction of immunity. Dashed arrows indicate speculation.

ADPR nor 2′,3′-cAMP/cGMP generation alone is sufficient for the induction of a cell death response and defence activation (Horsefield *et al.*, 2019; Wan *et al.*, 2019; Yu *et al.*, 2022). The combination of molecules produced by TNLs might act as a signal for host cell transcriptional reprogramming and/or HR cell death initiation. As some nucleocytoplasmic TNLs are known to be activated and function inside the nucleus (Xu *et al.*, 2014a), and DNA/RNA species were identified as potential TIR domain substrates (Yu *et al.*, 2022), it is conceivable that the generation of 2′,3′-cAMP/cGMP (but also of (c)ADPR) by activated TNLs inside the nucleus is essential for these processes (Fig. 3; please refer to Section V). In addition, activated nucleocytoplasmic TNLs may release their catalytic products from cytoplasmic RNA species or from $NAD^+$/$NADP^+$ inside the cytoplasm.

## IV. Defence signalling mediated by PRRs and NLRs is integrated into signalling networks across the cytoplasm and the nucleoplasm

Accumulating evidence suggests that PRRs and NLRs employ similar signalling pathways to induce partially overlapping immune responses, albeit at different amplitudes and dynamics. These responses include ROS production, $Ca^{2+}$ influx, protein kinase signalling cascades, transcriptional reprogramming, and production of phytohormones such as salicylic acid (SA), that mediates plant defence against biotrophic and hemi-biotrophic pathogens (Lu & Tsuda, 2021; Yuan *et al.*, 2021b). Indeed, PTI and ETI can function synergistically. Whereas NLRs utilise and require PRR activation for efficient immune responses including HR cell death, some PRRs also rely on helper NLRs for efficient immunity and cell death induction upon elicitor perception (Ngou *et al.*, 2021; Pruitt *et al.*, 2021; Kourelis *et al.*, 2021a; Yuan *et al.*, 2021a). Collectively, these results show that there is extensive PTI and ETI crosstalk and argue against the separation of different immune branches into distinct defence layers (Fig. 2). Rather, the plant immune system utilises functionally distinct receptor branches for pathogen detection, but shares signalling, defence activation, and output responses. Signalling of both activated immune receptor types appears to converge transcriptionally. Thus, it is likely that signal integration either occurs inside the nucleus or at the level of signal transmission into the nucleus, outlining the importance of nucleocytoplasmic communication in plant immune signalling. The spatial communication between both cellular compartments is regulated by the nuclear transport machinery. Transported cargos comprise NLRs and central defence signalling components, which localise to the nucleus or shuttle between the cytoplasm and the nucleoplasm (Fig. 3). Consistently, defects in the nuclear transport machinery can affect PRR- as well as NLR-mediated immune responses (see section VI).

For full induction of immunity, all characterised TNLs not only depend on helper NLRs, but also require downstream signalling functions of the nucleocytoplasmic defence regulator ENHANCED DISEASE SUSCEPTIBILITY1 (EDS1; Wiermer *et al.*, 2005; Wagner *et al.*, 2013; Bhandari *et al.*, 2019). Indeed, cell death upon transient expression of plant NLR TIR domains in *N. benthamiana* is abolished in *eds1* mutant plants, whereas *Arabidopsis eds1* mutants lack a full transcriptional response, SA accumulation and are hypersusceptible when challenged with virulent and avirulent pathogens (Bhandari *et al.*, 2019; Horsefield *et al.*, 2019; Saile *et al.*, 2020; Sun *et al.*, 2021; Yu *et al.*, 2022). The loss of a cell death response in *eds1* mutant plants further suggests that EDS1 is a key component required for conversion of TIR domain enzymatic products into HR cell death (Horsefield *et al.*, 2019; Yu *et al.*, 2022). EDS1 forms nucleocytoplasmic complexes with the lipase-like protein PHYTOALEXIN DEFICIENT4 (PAD4), which are distinct from predominantly nuclear EDS1 complexes with another related lipase-like protein, SENESCENCE ASSOCIATED GENE101 (SAG101; Fig. 2; Feys *et al.*, 2001, 2005; Rietz *et al.*, 2011). The lipase-like proteins appear to be directly connected to the helper NLRs ADR1 and NRG1 for defence regulation in *Arabidopsis* (Wu *et al.*, 2019; Pruitt *et al.*, 2021; Sun *et al.*, 2021). Strikingly, the formation of EDS1-SAG101-NRG1 is induced by ADP-ribosylated ATP (ADPr-ATP) or ADPr-ADPR (di-ADPR), while EDS1-PAD4-ADR1 complexes are induced by 2′-(5″-phosphoribosyl)-5′-adenosine mono-/di-phosphate (pRib-AMP/ADP), which constitute some of the TIR-type NLR produced ADPR small molecules. In recent publications, ADPr-ATP/di-ADPR and pRib-AMP/ADP were shown to trigger a conformational change in EDS1 complexes with SAG101 and PAD4, respectively to allow interactions with the NRG1 and ADR1 helpers (Huang *et al.*, 2022; Jia *et al.*, 2022).

Hypersensitive response cell death and transcriptional reinforcement for bacterial resistance are uncoupled from each other and require the distinct sets of EDS1 complexes and helper NLRs, respectively (Gassmann, 2005; Heidrich *et al.*, 2011; Lapin *et al.*, 2019; Saile *et al.*, 2020; Ngou *et al.*, 2021; Sun *et al.*, 2021; Yuan *et al.*, 2021a). Accordingly, a branched TNL signalling model was proposed, in which EDS1-PAD4-ADR1 mainly signal to restrict bacterial growth through transcriptional reinforcement inside the nucleus, whereas signal transmission by EDS1-SAG101-NRG1 is essential for HR induction (Bonardi *et al.*, 2011; Dong *et al.*, 2016; Cui *et al.*, 2018; Castel *et al.*, 2019; Lapin *et al.*, 2019; Wu *et al.*, 2019; Sun *et al.*, 2021). It thus appears, that the distinct nuclear/cytoplasmic EDS1 defence signalling branches are a central part of cell death induction and resistance based on transcriptional host cell reprogramming upon TIR-type NLR small molecule production (Lapin *et al.*, 2020; Huang *et al.*, 2022; Jia *et al.*, 2022). The complexes of NRG1 or ADR1 with EDS1/SAG101 and EDS1/PAD4, respectively, suggests that these associations are dynamically formed and have specific functions in the cytoplasm and/or nucleoplasm where the EDS1 defence signalling network localises (Fig. 3; Qi *et al.*, 2018; Sun *et al.*, 2021). It is conceivable that the defence regulatory complexes communicate across the nuclear compartment border via active shuttling and that compartment specific complexes are dynamically formed in a stimulus-dependent, transient manner. In *Arabidopsis*, complexes between EDS1 and PAD4 or SAG101 have been described as spatially distinct. While EDS1–PAD4 complexes are nucleocytoplasmic, EDS1–SAG101 appeared exclusively nuclear (Feys *et al.*, 2005; Lapin *et al.*, 2019). This conflicts with findings that the cytoplasmic

pool of EDS1 (Heidrich *et al.*, 2011) and helper NLRs are required for HR, thus requiring a cytoplasmic SAG101 localisation. However, functional SAG101 isoforms from Solanaceae are indeed nucleocytoplasmic (Zhu *et al.*, 2011; Gantner *et al.*, 2019; Lapin *et al.*, 2019), suggesting that subpools of these active complexes might also be of nucleocytoplasmic nature in other plant species, although at lower abundance (Lapin *et al.*, 2020). Such cytoplasmic localisation of a cellular sub-pool of SAG101 would be more consistent with the branched TNL signalling model (Fig. 3).

Direct interactions between EDS1 and some *At*TNLs in the cytoplasm or at the cytoplasmic side of endomembrane compartments, have also been reported (Bhattacharjee *et al.*, 2011; Heidrich *et al.*, 2011; Kim *et al.*, 2012). Such direct associations with small molecule producing TNL sensors might facilitate the activation of EDS1-containing complexes for subsequent interaction with helper NLRs at the plasma membrane, ER or NE. This mechanism may provide a direct molecular link between TNL sensors and helpers (Fig. 3). Whether TIR domain enzymatic products can be generated in the cytoplasm and the nucleus upon effector-triggered TNL oligomerisation, or whether these products translocate between compartments – either by passive diffusion or via active transport – is an important question to address. It also remains to be determined how and in which cellular compartment(s) NRG1/ADR1 and NRC dependent CNL sensors signal to their respective helper NLRs. As no enzymatic function has been identified for CNL sensors and they do not appear to form part of the helper NLR resistosome (Contreras *et al.*, 2022), one possibility is that in the absence/presence of a pathogen effector, they have a direct negative or positive regulatory function on resistosome formation by helper NLRs. Several examples have shown that a mis-localisation to nuclear or cytoplasmic compartments interferes with efficient immune signalling (please refer to Section V). This suggests that the nucleocytoplasmic transport machinery plays a vital regulatory role in spatial communication and complex formation between sensors, helpers, and downstream defence regulators involved in relaying signals derived from activated NLRs.

## V. Nuclear NLRs can function in effector perception, transcriptional reprogramming and cell death induction

The first report linking nuclear NLR receptor localisation to host cell transcriptional reprogramming for pathogen defence uncovered that the barley (*Hv*) CNL MLA10 is nucleocytoplasmic and shows increased nuclear accumulation upon activation by the *Blumeria graminis* effector $Avr_{A10}$ (Shen *et al.*, 2007). Although it is not clear in which cellular compartment *Hv*MLA10 perceives $Avr_{A10}$, the effector-activated *Hv*MLA10 directly associates with the transcriptional repressors, *Hv*WRKY1/2, and with the transcriptional activator of immune response genes, *Hv*MYB6 (Shen *et al.*, 2007; C. Chang *et al.*, 2013). *Hv*MLA10 association releases the *Hv*MYB6 activator from WRKY repression, inducing MYB6-mediated target gene expression and immunity (C. Chang *et al.*, 2013). Whereas the nuclear pool of *Hv*MLA10 confers fungal disease resistance, its cytoplasmic pool is sufficient to trigger host cell death signalling (Bai *et al.*, 2012). This suggests a cell compartment-specific bifurcation of *Hv*MLA10-mediated cell death and defence branches, which may also hold true for other NLRs that induce immune responses across compartment borders. Based on evidence from the activated *At*ZAR1 resistosome structure, it is conceivable that the cytoplasmic pool of *Hv*MLA10 forms a resistosome at the plasma membrane to induce HR cell death, whereas the nuclear pool mediates transcriptional defence against pathogens. Nuclear activities and interactions with transcription factors were also revealed for CNL sensors in other plant species, including chickpea and rice (*Os*) (Inoue *et al.*, 2013; Wang *et al.*, 2016; Hu *et al.*, 2017; Chakraborty *et al.*, 2018; Zhai *et al.*, 2019).

A nuclear function has also been determined for the autoactive variant of the *Arabidopsis* TNL sensor SNC1. Autoactive $SNC1^{E552K}$ as well as wild-type SNC1 are nucleocytoplasmic and a sufficient abundance of the $SNC1^{E552K}$ cellular pool inside the nucleus is required for manifestation of the *snc1* autoimmune phenotype (Palma *et al.*, 2005; Cheng *et al.*, 2009; Wiermer *et al.*, 2010; Lüdke *et al.*, 2021b). Inside the nucleoplasm, SNC1 engages multiple transcription modifiers including TOPLESS-RELATED1 (TPR1) and related co-repressors to repress the transcription of negative regulators of immunity, and the basic helix–loop–helix (bHLH) transcriptional activator bHLH84 and related paralogues for transcriptional defence mobilisation inside the nucleus (Zhu *et al.*, 2010; Xu *et al.*, 2014b). In addition, nuclear SNC1 negatively influences the accumulation of phasiRNAs, leading to a global upregulation of *NLR* transcripts (Cai *et al.*, 2018). In tobacco, the TNL sensor N confers resistance to tobacco mosaic virus (TMV) after recognition of the p50 helicase domain of the viral replicase proteins. Upon TMV infection, p50 recruits the chloroplastic sulfur transferase N RECEPTOR INTERACTING PROTEIN1 (NRIP1) and redirects its localisation to the cytoplasm and nucleus. In the cytoplasm, N recognises either the presence of the NRIP-p50 complex or a p50-induced modification of NRIP1. Activation of N leads to its nuclear interaction with the TF SQUAMOSA PROMOTER BINDING PROTEIN-LIKE6 (SPL6) to reprogram infected host cells for antiviral defence (Burch-Smith *et al.*, 2007; Caplan *et al.*, 2008; Padmanabhan *et al.*, 2013). As a TNL sensor, N depends on the helper NLR NRG1 for resistance against TMV (Peart *et al.*, 2005). As the *snc1* auto-immune phenotype also depends on the *At*ADR1 and *At*NRG1 helper NLR families (Dong *et al.*, 2016; Wu *et al.*, 2019), this suggests that nuclear functions of sensor NLRs in host cell transcriptional reprogramming could generally be helper NLR dependent. It is unclear how such NLR nuclear function could be supported by activated helpers that have been reported to function at the plasma membrane and potentially at other membrane compartments. It is conceivable that $Ca^{2+}$ signalling initiated at the plasma membrane relays back into the nucleus and is supported by nuclear sensor NLR transcriptional functions (Fig. 3). In addition, it remains to be seen whether the nuclear functions

and TF interactions of TNLs requires resistosome formation and TIR-domain enzymatic activity.

The NRC sensor Rx from potato (*St*) mediates extreme resistance to potato virus X (PVX) upon viral coat protein recognition and requires balanced nucleocytoplasmic partitioning to mediate full viral resistance (Bendahmane *et al.*, 1995, 1999; Slootweg *et al.*, 2010; Tameling *et al.*, 2010; Richard *et al.*, 2021). Significantly, activation of *St*Rx by the PVX coat protein (CP) is cytoplasmic and requires functional RanGAP2, which is tethered to the cytoplasmic side of the NE to regulate RAN-dependent nucleocytoplasmic transport. Therefore, RanGAP2 appears to sequester part of the cellular pool of Rx at the NE for recognition of PVX (Sacco *et al.*, 2007; Slootweg *et al.*, 2010; Tameling *et al.*, 2010). In tobacco plants, nuclear Rx is proposed to associate with and reduce the DNA binding activity of the TF GOLDEN2-LIKE1 (*Nb*GLK1) and the DNA-binding bromodomain containing protein *Nb*DBPC that negatively regulate Rx-mediated immune responses to PVX (Townsend *et al.*, 2018; Sukarta *et al.*, 2020). Moreover, *in vitro* DNA binding has been demonstrated for the NB-ARC domain of *St*Rx and other NLRs (Fenyk *et al.*, 2015, 2016). However, the biological relevance of such binding in potential transcriptional control needs to be determined. In contrast with a potential function in restricting pathogen growth via transcriptional control, the autoactive maize CNL Rp1-D21 requires nucleocytoplasmic mobility for the induction of a cell death response in *N. benthamiana* (Wang & Balint-Kurti, 2015). The resistance provided by paired NLRs *Os*Pikh-1 and *OsPikh*-2 also relies on a nucleocytoplasmic distribution and mislocalisation of *Os*Pikh-1 abolishes the cell death response that is triggered upon effector recognition (Zhai *et al.*, 2014). These examples indicate that a mis-localisation of NLRs might interfere with efficient signalling/communication between sensor and helper NLRs or with NLR transcriptional responses.

More examples of NLRs that dynamically distribute between the cytoplasm and the nucleus, and partially function inside the nucleus, include the Solanaceae domain (SD)-containing NRC-sensor Sw5b of tomato, which confers resistance to the tomato spotted wilt virus (TSWV; Brommonschenkel *et al.*, 2000; Spassova *et al.*, 2001). The SD domain of Sw5b is involved in the recognition of a conserved region in the viral movement protein NSm of TSWV (Zhu *et al.*, 2017), but also interacts with several NTRs via NLSs for its localisation to the nucleus (H. Chen *et al.*, 2021). The nucleocytoplasmic distribution and distinct functions of Sw5b within the cytoplasm and the nucleus are required for full immunity. Whereas exclusively nuclear Sw5b can restrict intercellular viral movement, the cytoplasmic pool is required for the induction of a cell death response that restricts viral replication (H. Chen *et al.*, 2021). Whether Sw5b interacts with transcriptional regulators inside the nucleus for defence gene induction that leads to a restriction of viral movement is unknown, but the dependency of Sw5b-mediated viral resistance on the NRC-helpers NRC2/3/4 has recently been revealed (Wu *et al.*, 2017; Z. Chen *et al.*, 2021).

Besides the roles of nuclear NLRs in host cell transcriptional reprogramming or cell death induction, some sensor NLRs require a nuclear localisation for the detection of effector proteins that localise to and function inside the nucleus. The potato late blight resistance protein R1 from *Solanum demissum* requires co-localisation with the *Phytophthora infestans* RxLR effector AVR1 inside the nucleus for activation of cell death (Du *et al.*, 2015). In *Arabidopsis*, the ID containing TNL RESISTANCE TO RALSTONIA SOLANACEARUM1-R (RRS1-R) harbours a WRKY-type TF DNA-binding domain at its C-terminus and cooperates genetically and molecularly with the TNL RPS4 inside nuclei to form a TNL pair. The nuclear localisation of RRS1-R and RPS4 is consistent with their function in recognizing the activity of pathogen effectors that manipulate defence-regulatory WRKY TFs (Deslandes *et al.*, 2003; Heidrich *et al.*, 2013; Sarris *et al.*, 2015; Le Roux *et al.*, 2016). In unchallenged tissues, RRS1-R and RPS4 form a nuclear complex in which RRS1-R functions as a sensor that represses the signalling activity of RPS4 and anchors the RRS1-R/RPS4 complex at chromatin via its WRKY domain (Williams *et al.*, 2014; Sarris *et al.*, 2015; Le Roux *et al.*, 2016; Huh *et al.*, 2017). The DNA-bound WRKY domain of RRS1-R recognises the *P. syringa*e effector AvrRps4, the *Ralstonia solanacearum* effector PopP2, and a yet unidentified effector of *Colletotrichum higginsianum* (Birker *et al.*, 2009; Narusaka *et al.*, 2009; Tasset *et al.*, 2010; Sarris *et al.*, 2015; Saucet *et al.*, 2015; Le Roux *et al.*, 2016). Whereas AvrRps4 is unlikely to possess enzymatic activity (Sohn *et al.*, 2012), PopP2 specifically acetylates lysine residues of multiple WRKY TFs to manipulate DNA promoter binding and transcriptional regulation of defence genes. The PopP2 enzymatic activity is sensed by the integrated WRKY-type domain of RRS1-R, resulting in the release of inhibition on RPS4 to activate NRG1s- and ADR1s-mediated defence (Deslandes *et al.*, 2003; Williams *et al.*, 2014; Sarris *et al.*, 2015; Le Roux *et al.*, 2016; Ma *et al.*, 2018; Castel *et al.*, 2019). As the RRS1-R TIR domain is lacking $NAD^+$ enzymatic activity, it requires the catalytically active TIR domain of RPS4 for signalling upon effector-induced RPS4 TIR domain homo-oligomerisation (Williams *et al.*, 2014; Horsefield *et al.*, 2019; Wan *et al.*, 2019). Whether nucleotide-based small molecules are generated inside the nucleus and/or in the cytoplasm upon redistribution of a potential signalling active RPS4 resistosome, and whether the TIR enzymatic activities in different cellular compartments have spatially distinct signalling functions in disease resistance and cell death, still needs to be determined for RPS4 and other nuclear TNLs. As TIR domains can function as nucleases that produce 2′,3′-cAMP/cGMP from DNA/RNA upon effector recognition, a nuclear localisation of RRS1-R and RPS4 may directly induce DNA/RNA degradation upon disturbance of the transcriptional machinery by effectors at chromatin level.

Notably, *At* RRS1-R and RPS4 also reside in the cytoplasm but accumulate in the nucleus upon pathogen recognition (Deslandes *et al.*, 2003; Wirthmueller *et al.*, 2007; Heidrich *et al.*, 2011), suggesting that NLRs exhibit a degree of effector-triggered mobility as well as functional cooperativity of both subcellular NLR pools. This idea is supported by the finding that forced nuclear localisation of AvrRps4 abolishes cell death responses but retains RPS4-mediated bacterial resistance. AvrRps4, when excluded from either compartment, fails to induce transcriptional reprogramming of defence genes normally observed in the presence of the effector. Thus, cooperativity of cytoplasmic and nuclear functions of RPS4 is required for full activation of immunity (Wirthmueller *et al.*,

2007; Heidrich *et al.*, 2011) and may potentially involve compartment specific TIR enzymatic activities.

In addition to WRKY-domain-containing NLRs there are several BED-domain containing NLRs encoded in wheat and rice genomes that could potentially have a function in DNA/chromatin binding inside nuclei (Yoshimura *et al.*, 1998; Das *et al.*, 2014; Marchal *et al.*, 2018). Indeed, the BED domain-containing rice NLR Xa1 directly interacts with the TF OsERF101 which is implemented in the recognition of transcription activator-like (TAL) effectors of *Xanthomonas oryzae* pv *oryzae* inside the nucleus (Yoshihisa *et al.*, 2021). Moreover, BED domain-containing NLRs that are required for pathogen resistance in wheat contain predicted NLSs, raising questions of whether these NLSs mediate nuclear import and whether they are required for NLR functionality in immunity (Marchal *et al.*, 2020). The presence of NLS signatures on an NLR suggests that it may recognise nuclear effector activities or is involved in transcriptional processes in association with transcriptional regulators or chromatin.

Using NLS prediction tools on the RefPlantNLR dataset (Kourelis *et al.*, 2021b) to detect NLRs that may undergo classical importin-α dependent nuclear transport resulted in the identification of several NLRs predicted to shuttle into the nucleus (Fig. 4; Supporting Information Dataset S1). This includes the known nuclear NLRs *At*RRS1-R/*At*RPS4, *Hv*MLA10 and *Os*Xa1. Whether the predicted NLSs are functional and lead to a nuclear or nucleocytoplasmic localisation requires experimental validation. As some reported nucleocytoplasmic/nuclear NLRs (e.g. *At*SNC1) do not score high for canonical NLSs, alternative localisation signals and importin-α independent nuclear transport pathways might be required for these NLRs. In general, NLR mobility across cellular compartment borders might broaden the cellular surveillance capacities of sensor NLR for pathogen effectors and extend the effector detection and downstream signalling capabilities of the cellular NLR network.

## VI. The nuclear transport machinery directly contributes to the regulation of NLR-mediated plant immunity

The first evidence for a contribution of the nuclear transport machinery to plant immunity was uncovered in an *Arabidopsis* forward-genetic screen for mutants termed *modifiers of snc1* (*mos*). The *mos* screen identified suppressors of autoimmunity activated by the deregulated TNL sensor variant SNC1$^{E552K}$ (Zhang *et al.*, 2003; Zhang & Li, 2005). Some identified *MOS* genes (i.e. *MOS3/NUP96*, *MOS6/IMPORTIN-α3*, *MOS7/NUP88* and *MOS14/TRANSPORTIN-SR*) encode components of the nucleocytoplasmic transport machinery, revealing that this fundamental cellular process is important for deregulated SNC1 signalling, as well as for basal resistance to virulent microbes and for immunity conferred by several other NLRs (Johnson *et al.*, 2012).

### 1. NTRs regulate NLR-mediated plant immune responses

Mutations in the importin-α NTR *MOS6* (*MODIFIER OF SNC1, 6*) partially suppress the autoimmunity of *snc1* and attenuate resistance (Palma *et al.*, 2005; Wirthmueller *et al.*, 2015). *MOS6* encodes IMPORTIN (IMP)-α3, one of nine members of the *importin-α* gene family in *Arabidopsis* (Palma *et al.*, 2005; Wirthmueller *et al.*, 2013). The expansion of the *importin-α* gene family in plants and other higher eukaryotes compared with yeast, which encodes only a single importin-α gene (Conti *et al.*, 1998), supposedly enables tissue- and/or stimulus-specific regulation of nuclear protein import (Wirthmueller *et al.*, 2013). In addition, the presence of multiple paralogues may effectively buffer signalling pathways against pathogen interference or mutations. In plants, there are examples of functional redundancies among importin-α family members for certain cargo proteins, but there is also evidence for cargo selectivity (Lüdke *et al.*, 2021a). Examples of importin-α binding selectivity of transported cargo clients includes NLR proteins and downstream signal transducers. For instance, the truncated NLR protein TN13 interacts with MOS6/IMP-α3 but not with its closest homologue IMP-α6 (Roth *et al.*, 2017). Consistent with the genetic dependency of *snc1* autoimmunity on functional *MOS6*, and with the requirement of the nuclear pool of autoactive SNC1$^{E552K}$ for the *snc1* autoimmune phenotypes (Cheng *et al.*, 2009; Wiermer *et al.*, 2010; Xu *et al.*, 2014b), SNC1 forms nuclear import complexes with MOS6 *in planta*, but only weakly associates with the other isoforms (Lüdke *et al.*, 2021b). Considering the high sequence similarity of the cargo-NLS binding sites among the *Arabidopsis* α-importins (Wirthmueller *et al.*, 2013, 2015), it is surprising that MOS6 preferentially associates with SNC1 and TN13, and that only mutations in *MOS6*, but in none of the other *importin-α* genes, suppresses *snc1* nor causes defects in basal immunity (Palma *et al.*, 2005; Roth *et al.*, 2017; Lüdke *et al.*, 2021b). Stimulus-induced transcriptional and posttranslational modulation of importin-α protein levels and NLS binding activities, respectively, may be potential mechanisms to allow importin selectivity (Christie *et al.*, 2016). However, the specificity determinants that could explain the high preference of NTRs are not known and functional evidence on how and to what extend plants actively regulate nuclear protein import kinetics and specificities in response to environmental and developmental signals remains poorly understood.

Whereas MOS6/IMP-α3 is likely to mediate nuclear import of SNC1 and positively regulates the autoimmunity of *snc1*, the importin-β NTR KA120 constrains the nuclear accumulation of SNC1 to prevent SNC1-dependent autoimmunity (Jia *et al.*, 2021). Inside the nucleus, autoactive SNC1 associates with TPR1 and other related transcriptional corepressors to repress the expression of negative immune regulators, therefore activating immunity (Zhu *et al.*, 2010). A recent study found that the nuclear export activity of the exportin XPO4 antagonises the accumulation of TOPLESS (TPL) and TPR proteins inside the nuclei of *constitutive expresser of PR genes5* (*cpr5*) plants, thereby modulating SA-dependent autoimmune responses that are activated in the *cpr5* nucleoporin mutant (please refer to the following section for further details on CPR5 functions in NLR dependent immunity; Xu *et al.*, 2021).

Another *NTR* gene that was identified from the *mos* genetic screen is *MOS14*, which encodes the importin-β superfamily protein TRANSPORTIN (TRN)-SR. Consistent with MOS14 permitting nuclear import of serine/arginine-rich (SR) splicing

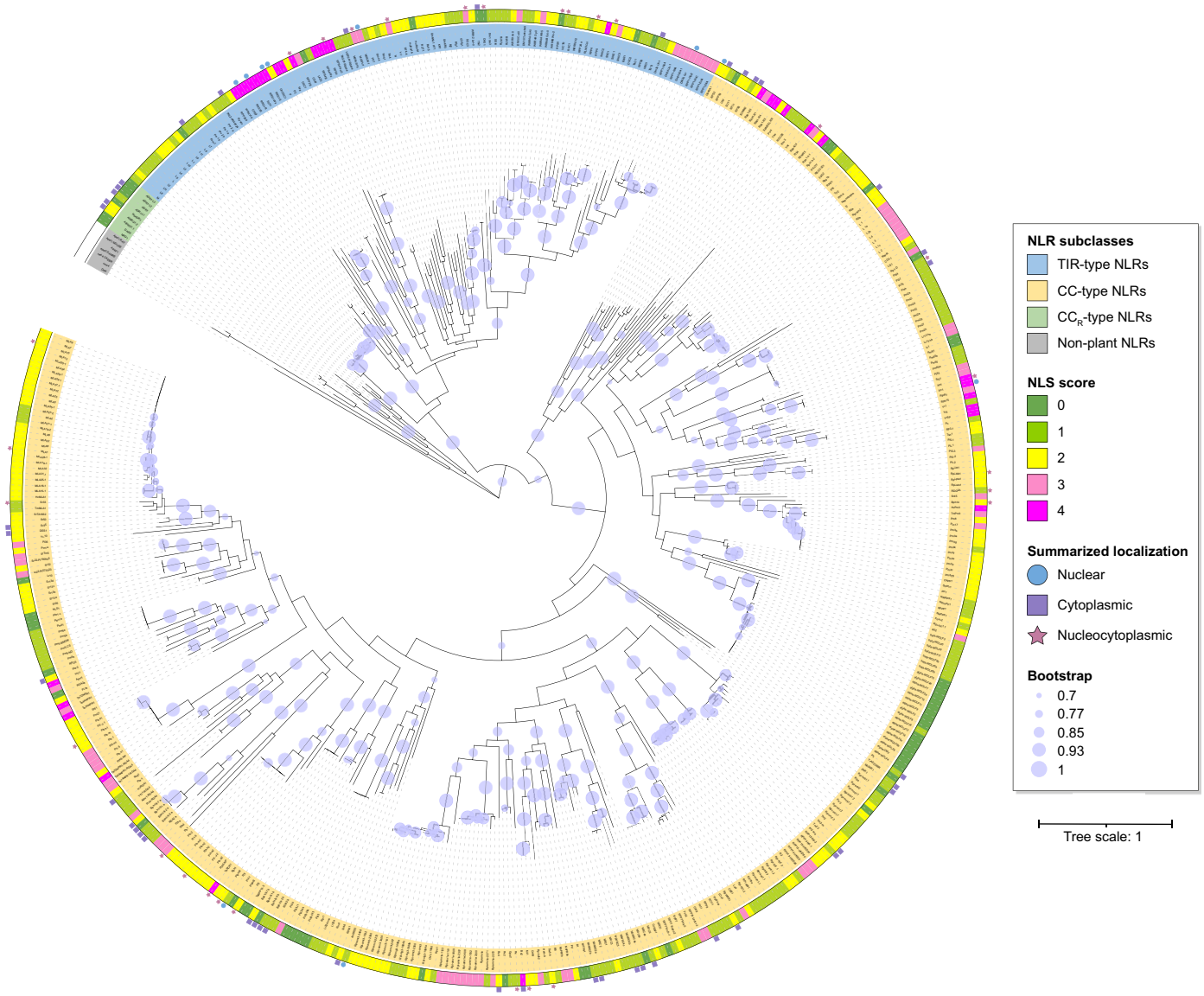


**Fig. 4** Phylogenetic relationship, NLS-scores and experimentally observed subcellular localization of plant nucleotide-binding leucine-rich repeat immune receptors (NLRs). Maximum-likelihood tree based on the NB-ARC domains (provided by RefPlantNLR; Kourelis *et al*., 2021b), using a Jones–Taylor–Thornton substitution model with 100 bootstraps. Numbering in square brackets in the protein name indicates the position of the NB-ARC domain according to the domain position for cases where multiple NB-ARC domains are present. Non-plant NLRs serve as outgroup. The NLR subclades are indicated by colouring of the protein names. The nuclear localization signal (NLS) score is provided as a color-coded scale from 0 (low) to 4 (high). For calculation of the NLS scores, the full-length protein sequences were submitted to NLStradamus (Nguyen Ba *et al*., 2009; cutoff 0.4), NLSdb (Bernhofer *et al*., 2018), NucPred (Brameier *et al*., 2007; cutoff 0.7) and cNLSmapper (Kosugi *et al*., 2009; cutoff 0.3). For batch submission to cNLSmapper, a previously published ruby script was used (Oehring *et al*., 2012). When an NLS or a nuclear localization was predicted by any program, a score of 1 was assigned, independently of the number of predicted NLSs. Scores received from each program were added for each protein to receive the final NLS score as an approximation for a possible nuclear localization. An overview of the prediction results can be found in Supporting Information Dataset S1. The summarized experimentally observed subcellular localisation is depicted by different symbols.

factors, *mos14* mutant plants show specific splicing defects of *SNC1* and *RPS4* transcripts and, accordingly, are compromised in *snc1*- and *RPS4*-dependent (auto-)immunity (Xu *et al*., 2011). It is unknown whether the overall decreased accumulation of *SNC1* and *RPS4* transcripts observed in *mos14* is caused by nuclear retention or the elevated decay of aberrantly processed mRNAs. Another nuclear MOS protein implicated in RNA metabolism is the predicted RNA-binding protein MOS11. The functional relationship of MOS11 and MOS14 is unclear. MOS11 appears to function in nuclear export of mRNAs, including transcripts that encode positive regulators of the *snc1* autoimmune pathway (Germain *et al*., 2010).

## 2. NPC integrity is a requirement for regulating NLR-mediated plant immune responses

The *mos* screen also revealed regulatory roles of the NPC in NLR mobility and in spatial coordination of resistance pathways

between the cytoplasm and the nucleus, which appear to provide plants with a flexible system to control and/or fine-tune defence outputs. *MOS7* encodes *Arabidopsis* NUP88 and the complete loss of its function is lethal (Cheng *et al.*, 2009). The *mos7-1* mutation is a partial loss-of-function allele resulting in a four amino acid deletion that impairs its interaction with NUP98A/B, two FG-NUPs involved in regulating the NPC permeability barrier (Genenncher *et al.*, 2016). *Mos7-1* mutants show broad defects in immunity to biotrophic, hemi-biotrophic and necrotrophic bacterial, fungal and oomycete pathogens, including autoimmunity of *snc1* and immunity mediated by both TNLs and a subset of CNLs. Consistent with these immunity defects *mos7-1* plants are impaired in nuclear retention of the autoactive NLR $SNC1^{E552K}$, and of important nucleocytoplasmic immune regulators such as EDS1 and the protein kinase MPK3 (Cheng *et al.*, 2009; Genenncher *et al.*, 2016).

It was proposed that the wild-type MOS7 protein tethers NUP98A/B to the NPC to attenuate NTR-mediated nuclear export of defence regulators, therefore promoting their nuclear accumulation and immune response activation (Genenncher *et al.*, 2016). Because NTR conformations can be influenced by specific cargos, and the NTR–cargo conformation can determine the binding sites within the central transport channel, and therefore the export route of transport complexes through the NPC (Wu *et al.*, 2001; Yang *et al.*, 2004; Kubitscheck *et al.*, 2005; Wohlwend *et al.*, 2007; Ma *et al.*, 2012), we speculate that certain immune regulatory cargos may impose a NTR conformation that depends on binding to NUP98/MOS7 for nuclear retention. Therefore, MOS7 may be involved in signal integration and crosstalk regulation of multiple defence pathways to modulate plant immune responses at the level of cargo translocation across the NPC.

Whereas the *mos7-1* mutation compromises plant (auto)immune responses, mutation of the plant-specific transmembrane nucleoporin CPR5 results in autoimmunity and spontaneous cell death (Bowling *et al.*, 1997). CPR5 is implicated as a regulatory module of nuclear pore permeabilisation during NLR-mediated immunity and cell death (Gu *et al.*, 2016). In uninduced tissues, CPR5 forms homo-oligomeric complexes at the NPC and behaves as a negative regulator of NLR-mediated immunity and HR cell death. Nucleotide-binding leucine-rich repeat immune receptor signalling is proposed to disrupt CPR5 oligomer formation and therefore the NPCs selective permeability barrier. This not only provides nuclear access for stress signals, but also allows the dissociation of cyclin-dependent kinase inhibitors (CKIs) from the NPC to permit their nuclear translocation for noncanonical activation of immune gene expression (Wang *et al.*, 2014; Gu *et al.*, 2016). Therefore, there is evidence that, upon activation of NLR-mediated immunity, the NPC undergoes a conformational change and has an active regulatory role in coordinating nucleocytoplasmic transport and signal transduction for the activation of immunity. Intriguingly, the *mos7-1* mutation rescues autoimmunity of *cpr5*, suggesting that the CPR5-gated nuclear influx of stress signal transducers requires subsequent MOS7-mediated nuclear cargo retention to mount sufficient (auto)immunity and cell death (Gu *et al.*, 2016).

Several members of the *Arabidopsis* NUP107-160 NPC subcomplex also play important roles in plant (auto)immune responses. For example, a mutation in *Arabidopsis NUP96* was identified and named *MOS3* (Zhang & Li, 2005). The evolutionary conserved NUP107-160 complex is the largest subcomplex of the NPC, comprising approximately one-fourth of the *c.* 40 constituent NUPs (Tamura *et al.*, 2010; Tang *et al.*, 2020; Kang *et al.*, 2022). Further forward- and reverse-genetic approaches in *Arabidopsis* have uncovered additional NUP107-160 complex members as components of the plant immune system, some of which appear to connect cell surface PRR-triggered and intracellular NLR-triggered defence signalling branches (Wiermer *et al.*, 2012; Du *et al.*, 2016). For example, *NUP85* is required for the autoimmunity and spontaneous cell death activated by the simultaneous loss of the RLK BRI1-ASSOCIATED KINASE1 (BAK1) and its closest homologue BAK1-LIKE1 (BKK1; He *et al.*, 2007; Du *et al.*, 2016). The *bak1 bkk1* double mutant phenotypes also depends on the NUP107-160 complex members NUP160, MOS3/NUP96 and SEH1, as well as on the NUP107-160 complex associated DEAD-box RNA HELICASE1 (DRH1) that is required for nuclear mRNA export. By contrast, mutations in other NUP107-160 complex members did not suppress *bak1 bkk1*-induced autoimmune responses (Du *et al.*, 2016). This selective involvement in *bak1 bkk1*-triggered autoimmunity is consistent with the genetic requirement of *NUP160*, *MOS3/NUP96* and *SEH1* in surface receptor-triggered defence responses to virulent *P. syringae* bacteria (Wiermer *et al.*, 2012). *NUP160*, *MOS3/NUP96* and, to a lesser extent, *SEH1* are also important for *snc1*-dependent autoimmunity and immunity mediated by other TNLs against avirulent pathogen isolates (Zhang & Li, 2005; Roth & Wiermer, 2012; Wiermer *et al.*, 2012), further highlighting that transport processes across the NPC are potential integration and convergence points in PRR- and NLR-mediated signal transduction. As a mutation in *MOS7* but not in the *Arabidopsis* NUP107-160 complex members *NUP85*, *NUP160* and *NUP96* rescues the *cpr5* autoimmune phenotype (Gu *et al.*, 2016), there may be a differential requirement for certain members of the NPC in immune response regulation.

The induction of a cell death response in *bak1 bkk1* double mutants, its genetic dependency on certain nucleoporins, and the finding that certain NUPs control the NPC permeability during NLR-mediated signalling, suggests that the protein abundance of the RLKs BAK1 and BKK1 at the plasma membrane is monitored by an NLR sensor. Indeed, the autoimmune and cell death phenotypes of *bak1 bkk1* depend on the ADR1 family of helper NLRs (Wu *et al.*, 2020). Accordingly, depletion of activated BAK1 and its paralogues by the *P. syringae* effector protein HopB1 also triggers an *At*ADR1-dependent cell death response (Wu *et al.*, 2020). In a recent preprint, the TNL protein *At*CSA1 and the genetically linked *At*CHS3 were uncovered as components of autoimmune responses triggered by the loss of BAK1 and BAK1-INTERACTING RECEPTOR3 (BIR3), suggesting that the *At*CSA1–*At*CHS3 pair is involved in guarding the cellular homeostasis of a BAK1/BIR3 receptor complex at the cell surface (Schulze *et al.*, 2021). Whereas the *bak1 bkk1* cell death is fully dependent on the ADR1 family of helper NLR proteins, the cell death of *bak1 bir3* also requires the NRG1 helper NLR family, consistent with *At*CHS3 being *At*NRG1 dependent (Schulze *et al.*,

2021). These findings are also in line with several recent reports describing the mutual potentiation and functional interdependence of PRR- and NLR-mediated immunity in plants, which appear to be modulated by the nuclear trafficking machinery (Ngou *et al.*, 2021; Pruitt *et al.*, 2021; Kourelis *et al.*, 2021a; Yuan *et al.*, 2021a). Accordingly, PRR- and NLR-mediated immune responses rely on the transcriptional reprogramming of a similar set of genes inside the nucleus, and defects in certain members of the NPC and the nucleocytoplasmic transport machinery affect both pattern- and effector-triggered immune responses. It therefore appears plausible that some signalling cascades initiated from activated PRRs and NLRs converge at the level of the NPC when a common defence signal is transmitted into the nucleus for conversion into transcriptional responses. Whether the nuclear transport machinery is involved to the same extent in mediating immunity in pathogen-infected and -uninfected neighbouring/systemic cells remains to be investigated.

## VII. Conclusions

In the past few years, considerable progress has been made in understanding how intracellular NLR immune receptors relay effector perception into host cell death and pathogen resistance. Recent structure–function analyses of tetrameric TIR holoenzyme formation by pathogen-activated sensor TNLs, pentameric pore formation at the host plasma membrane by the activated MADA motif-containing singleton CNLs *At*ZAR1 and wheat Sr35, as well as the studies on $CC_R$-type helper NLRs NRG1 and ADR1, provide exceptional new insights into NLR resistosome signalling events. However, plant NLRs locate to different cellular compartments, including the plasma membrane, ER, cytoplasm and nucleus, and additional research is required to reconcile these localisations with NLR activation and resistosome formation. Therefore, key questions that remain unanswered are whether activated helper NLR resistosomes target other membrane-enclosed compartments such as the ER or the ONM and INM of the NE for perturbing cellular ion homeostasis via pore formation. Another pressing question is whether TNL holoenzymes are enzymatically active in the cytoplasm and/or the nucleoplasm and whether their catalytic products require signal transmission across cellular compartment borders for the induction of transcriptional defences and/or host cell death mediated by helper NLRs. As at least a subset of sensor NLRs directly interacts with transcription factors and initiates transcriptional changes within the nucleus, yet still genetically requires the function of helper NLRs in some cases, a deeper understanding of the connection and the molecular signalling mechanisms between sensors and corresponding helper NLRs across compartment boundaries is required. Therefore, investigating spatially and temporally resolved *in vivo* pre- and postactivation NLR dynamics and complex formations with downstream signalling components such as the lipase-like proteins EDS1, PAD4 and SAG101 will be another future research challenge towards a deeper understanding of NLR-mediated immune signalling and its interplay with surface receptor-triggered defences at subcellular resolution. To this end, the NPC and its associated transport machinery provide both intracellular and surface receptor defence branches with a highly selective and tunable system to mediate signal integration and communication between the nucleus and the surrounding cytoplasm for the induction of defence responses.

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## Data availability

The data that support the findings of this study are openly available at doi: 10.1371/journal.pbio.3001124 and in Dataset S1.

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## Supporting Information

Additional Supporting Information may be found online in the Supporting Information section at the end of the article.

**Dataset S1** Overview of nuclear localisation signal (NLS) scores for NLRs.

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