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The NLR gene family: from discovery to present day

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Abstract

The mammalian nucleotide-binding domain leucine-rich repeat containing (NLR, NBD-LRR or NOD-like receptor) family was reported over 20 years ago, although several genes later grouped in the family were already known. While it is widely known that NLRs include inflammasome receptors/sensors leading to the maturation of caspase 1, IL-1β, IL-18 and gasdermin D to drive inflammation and cell death, the other functions of NLR family members are much less known to the scientific community. Examples include CIITA, a master transcriptional activator of MHC class II genes, which is the first mammalian NBD-LRR containing protein identified and NLRC5, which regulates MHC class I genes. Other NLRs regulate key inflammatory signalling pathways or interferon responses and several NLR family members serve as check points of innate immunity by serving as negative regulators. Multiple NLRs regulate the balance of cell death, cell survival, autophagy, mitophagy and even cellular metabolism. The least mentioned is a group of NLRs that play important non-immune functions to affect the mammalian reproductive system. The focus of this review is to provide a synopsis of the NLR family, both the intensively-studied and the underappreciated members. We will focus on their function, structure and disease relevance and include issues that have received less attention in the NLR field that may serve as an impetus for future research on their conventional and nonconventional roles within and beyond the immune system.

Introduction

The initial description of the human NLR family was preceded by the identification of a related family in plants (Fig. 1C). The plant nucleotide-binding sequence leucine-rich repeat (NBS-LRR)-containing proteins are the largest group of plant disease resistance (R)

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proteins[1]. These proteins contain a nucleotide-binding domain (NBD) and LRR domain with variable C- and N-terminal domains. The majority of plant NBS-LRR proteins have either a TIR (Toll/ IL-1 receptor) domain — referred to as TNLs (TIR-NBS-LRRs) — or coiled-coil (CC) domains — referred to as CNLs (CC-NBS-LRRs) — and these domains are considered important for protein–protein interaction. NBS-LRR proteins are critical for host defense against viruses, bacteria, nematodes, fungi, oomycetes and insects[2,3].

In 2000, our group noted that similarities between NBS-LRR proteins, MHC class II transactivator (CIITA)[4] **[G]** and nucleotide-binding oligomerization domain-containing protein 1 (NOD1, also known as CARD4) in terms of their nucleotide-binding domain (NBD) and LRR sequences and additionally noted the similarity in size and spacing of these domains[5]. Subsequently we identified a large family of 22 NBD-LRRs encoding human genes, with CIITA as the founding member[6] (Fig. 1B and Fig. 2, Timeline). These genes were identified by BLAST homology searches of available genome sequences before the human genome was fully assembled. Family members have divergent N-termini, including the acidic transactivation domain of CIITA, baculovirus inhibitor of apoptosis repeat domain (BIR), pyrin domain (PYD) or caspase recruitment domain (CARD).

Several other research groups had parallel findings regarding NBD-LRR family members. Human neuronal apoptosis inhibitory protein (NAIP) was originally thought to be deleted in spinal muscular atrophy[7], but the deletion was later attributed to a neighboring genetic region. Nonetheless the encoded protein was noted as having BIR and NBD-LRR domain and negatively regulates apoptosis[8]. Koonin and Aravind used NAIP, CIITA and two other proteins to define the conserved NACHT domain **[G]** which includes the sequences that cover the ATP/GTPase specific P-loop, the Walker A and B motifs and five additional motifs[9]. Two CARD containing proteins, NOD1/CARD4[10,11] and NOD2/CARD15[12] were found to activate NF-κB and are sensors of processed fragments of bacterial peptidoglycan[13–16]. Additionally, NOD2 frameshift and missense variants are genetic risk factors associated with Crohns' disease[17,18], first establishing these as pathogen recognition molecules important in inflammatory diseases. Inohara and Nunez noted similarities in the nucleotide-binding and oligomerization domain (NOD) of Apaf-1 **[G]**, Ced-4, NOD1, NOD2 and the plant disease resistance genes and proposed that these constitute a family — the NOD family [19]. Another CARD-NBD-LRR protein, IPAF (now referred to as NBD-, LRR- and CARD-containing protein 4 (NLRC4)), was discovered by Poyet et al. and found to associate with pro-caspase 1, leading to caspase 1 maturation[20]. Two other groups focused on the PYD-containing subgroup. Martinon, Burns and Tschopp first showed that NALP1 (now referred to as NBD-, LRR- and PYD-containing protein 1 (NLRP1)), has caspase maturation activity which they coined the term "the inflammasome" [21], and later reported a 14-member PYD-containing family[22]. Bertin's group focused on the PYD-containing Apaf1-like proteins — which they named PYPAFs — and showed that PYPAF7 (now known as NLRP12) and PYPAF5 (now known as NLRP6) induced caspase 1-dependent cytokine processing activity and NF-κB-activating function when co-expressed with the ASC **[G]** adaptor protein[23,24]. The link of these proteins to human was first demonstrated by transformative human genetics study from Hoffman et al. in 2001 which identified mutations in *CIAS1* (cold-induced autoinflammatory syndrome 1; now known as *NLRP3*) to be the

cause of two rheumatological diseases, namely familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome[25]. NLRP3 was later shown to direct the cleavage of pro-caspase 1 as well, thus representing the second inflammasome effector protein to be described[26]. These initial discoveries of NLR family members in the 1990s to the early 2000s kicked off over two decades of exciting progress in the field of innate immunity (Fig. 2, Timeline). In a surprising twist, a family of prokaryotic anti-viral STAND **[G]** (Avs) proteins was recently described that utilizes a similar oligomerizing NBD and sensor domain architecture to eukaryotic NLRs (Fig. 1D)[27]. Some of these Avs proteins use their sensor domains to detect the presence of phage proteins, and oligomerization brings N-terminal endonuclease domains into a complex to degrade phage DNA. Thus, this threat dependent, induced-proximity mechanism has remarkably been consistently utilized for cellular defense in all kingdoms of life.

In this Review, we will provide an overview of our current understanding of the NLR protein subgroups and discuss their biology, mechanisms of action and physiological relevance. Due to the expansiveness of this topic, we cannot credit all relevant work in the field; we apologize for this and refer the reader to other reviews for topics that have been extensively reviewed[28,29]. The intention here is to present a brief overview of well-known NLRs but to also discuss those members that have received less attention. NLR family members mediate a wide variety of functions, including serving as transactivators of MHC gene transcription, as inflammasome receptors and sensors, as positive and negative modulators of signalling pathways and in a variety of cell death processes. We discuss the key roles of each of these NLR functional subgroups and offer a forward-looking perspective on the field.

NLRs as transcriptional regulators

Although NLR proteins are primarily thought of as innate immune sensors, the founding member, CIITA, and the related protein NLRC5, are master transcriptional regulators of MHC class II (MHC II) and MHC class I (MHC I) genes, respectively (Fig.1, Table 1). CIITA was identified via complementation cloning using a mutant cell line devoid of MHC II expression, and mutations in *CIITA* were found in bare lymphocyte syndrome (BLS), an immunodeficiency caused by the lack of MHC II[4]. CIITA shuttles between the nucleus and cytoplasm[30], and its expression pattern precisely matches that of MHC II and its accessory proteins[31,32]. Consistent with its role as a transcriptional co-activator, CIITA contains an N-terminal acidic transactivation domain. The NACHT domain of CIITA was shown to bind GTP although this study was not conducted with highly purified protein[33]. There is no clear evidence that CIITA binds DNA directly, and therefore it mediates its activity via interactions with transcription factors bound to the SXY cis-elements **[G]** [34] in the promoters of all MHC II genes, leading to recruitment of chromatin modifiers including histone acetyltransferases and methylases[35]. CIITA has interesting associations with cancer, including its absence in some cancers[36,37], its transduction to active tumour immunity[38], and its role as a gene fusion partner in lymphoid cancers[39].

Similarly to CIITA, NLRC5 also shuttles between the nucleus and cytoplasm, and its primary function is to upregulate MHC class I and accessory protein gene expression[40]. NLRC5 also requires an SXY cis-acting module in MHC I promoters for transcriptional

activation. In contrast to CIITA, the N-terminus of NLRC5 is composed of an atypical CARD and lacks an acidic activation domain. NLRC5 also contains a much larger C-terminal LRR region with up to 38 LRRs. In contrast to the highly restricted expression of CIITA, NLRC5 is expressed constitutively with elevated expression observed in T cells, B cells and NK cells. The role for NLRC5 in MHC I gene expression was clearly shown in the NLRC5-deficient mice generated by several groups[41–43]. The loss of NLRC5 has the greatest effect on MHC I expression in T cells, natural killer (NK) cells, and natural killer T (NKT) cells, whereas MHC I expression in macrophage is more modestly reduced in NLRC5-deficient mice. The role of NLRC5 in controlling MHC I expression in other cell types is modest to absent. Hence, NLRC5 differs from CIITA in that its impact is not observed in all MHC I positive cells. Similarly to CIITA, it is also a target of immune evasion in cancer[44]. An additional role in regulating inflammatory cytokines has been proposed for NLRC5. In one model, direct interaction between NLRC5 and IKKα/β blocks interaction with IKKγ resulting in reduced NF-κB activation[45]. Analysis of NLRC5-deficient mice has not consistently verified this physiological role for NLRC5, and these conflicting studies have been reviewed elsewhere[46].

NLRs in inflammasomes and pyroptosis

In this section, we provide an overview of the NLR family members that form inflammasomes (Fig. 3, Table 1.). Regulated inflammasome signalling is vital for homeostasis and tissue repair, but dysregulated inflammasome signalling is central to many diseases (Fig. 3, Table 1.).

NLRP3 inflammasomes.

NLRP3 is the best studied of the inflammasome sensors, and it detects pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Its significance in autoinflammatory diseases and its mechanisms of activation have been detailed in many excellent reviews[29,47]. This section is not intended to provide a comprehensive review of this topic. NLRP3 inflammasome assembly with pro-caspase 1 and ASC leads to proteolytic maturation of caspase 1[48]. Caspase 1 in turn cleaves and activates more than 70 substrate proteins, including the pro-inflammatory cytokines IL-1β and IL-18. Cleavage of Gasdermin D (GSDMD) by caspase 1 was found to be necessary and sufficient for pyroptosis[49,50]. The N-terminal fragment of GSDMD forms a multimeric membrane pore to cause pyroptotic cell death[51–54] and facilitate the release of IL-1β and IL-18 via a non-conventional mode of secretion. The discovery of NLRP3's inflammasome activity helped to define its role in IL-1β release in cryopyrin-induced autoinflammatory syndromes (CAPS) **[G]** [25,26]. CAPS include several diseases with increasing disease severity, including FCAS1, Muckle-Wells syndrome and the severely debilitating chronic infantile neurological cutaneous and articular syndrome[55] (CINCA; also known as neonatal-onset multisystem inflammatory disorder (NOMID)). The NLRP3 inflammasome has also been implicated in many other diseases, ranging from autoinflammatory, metabolic and neurodegenerative to infectious diseases[48].

Assembly of the fully functional NLRP3 inflammasome is initiated by two distinct steps: priming and activation. The priming step involves the recognition of PAMPs or DAMPs via receptors such as TLRs or NOD2, or the detection of TNF and IL-1β, which leads to NF-κB activation and increased cellular expression of NLRP3, caspase 1 and IL-1β[56–58]. In addition, post-translational modifications (PTMs) of NLRP3 including phosphorylation[59] and deubiqitination[60,61] promote NLRP3 activation, while ubiquitination[62] and sumoylation[63] suppress NLRP3 inflammasome activity. In the activation step, NLRP3 oligomerizes through homotypic interactions between NACHT domains, which serves as a scaffold to nucleate ASC through PYD–PYD interactions[64,65]. ASC and pro-caspase 1 combine via CARD–CARD interactions leading to the formation of prion-like filaments. Pro-caspase 1 undergoes auto-proteolytic cleavage and processing into mature caspase 1 within this complex[66]. Several groups identified NIMA-related kinase 7 (NEK7) as an essential component of NLRP3 inflammasome activation[67–69](Fig. 3). NEK7 oligomerizes with NLRP3 to form a complex that promotes ASC speck formation and caspase 1 activation[70]. NEK7 interacts with NLRP3 but not with the NLRC4 and AIM2 inflammasome sensors.

Whereas the so-called ‘canonical’ activation of NLRP3 inflammasome activates caspase 1, non-canonical activation of NLRP3 inflammasome activates caspase 4 and caspase 5 in humans, and caspase 11 in mice[71–73]. Non-canonical NLRP3 inflammasome activation occurs in response to intracellular LPS sensing by caspase 4/11, resulting in the secretion of IL-1β and IL-18 and the induction of pyroptosis, which can lead to endotoxemia-induced death [72,74,75]. Caspase 11 can be induced by TRIF and senses intracellular LPS from cytosolic gram-negative bacteria that have escaped vacuoles[73]. Caspase 8 can activate canonical and non-canonical NLRP3 inflammasomes in response to many pathogenic stimuli[76–79]. Caspase 8 initiates apoptosis in response to FASL and TNF and protects against necroptosis.

Several studies have reported that inflammasome activation can involve more than one sensor. For example, NLRP3 and NLRC4 both activate caspase 1 in response to PAMPs from *Salmonella typhimurium*[80,81] and to DAMPs, such as lysophosphatidylcholine, which causes demyelination[82]. NLRP3 and AIM2 **[G]** inflammasomes are activated by *Plasmodium* parasite-derived hemozoin and DNA[83] and by *Aspergillus* fungi[84]. Cytosolic DNA sensed by the cGAS–STING pathway, activates the NLRP3 and AIM2 inflammasomes via cGAMP production[85]. Dual-sensing mechanisms may reflect cooperative function within a cell or independent inflammasomes within a cell.

Despite extensive studies, the precise mechanism through which NLRP3 becomes activated remains unclear (see also later section on ‘Structure of NLR proteins’). However, NLRP3 can be activated by many diverse pathways, including through the chemical disruption of glycolysis[86] or accumulation of cholesterol crystals[87] or free fatty acids[88]. It is presumed that common downstream molecules associated with cellular damage are the critical activators of NLRP3. Mitochondrial DNA is a candidate for a downstream mediator that can increase NLRP3 activation[89,90]. RNA also has been shown to activate NLRP3, and the mitochondrial antiviral signalling protein (MAVS) has been implicated in this process[91–94]. Although K^+ efflux is also suggested to be a common activation pathway of NLRP3[95],

N-acetylglucosamine-induced hexokinase relocalization promotes NLRP3 inflammasome activation independently of K^+ efflux in certain bacterial infections[96].

The intense focus on the role of NLRP3 inflammasome activation and pyroptosis in numerous disease models has led to the development of many NLRP3 inhibitors[97]. While some of these inhibitors affect the conformation of NLRP3 (Oridonin, MCC950, and tranilast), others affect its function (OLT1177 and Parthenolide) or binding to signaling partners (BAY11–7082 and VI-16)[98]. These inhibitors show promise as future therapeutics for a range of inflammatory diseases.

NLRP1 inflammasomes.

Human NLRP1[21] (also known as DEFCAP, CARD7, NAC and NALP1)[99–101] is a PYD- and CARD-containing NLR protein first found to induce pro-IL-1β cleavage in an in vitro, cell-free reconstitution assay when combined with caspase 1, caspase 5 and ASC. Indeed, experiments with NLRP1 led to the term ‘inflammasome’ being coined (Fig. 2). NLRP1 is highly expressed in keratinocytes and has been associated with several skin diseases[102–107] (Table 1.). NLRP1 is also found in the lung and is associated with chronic obstructive pulmonary disease (COPD)[108] and recurrent respiratory papillomatosis[109]. Finally, *NLRP1* polymorphisms are associated with a novel autoinflammatory disorder, NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD)[107].

NLRP1 exhibits significant genetic divergence in different species. Humans have one *NLRP1* gene, while mice have four *Nlrp1* homologue/paralogue genes[110]. Human and mouse NLRP1 are also divergent in their protein structure. Human NLRP1 contains an N-terminal PYD and a C-terminal CARD that flank a central NACHT, LRR and FIIND (function to find) domain, while mice have an N-terminal NR100 **[G]**. Although the N-termini of human and mouse NLRP1 are different, they both represent autoinhibitory domains[111,112], which are removed by proteolytic cleavage of the N-termini resulting in its activation[113,114]. For example, the N-terminal NR100 domain of mouse NLRP1B[115] and rat NLRP1[116] is cleaved by *B. anthrax* lethal toxin (LT)[117–119]. In contrast, the human N-terminal PYD is resistant to LT. This cleavage exposes a new N-terminus which undergoes N-end rule-mediated degradation by ubiquitin ligase-mediated degradation, resulting in the release of the C-terminus, which is freed to interact and recruit pro-caspase 1 through its CARD, resulting in caspase 1 maturation[120–122]. Ubiquitin ligases and proteases that can cause NLRP1 cleavage include ubiquitin ligase UBR2[122], *Shigella flexneri* IpaH7.8 [121], and picornavirus 3C proteases[123]. The 3C protease cleaves human NLRP1, exposing a new N-terminus, which then undergoes N-glycine-mediated degradation, thus liberating the UPA (UNC5, PIDD and ankyrin) and CARD domains to form an inflammasome.

The FIIND domain of NLRP1 also undergoes proteolytic cleavage. The serine proteases dipeptidyl peptidase 8 (DPP8) and DPP9 interact with the FIIND domain of human NLRP1 to maintain it in an inactive state, and a DPP8/9 inhibitor, ValboroPro (VbP, or Talabostat) reverses this inhibition[111,124–126]. VbP causes the proteasome-dependent degradation of the N-terminus of NLRP1 and the autoproteolytic cleavage of the FIIND domain at the ZU5 (ZO-1 and UNC5) and UPA subdomains, releasing the C-terminal domain that includes CARD to recruit pro-caspase 1 [113,114,127]. Cryo-EM shows a ternary complex of DPP9

full-length NLRP1 and the C-terminus of NLRP1[128,129]. It is postulated that the full length NLRP1 inhibits activation of the C-terminal NLRP1 since an autocatalytic deficient full-length NLRP1 promotes inhibition of the C-terminal fragment. Thus, VbP weakens NLRP1-DPP9 interaction to induce inflammasome activation.

NLRP1 can also be activated by *Toxoplasma* parasites, bacteria, viruses and long dsRNAs[130–133]. Regarding the last, it was shown that human but not mouse NLRP1 binds dsRNA through its LRR domain[134]. NLRP1B can also be activated by energy deprivation and nutrient depletion of ATP. In contrast to other NLRs, where ATP binding is necessary for their functional activity, the ATP-binding domain in NLRP1B inhibits its function[135] and this inhibition of NLRP1B by ATP also requires the FIIND region[136]. A recent paper sheds some light on the effect of ATP on NLRP1 activation. It shows that oxidized but not reduced thioredoxin-1 (TRX1) can interact with NLRP1 NACHT-LRR domain to restrain the activation of NLRP1, and this process is ATP-dependent process[137]. Furthermore, both patient-derived and ATPase-deficient mutant blocked binding to oxidized TRX1 leading to inflammasome activation. The authors suggest that under reductive stress when oxidized TRX1 is reduced, NLRP1 can be activated. Others have shown that inhibition of TRX1 activity induces the β-amyloid activated NLRP-1/caspase-1/GSDMD pyroptotic response[138]. Recently, another form of stress, ribosome stress, is also found to cause the hyperphosphorylation and activation of human NLRP1 by the ribotoxic stress response kinase ZAKα (also known as MAP3K20) and p38 [139]. Thus NLRP1 is activated by a number of cell stress inducers.

NLRC4/NAIP inflammasomes.

NLRC4 was the first NLR shown to associate with pro-caspase 1 leading to caspase 1 activation and subsequent cell death[20]. NLRC4 is important for caspase 1 activation after exposure to *Salmonella typhimurium*[140] due to *Salmonella* flagellin[141]. Components of the bacterial type III secretion system (T3SS) **[G]** can also induce mouse NLRC4-dependent caspase 1 activation in the absence of flagellin, showing multi-component activation of the NLRC4 inflammasome[142]. However, NLRC4 is not the direct receptor for bacterial PAMPs, but instead, pairs with mouse NAIP5, which recognizes flagellin[143], and NAIP1 and NAIP2, which respectively recognize T3SS needle[144,145] and rod proteins[143]. Thus, the NAIP proteins recognize bacterial components and recruit NLRC4 to activate caspase 1. NAIPs contain N-terminal BIR domains, while NLRC4 displays an N-terminal CARD. Humans only have one NAIP gene and it responds to flagellin and both T3SS needle and rod protein. NLRC4 and NAIP5 also mediate pyroptosis in response to flagellin[146,147], and pyroptosis induced by bacterial T3SS needle proteins is NLRC4 dependent[142].

Gain-of-function mutations in human *NLRC4* lead to inflammasomopathies **[G]** that are associated with the spontaneous formation of the NLRC4 inflammasome, production of IL-1β and IL-18 and inflammatory cell death[148]. Three NLRC4 inflammasomopathies have been described: autoinflammation with infantile enterocolitis (AIFEC), neonatal-onset multisystem inflammatory disease (NOMID) and FCAS4[148]. Endogenous short interspersed nuclear element (SINE) RNAs — which promote atrophic macular degeneration and systemic lupus erythematosus — induce NLRC4 inflammasome activation with DDX17

helicase-mediated sensing of these RNAs independent of NAIPs[149]. In addition, NLRC4 has been implicated in microglial cell death in models of stroke[150].

NLRP6 inflammasome and inflammasome-independent functions.

NLRP6 (also known as PYPAF5 [24]) is expressed by immune and stromal cells, but its expression in typical lymphoid tissues is low while its expression is high in intestinal colonic myofibroblasts and epithelial cells[11,151,152]. Overexpression of NLRP6 leads to its assembly with ASC to form specks (that is, large protein complexes) in cells and these coordinate the activation of NF-κB and pro-caspase-1 [24]. It is regulated post-translationally by the deubiquitinase CYLD, which targets K63-linked ubiquitination of NLRP6 to prevent its binding to ASC[153].

NLRP6 functions as an inflammasome in the dextran sodium sulfate (DSS)-induced colitis model and protects against colitis by driving IL-18 release, which promotes epithelial barrier integrity[151,152,154] via the promotion of Lgf5+ stem cells and anti-microbial response[155]. NLRP6 also protects against colon cancer by inducing IL-18 [154], resulting in reduced intestinal inflammation and reduced proliferative signals such as SMARRC1, p53, Wnt and Notch pathways all of which have been linked with intestinal tumourigenesis[151]. Additionally, NLRP6 enhances mucin secretion by intestinal Goblet cells through the promotion of autophagy[156]. NLRP6 is also reported to influence the intestinal microbiota, although this is controversial. Some have found that NLRP6 expression affects components of the microbiota such as *Prevotella*[152], while others have failed to see this association using littermates from different animal facilities[157,158].

In addition to functions in the intestine, NLRP6 is expressed in the liver and can affect disease development in this tissue. For example, expression of NLRP6 was shown to attenuate non-alcoholic fatty liver disease[159], alcoholic hepatitis[160], and hepatocarcinoma (HCC) in mice[161]. These are found to mediated by the reduced inflammatory cytokines such as TNF, reduced NF-κB and TLR4 signalling by NLRP6. By contrast, others found that *C. albicans* infection promotes hepatocarcinogenesis in patients may occur in an NLRP6-dependent fashion by increasing metabolites that can promote tumorigenesis [162]. Thus, the impact of NLRP6 expression may be dependent on the disease and tissue context.

In the setting of infection, NLRP6 can be activated by the microbial metabolite taurine[163], bacterial lipoteichoic acid[164], and viral RNA through the RNA helicase Dhx15 to induce type I and type III interferon[165]. Furthermore, viral infection, dsRNA, TNF and type I interferon can enhance NLRP6 expression[165]. A seminal paper showed that during virus infection, NLRP6 is activated by binding to dsRNA and undergoes liquid–liquid phase separation (LLPS) and that a disordered poly-lysine sequence (K350–354) in the protein is important for its function[166].

In addition to its role in inflammasome assembly, NLRP6 has an alternative role in suppressing inflammatory responses and signals. NLRP6-deficient mice show enhanced resistance to bacteria, accompanied by increased NF-κB and MAPK activation after TLR activation[167]. NLRP6 also reduces neutrophil influx and granulocytic bactericidal activity during gram-positive bacteria infection[168]. NLRP6 expression in inflamed periapical tissues

and human periodontal ligament cells negatively regulates IL-6 and TNF by inhibiting NF-κB and ERK signaling[169]. Thus, NLRP6 has both inflammasome-dependent and independent functions.

In summary, a major function of multiple NLR proteins lies in inflammasome function. While the ligands for some are well defined, others are not. Furthermore, some inflammasome NLRs have alternative functions such as reducing inflammatory responses. In the next section, the focus will be on NLRs that control a variety of signalling pathways.

NLRs as regulators of diverse signalling pathways

This section focuses on NLRs that contribute to pathogen sensing and diverse immune signalling responses independently of inflammasome assembly (Fig. 4), with the exception of NLRP12 (Fig. 3) and NLRP11. NLRP12 has been reported to assemble inflammasomes in response to certain infections, but we include this NLR in this section due to its well-described role in negatively regulating inflammation. NLRP11 does not itself form an inflammasome, and is reported to regulate the NLRP3 inflammasome, as discussed below.

Sensing of peptidoglycan fragments by NOD1 and NOD2.

NOD1 and NOD2 represent the earliest and best-characterized signalling NLRs, and they function to detect PAMPs and activate inflammatory signalling pathways. These two proteins have been exhaustively reviewed, hence only a brief synopsis is provided here[170,171]. In addition to a central NACHT domain and C-terminal LRR domain, the N-terminus of NOD proteins consists of a single CARD (in the case of NOD1) and two CARDs (for NOD2). NOD1 and NOD2 detect the cytosolic presence of processed fragments of peptidoglycan derived from bacterial cell walls, γ-D-glutamyl-meso-diaminopimelic acid (iE-DAP)[13,14] and muramyl dipeptide (MDP)[15,16], respectively. A recent study highlights the critical role of host peptidoglycan processing by showing that MDP is phosphorylated by N-acetylglucosamine kinase (NAGK), and this modification is essential for the activation of NOD2 in THP-1 cells and primary mouse macrophages[172]. Recognition of these PAMPs results in oligomerization, CARD-mediated recruitment of receptor-interacting serine/threonine kinase 2 (RIPK2 or RIP2) and the downstream activation of NF-κB and MAPK signalling pathways[173], leading to production of inflammatory cytokines, chemokines and inflammatory cell recruitment. In addition, NOD1 can cause apoptosis in a caspase 8 and RIPK2 dependent fashion[174].

NOD1 is expressed in a wide variety of cell types, including epithelial cells[10], and studies in intestinal epithelial cells have illustrated key roles for NOD1 in the immune response to intestinal pathogens. By contrast, NOD2 is primarily expressed in cells of the myeloid lineage[12], and specialized cells such as intestinal Paneth cells. Gain-of-function mutations in NOD2 were found to be associated with the human inflammatory disease, Blau syndrome[175]. Blau syndrome mutations are restricted to the NACHT domain, and the resultant amino acid changes are predicted to destabilize the autoinhibited conformation of NOD2 leading to constitutive activation[176]. In contrast, mutations that lead to impaired function of *NOD2* represent the most significant risk factor for development of Crohn's disease[17,18]. Crohn's associated mutations are dispersed throughout both the NACHT

and LRR domains potentially interfering with oligomerization, localization, or ligand sensing[176]. Both NOD1 and NOD2 have been shown to associate with endosomes, and this localization efficiently places these sensors in position to encounter their ligands transported by endosomal peptide transporters[177,178]. Membrane localization of NOD1/NOD2 is dependent on S-palmitoylation mediated by the palmitoyltransferase ZDHHC5, and mutations that disrupt palmitoylation result in impaired NF-κB signalling in response to NOD activators[179].

The mitochondrial sensor NLRX1.

NLRX1 is ubiquitously expressed in mammals. It has a central NACHT and LRR domain and a unique N-terminus, which functions as a mitochondrial targeting sequence (MTS)[180–182]. The C-terminus of human NLRX1 was found to be required for oligomerization and it binds ssRNA, dsRNA, lipid metabolites but not DNA[183–185]. The precise location of NLRX1 in mitochondria may be dynamic. It is found in the mitochondrial outer membrane and thought to interact with the CARD of MAVS through its LRR domain[180]. Others found that it localizes to the mitochondrial matrix to regulate mitochondria reactive oxygen species (ROS) production[181,182]. Multiple studies have shown that NLRX1 negatively regulates MAVS-mediated activation of IRF3 and type I IFN induction in virus infection[180,186,187]. It also blocks STING–TBK-mediated antiviral responses in HIV-1 infection[188], negatively regulates NF-κB signalling through interacting with TNF receptor-associated factor 6 (TRAF6)[187,189] and has been shown to function as a tumour suppressor in cancer[190,191]. However, in contrast to these roles in negatively regulating IRF3- and NF-κB-mediated antiviral responses, NLRX1 has been shown to support early antiviral responses by post-transcriptionally regulating IRF1 abundance[192].

NLRX1 also functions in autophagy and mitophagy[186]. NLRX1 was first reported to induce autophagy by interacting with the Tu elongation factor mitochondrial (TUFM)–ATG5-ATG12 pathway to promote virus-induced autophagy and to inhibit RLR-induced type I IFN production upon virus infection[193]. NLRX1 also interacts with Beclin-1 or E7 protein of oncogenic human papillomavirus (HPV16) to promote autophagy in cancer cells[194,195]. Additionally, it promotes LC3-associated phagocytosis (LAP, a non-canonical form of autophagy), and activates the MAPK pathway upon fungal infection[196]. Furthermore, NLRX1 acts as an LC3 interacting region (LIR)-containing mitophagy receptor to promote mitophagy during *Listeria monocytogenes* infection[197]. It also regulates mitophagy in metastatic mammary tumours[198], in intestinal ischaemic–reperfusion injury[199], and mediates morphine-induced immunosupression in microglia by activating an insufficient mitophagy response[200]. In contrast to these aforementioned studies, NLRX1 was reported to negatively regulate autophagy during Group A *Streptococcus* infection[201]. However, the findings of a majority of the studies indicate that NLRX1 may represent a therapeutic target when increased autophagy or reduced inflammation is desired. Indeed, an activator of NLRX1, NX-13, is found to attenuate inflammatory bowel disease model by decreasing multiple aspects of immune activation[202].

Negative regulation of immune cell activation by NLRC3.

NLRC3 is a CARD-containing NLR and is expressed in both human and mouse immune cells[6,203]. Its highest expression is in T cells, and T cell activation downregulates NLRC3 expression, suggesting that it may serve as a suppressor of T cell activation[203]. Indeed, NLRC3 reduces K63-linked ubiquitination of TRAF6 to downregulate NF-κB signalling, expression of interferon-γ and TNF, and the mTOR pathway in CD4+ T cells in the context of viral infection, T cell-mediated autoimmunity[204] and *M. tuberculosis* infection[205]. In peritoneal macrophages, NLRC3 negatively regulates TLR4- and LPS-induced NF-κB activation by interacting with TRAF6 to mediate its deubiquitination in macrophages[206]. Additionally, NLRC3 also attenuates innate immune cell responses to cytosolic DNA, cyclic di-GMP and DNA viruses. It does this by interacting with the DNA sensor stimulator of interferon genes (STING) and TBK1 to impede the STING–TBK1 interaction, thereby limiting interferon production and NF-κB activation[207]. Upon binding of viral dsDNA and dsRNA to the LRR domain, NLRC3's ATPase activity is increased and STING–TBK1 is released[185]. Additionally, NLRC3 NACHT can interact with a scaffold IQGAP1 and this disrupts the NLRC3-STING association in regulating type I IFN responses[208]. Overall, these studies reveal the impact of NLRC3 in regulating STING–TBK-mediated type I IFN signalling and NF-κB pathways to control cellular immune responses. In human cancer, NLRC3 expression is found to be a positive prognostic factor[209,210], and NLRC3 was shown to mediate protection in a mouse model of colon cancer by inhibiting the PI3K–mTOR pathway [211].

Cell-specific regulation of inflammation by NLRP12.

NLRP12 is expressed in different myeloid cell populations, with prominent expression in granulocytes and dendritic cells[212]. NLRP12 functions as both a negative regulator of inflammation and as an inflammasome. It attenuates canonical and non-canonical NF-κB signalling pathways by blocking IRAK1 activation[213] and by increasing the degradation of the NF-κB-inducing kinase (NIK)[214], respectively. Additionally, NLRP12 can interact with TRAF3, which is involved in NIK degradation. Others have shown that it associates with ASC to mediate caspase 1 activation[23], leading to IL-1β and IL-18 release in bone marrow-derived macrophages (BMDMs) infected with *Yersinia pestis* and *Plasmodium chabaudi*[215,216] thus serving as an inflammasome sensor.

NLRP12 activity in myeloid cells is essential for colonic homeostasis[217,218]. Inhibition of NF-κB and ERK signalling by NLRP12 suppresses colonic inflammation and colitis-associated colorectal cancer in mouse models. NLRP12 also mitigates colitis by regulating the gut microbiota — for instance, its expression maintains the presence of protective commensal strains of *Lachnospiraceae* in the gut[219,220]. Interestingly, colonic inflammation and dysbiosis of the microbiota in NLRP12-deficient mice can contribute to obesity via enhanced inflammation[221].

NLPR12 has also been associated with cell proliferation. NLRP12-deficient microglia show increased proliferation while NLRP12-deficient tumour cells show decreased cellular proliferation in glioblastoma[222]. Human glioblastoma tissue shows elevated NLRP12 expression. In response to *Leishmania major* Nlrp12 deficient neutrophils showed increased

neutrophil migration towards the chemokine CXCL1 and the neutrophil parasite Leishmania major, revealing NLRP12 as a negative regulator of directed neutrophil migration in vitro[223].

Mutations in *NLRP12* are associated with the systemic autoinflammatory disease FCAS2[224]. This is a cold-induced autosomal dominant disease characterized by noninfectious periodic fevers and inflammatory symptoms in joints, muscles, digestive organs, skin and nerves. Interestingly, the IL-1 receptor antagonist (Anakinra) **[G]** only partially relieves the symptoms seen in patients with FCAS2[225], whereas this drug is potently protective in patients with the NLRP3-associated diseases CAPS and FMF . It remains to be explored if the clinical manifestations are reflective of the divergent functions attributed to NLRP12.

A potential anti-inflammatory role for NLRP10.

NLRP10 (also known as PYNOD) contains an N-terminal PYD in addition to a NACHT domain, but it is the only mammalian NLR family member that lacks an LRR domain[226]. NLRP10 is expressed in a variety of tissues, and is highly expressed in heart, skeletal muscle, brain and skin[226,227]. Exogenous expression studies in cell lines[226] and transgenic mice[227] found that overexpressed NLRP10 inhibits IL-1β processing. NLRP10 overexpressing transgenic mice were resistant to lethal doses of LPS injection, although serum levels of TNF-α were more significantly reduced when compared to IL-1β[227]. Attempts to examine the physiological role of NLRP10 in knockout mice were temporarily hindered by the presence of a secondary genetic mutation that was responsible for the initially described phenotype[228,229]. Extensively backcrossed NLRP10-deficient mice were shown to have increased inflammatory responses in response to *Leishmania* infection, supporting a potential anti-inflammatory role for NLRP10[230]. Additional NLRP10 KO lines have been created and are phenotypically normal in the absence of an inflammatory challenge[231,232]. However, while one line of NLRP10 KO mice showed reduced inflammation in a contact hypersensitivity model[231], another group saw no difference between NLRP10-deficient and wild type mice in a similar model[232]. NLRP10 remains an enigmatic NLR protein, and future studies will be required to determine its physiological role.

Regulation of inflammatory signalling and autophagy by NLRP4.

NLRP4 is strongly expressed in placenta, oocytes, testis, spleen, pancreas, liver, lung, kidney, and thymus[233–235]. Similar to other NLRPs, NLRP4 has an N-terminal PYD, but the NLRP4 PYD contains unique features and does not interact with ASC[236]. Initially, NLRP4 was found to negatively regulate TNF- and IL-1β-induced NF-κB activation[234]. Subsequently, NLRP4 was also reported to negatively regulate type I interferon signalling in response to dsRNA, DNA or viral infection. The NACHT domain of NLRP4 interacts with the E3 ubiquitin ligase DTX4 to direct the K48-linked polyubiquitination of TBK1, resulting in its degradation and this blocks the TBK1-mediated phosphorylation and translocation of IRF3[235].

Aside from its role in regulating these immune signalling pathways, NLRP4 regulates autophagy in response to bacterial infection and interacts with the autophagy regulator,

Beclin-1, via its NACHT domain. Upon infection with Group A *Streptococcus*, NLRP4 is recruited to autophagosomes and dissociates from Beclin-1, allowing the initiation of autophagy[237]. Additionally, NLRP4 associates with the class C vacuolar protein-sorting complex to inhibit autophagosome maturation. NLRP4 also interacts with Rho GDP dissociation inhibitor α to regulate Rho GTPase signalling and facilitate actin-mediated antibacterial autophagy during *Streptococcus* infection[238].

NLRP11 in the regulation of signal transduction and in NLRP3 inflammasome formation.

NLRP11 is a primate-specific protein and is highly expressed in monocytes, THP-1 (human monocyte line), B cells, B cell lymphoma lines, testis, ovary, and lung [239–242]. NLRP11 is induced by type I IFN and translocates to the mitochondria to interact with MAVS by its LRR and NACHT domain upon RNA viral infection [243]. Furthermore, NLRP11 binds to TRAF6 to promote its degradation in a MAVS-dependent manner, reducing type I IFN signalling and virus-induced apoptosis[243]. NLRP11 also inhibits TLR signalling by recruiting the ubiquitin ligase RNF19A to catalyze K48-linked ubiquitination of TRAF6 for its degradation, resulting in the suppression of NF-κB activation, MAPK signalling, and pro-inflammatory cytokine production[239].

In addition to its roles in regulating these immune signalling pathways, NLRP11 has been shown to negatively regulate NLRP3 inflammasome activation in cultured human cell lines by interacting with DEAD-box protein 3 (DDX3X)[244], a protein shown to activate the RLR pathway[245]. This interaction causes NLRP11 to inhibit DDX3X's function in enhancing type I IFN responses and NLRP3 inflammasome activation[244]. In contrast, another study found that NLRP11 can support NLRP3 assembly by functioning as a scaffold. NLRP11 interacts with NLRP3 via its LRR domain and ASC via its PYD domain to promote NLRP3 inflammasome assembly and activation but does not affect the assembly of other inflammasomes[246]. This study also reported that NLRP11 is necessary for NLRP3 inflammasome responses driven by CAPS-linked *NLRP3* mutations[246]. The exact reason for these differences is currently unknown. This underscores the need for a deeper investigation of these understudied NLR.

Above, we have primarily focused on the immune-associated functions of NLRs. However, NLRs also regulate other biological processes including studies to indicate their importance in the reproductive system which are discussed below.

NLRs in reproduction

There is growing evidence for a mammalian reproduction-associated NLR gene cluster which include *NLRP2*, *NLRP4*, *NLRP5*, *NLRP7*, *NLRP8*, *NLRP9*, *NLRP11*, *NLRP13* and *NLRP14*. Human NLRs in this reproductive gene cluster — as well as their murine orthologues, namely *Nlrp2*, *Nlrp4a-Nlrp4g*, *Nlrp5*, *Nlrp9a-Nlrp9c* and *Nlrp14*, — are highly expressed in oocytes and in the ovaries[241,247,248]. Except for the gene encoding NLRP14, all reproduction-associated NLRP-encoding genes in the human genome are located on chromosome 19, whereas all mouse reproduction-related *Nlrp* genes are located on chromosome 7, with the exceptions of *Nlrp4g* (chr 9) and *Nlrp4f* (chr 13)[248]. In this section, we focus on our growing understanding of the functions of some of these proteins.

Regulation of nucleic acid signalling and fertilization by NLRP14.

NLRP14 is expressed in the gonads[241] and several *NLRP14* mutations are linked to spermatogenic failure[249]. Interestingly, NLRP14 was reported to function as a negative regulator of the nucleic acid-sensing (NAS) pathway in germ cells by interacting with TBK1 through its N-terminus to suppress TBK1-mediated IFNγ production for supporting fertilization[250]. Furthermore, NLRP14 was found to interact with MAVS and STING through its LRR domain to negatively regulate the NAS pathway, however, MAVS and STING also resulted in the degradation of NLRP14, hence revealing a feedback loop to prevent the sustained immunosuppressive function of NLRP14[250]. Although these studies were performed in 293T cells, another group reported that NLRP14 promotes primordial germ cell-like cell differentiation and spermatogenesis through a complex with HSPA2 and BAG2[251]. These studies provide physiological insights on the functions of NLRP14 and indicate its roles in both immune and gonadal regulation.

NLRP2 in inflammation, proliferation, reproduction, and genomic imprinting.

NLRP2 was one of the first NLRs found to interact with ASC to assemble an inflammasome, leading to IL-1β generation[26,252]. By contrast, NLRP2 also acts as an inhibitor of the NF-κB pathway and a nonfunctional allelic variant within the NLRP2 NACHT contributes to the hyperactivation of NF-κB pathway and subsequent downstream inflammatory responses[252,253]. Along with being an inhibitor of NF-κB, NLRP2 also regulates inflammation or cell proliferation by suppressing NF-κB activation in hepatic steatosis[254], HLA-C expression in trophoblasts[255] and in cancer[256]. Additionally, it interacts with TBK1 and negatively regulates type I IFN signalling upon viral infection[257]. In the reproductive system, NLRP2 is essential for early embryogenesis but not oocyte maturation in ice and humans[258,259], and interacts with FAF1 (Fas-associated protein factor 1) in mouse ovaries[259,260]. A germline frameshift mutation in exon 6 of NLRP2 is linked to Beckwith-Wiedemann syndrome, which is a human imprinting disorder **[G]** [261] that is also associated with NLRP5 and NLRP7 mutations[262]. NLRP2 also maintains proliferation and viability in human umbilical vein endothelial cells (HUVECs) by promoting MAPK signalling[263]. These studies demonstrate the potential of NLRP2 in inflammasome activation but also in the dampening of inflammatory and interferon activation. The latter may contribute to the establishment of immune tolerance at the maternal–fetal interface to prevent aberrant immune activation.

NLRP5 regulates embryogenesis

MATER (Maternal Antigen That Embryos Require), a murine counterpart of NLRP5, was one of the first-discovered maternal-effect genes encoding an oocyte-specific protein. It is associated with autoimmune oophoritis and is required for embryonic development in mice[264]. Additionally, NLRP5 was found to localize in oocyte mitochondria and nucleoli[265] and is essential for assembly of the subcortical maternal complex (SCMC), which is a multiprotein complex encoded by maternal-effect genes specifically expressed in oocytes and early embryos in mice[266]. NLRP5 also regulates mitochondrial biogenesis and its respiratory activity, and it may affect other cell death molecules that contributes to its function in successful preimplantation during early embryogenesis[267]. In human, NLRP5

is predominantly expressed by oocytes and follicular cells[268,269], and has been found to represent a tissue-specific autoantigen involved in hypoparathyroidism in patients with autoimmune polyendocrine syndrome type 1 (APS-1)[270]. Additionally, NLRP5 variants are not only found in the Beckwith-Wiedemann syndrome, but also in multi-locus imprinting disturbance (MLID) in female patients and is associated with maternal reproductive fitness[271]. Its direct role in these diseases will be of interest for future investigation.

NLRP7 regulates inflammation and embryogenesis.

NLRP7 is only found in primates[241]. It is highly expressed in reproductive organs but also broadly expressed in cell lines and most other tissues, except for skeletal muscle, heart and brain. Expression of NLRP7 is increased in LPS- and IL-1β-stimulated PBMCs and macrophages[272]. *NLRP7* mutations specifically affect the female (but not male) reproductive system and are associated with abnormal embryogenesis (recurrent hydatidiform moles **[G]** in humans)[273–275]. In contrast to NLRP2, which inhibits NF-κB but not IL-1β production, NLRP7 inhibits caspase 1-dependent IL-1β production[272]. Another report showed that NLRP7 failed to interact with ASC and activate NF-κB[24]. By contrast, microbial acylated lipopeptides from bacteria can activate the NLRP7 inflammasome function in macrophages leading to downstream IL-1β production but not pyroptosis [240]. The precise structures of the NLRP7 PYD interacting with ASC or the LRR sensing different ligands need to be further investigated to solve these controversial findings. These results suggest that certain NLRs might be either positive or negative regulators in different signalling pathways upon different stimulations in a cell-type specific manner. Others have found that the TLR agonists LPS and Pam3CSK4 can activate NLRP7 inflammasome activity and that a deubiquitinase, STAM-binding protein, increases NLRP7 activity by preventing its trafficking to the lysosome where it is normally degraded[276]. Additionally, higher NLRP7 expression was reported to promote tumour cell proliferation and metastasis in human colon cancer and to promote the development of M2-like macrophages **[G]** by increasing NF-kB activation and CCL2 to promote tumor progression[277]. It will be of interest to investigate if the role of NLRP7 in regulating the inflammasome or NF-κB signaling, which has not been studied in cells of the reproductive system, can be extended to reproductive cells or disorders.

As a final point of interest, in the consensus phylogenetic cluster, the NLRP2 cluster contains NLRP7, suggesting that NLRP7 might originate from a duplication of the NLRP2/7 ancestor in primates[241,248]. Given that both are highly expressed in the reproductive organs and regulate inflammatory signaling, these two might have overlapping functions in regulating the physiological and pathological inflammatory processes of pregnancy.

NLRP9 in reproduction and immunity.

NLRP9 is mainly expressed in the reproductive system of human and bovine, and mice (Nlrp9a-Nlrp9c) [241,278]. In mice, NLRP9 is specifically expressed in ovarian follicles during early embryonic preimplantation[279,280]. However Nlrp9b, but not Nlrp9a and Nlrp9c, is also uniquely expressed in intestine epithelial cells and associates with an DExH-box RNA helicase 9 (DHX9) to recognize double-strand RNA and functions as an inflammasome for viral clearance during rotavirus infection in mice[281]. Additionally, NLRP9 expression has been reported in lung cells, brain pericytes and endothelial cells, and microglia[278].

Human NLRP9 also interacts with ASC to form the inflammasome upon DHX9-mediated rotaviral RNA recognition in HEK293 T cells[281]. However, two groups recently have reported the crystal structure of human NLRP9 PYD (hNLRP9^{PYD}) and showed that it forms a monomer but not oligomers in solution[282,283]. One paper also found that it does not nucleate ASC specks in HEK293T cells, which is in contrast to NLRP3, NLRP6 and AIM2 inflammasomes[282]. Additionally, hNLRP9^{PYD} might exhibit autoinhibitory function based on: (1) charge inversions in the interfaces of hNLRP9PYD which might cause repulsive effects to prevent self- oligomerization and activation[282]; (2) a bent N-terminal loop of hNLRP9PYD oriented toward the interior of the helical bundle which might prevent filament formation structure and subsequent NLRP9 inflammasome assembly[283]. NLRP9 is also linked to several inflammatory diseases [278]. One study demonstrated that the lack of NLRP9b resulted in reduced neutrophil inflammation but elevated proinflammatory cytokines, NF-κB activation, and oxidative stress in the mouse acute lung injury model[284]. Much remains unknown regarding NLRP9. The analysis of mice lacking this gene will help understand its role in inflammatory diseases and infections in addition to its role in reproduction system.

In the sections above we have detailed the diverse functions that are mediated by NLR family members. A better understanding of the structure of the different NLR proteins should help us to better define their biology. Indeed, impressive progress has been made in deciphering the structure of several NLR proteins described below.

Structure of NLR proteins

Apaf-1, plant R proteins, and NLRs are members of the STAND subgroup of P-loop ATPases related to the AAA+ superfamily[285] **[G],** a large family of ATPases with diverse molecular functions and a wide assortment of accessory domains. AAA+ superfamily proteins share a common arrangement of an N-terminal αβα fold (NBD) followed by a helical bundle (HD1). Early in the field, X-ray crystallography studies for NLRs were limited to isolated domains, including the PYD, CARD, and LRR domains. A significant milestone was the determination of the crystal structure for the NACHT–LRR domain of NLRC4 in the ADP-bound, autoinhibited state[286] (Fig. 5A, left panel). At the time, the structure of the NLRC4 NACHT domain was most similar to the structure determined for Apaf-1 in its inactive state[287]. Both structures showed that ADP binding involved contributions from the NBD, HD1, and WHD, resulting in a compact, closed conformation. For NLRC4, interdomain interactions between the first LRR and the NBD are also observed in the autoinhibited conformation. Mutations that disrupt WHD-ADP binding or the LRR–NBD interaction destabilize the closed conformation resulting in auto-activation of NLRC4 and caspase 1 processing. These two basic principles for the autoinhibited state were echoed in the crystal structure for the NACHT–LRR domains of NOD2[176]. Similarly to NLRC4 and Apaf-1, ADP binding involves involves interactions with the NBD, HD1, and WHD resulting in a compact, closed conformation. In addition, the first two LRR units of NOD2 interact with the HD1 and HD2 subdomains within the NACHT domain. The interaction of the LRR and NACHT domains aligns with the hypothesis that ligand binding to the LRR domain disrupts LRR–NACHT interactions and exposes a surface on the NACHT domain for oligomerization.

The advent of cryo-EM for high-resolution structural analysis of large proteins and proteins complexes allowed for breakthroughs in NLR structure determination. High-resolution structures for full-length NLRs and oligomerized complexes have now been determined. Cryo-EM structures for an inflammasome in the activated, oligomerized state were solved for NAIP2-NLRC4 inflammasomes activated by the bacterial type III secretion inner rod protein PrgJ [288,289]. These studies show that PrgJ binding to NAIP2 results in a 90° rotation at a hinge site between HD1 and WHD. This conformational change exposes a surface in the NACHT of NAIP2, which can interact with an acceptor surface in NLRC4, and the activated NLRC4 can promote a similar conformational change in another NLRC4 molecule. Propagating NLRC4 activation results in the formation of a disc-like structure composed of a single NAIP with ten NLRC4 molecules (Fig. 5A, right panel). Subsequent cryo-EM studies of the NAIP5-NLRC4 complex with bound flagellin provided the first glimpse into the molecular interaction of an activating ligand with an NLR sensor. The flagellin-NAIP5 interaction shows that binding of ligand involves multiple domains including the NACHT, LRR, and BIR domains[290]. Whether this mode of ligand-sensor interaction extends to other NLR proteins remains to be determined.

A simplistic model for inflammasome formation involves activation of cytosolic, monomeric NLRs by a ligand leading to oligomerization and recruitment of pro-caspase 1. However, recent cryo-EM studies of NLRP3 suggest that there are additional layers of regulation beyond the presence of ligand that determine whether an inflammasome will form. Cryo-EM studies with NLRP3 alone revealed an oligomeric complex in which the pyrin domains are sequestered within a cage[291–293] (Fig.5B, left panel). Isolation of pyrin domains in such a manner would prevent spurious interaction with ASC, providing protection against inappropriate inflammasome activation (Fig. 5B, middle panel). Interestingly, a previous cryo-EM structure for NLRP3 had been determined in a complex with NEK7[70] which is known to license NLRP3 activation (Fig. 5B, right panel). Both the caged NLRP3 and NLRP3-NEK7 structures contain NLRP3 in an autoinhibited, ADP-bound conformation. In vitro addition of NEK7 disrupts the caged oligomers, suggesting that NLRP3 inflammasome activation involves more than just the presence of activating ligand. Future studies will determine if other NLRs employ additional regulatory mechanisms.

Emerging concepts and conclusions

In the past two decades, the NLR field has gone through a revolution. However, while some NLRs are exceedingly well investigated, many are understudied. We propose some emerging concepts as well as areas that are deserving of further attention.

First, aside from well-established reports on activation and functions of NLRs in innate immunity, there are accumulated evidence suggesting NLRs function in other cell types. We have discussed the area of NLRs in the reproductive system, bolstered by fascinating genetic data supporting key roles for NLRs in this setting. Furthermore, several NLRs have roles for regulating adaptive immunity and immunometabolism in cells. NLRP3 is the first and most intensively linked to crosstalk between innate and adaptive immunity[294] and metabolism[29,295]. Adenosine-induced NLRP11 can reduce IFN-γ and IL-17A production of human peripheral CD4+ T lymphocytes[296]. NLRC3 attenuates TRAF6 and modulates

$CD4^+$ T cell metabolism. NLRX1 has also been found to regulate glycolysis and oxidative phosphorylation in T cells[297,298]. These studies shed light on the roles of NLRs in an array of cell types and provide a much broader perspective regarding their importance beyond innate immunity.

Second, many NLRs exhibit multiple functional roles, and this may be attributed to numerous reasons. One is that their cellular localization may be dynamic. NLRs are located in different cellular compartments and their organelle-specific, membranous or non-membranous localization may determine their ultimate functions. The mitochondrial location of NLRX1, and the nuclear localization of transcriptional regulators CIITA and NLRC5 have long been known. NLRP3 has been shown to be associated with mitochondria and the dispersed trans Golgi network[299]. NOD1 and NOD2 associate with the plasma membrane and endosomes[177,187], and membrane localization is dependent on S-palmitoylation[179] raising the possibility that post-translational modifications may influence localization of other NLRs. Another possibility is that different NLR isoforms, perhaps generated via alternative splicing or post-translational modification, may show distinct functions. One possible approach to address these different possibilities is to assess if distinct interactomes are formed by an NLR protein to conduct different functions in different cell types. Such interactomes may vary depending on all of the factors described above, including differential expression in cells with distinct protein compositions, divergent localization in organelles, varied post-translational alterations and different isoforms. Finally, it is important to re-evaluate data obtained with in vitro cell lines especially in the context of overexpressed proteins without validation in vivo, since these may result in nonphysiologic findings.

Third, several NLRs are paired to perform their function. The most prominent examples are the pairing of NAIPs and NLRC4. NLRP3 and NLRC4 are important for the simultaneous activation of inflammasomes in response to some stimuli. However, opposing functions have also been described; for example, NLRP12-dependent degradation of NOD2 results in the functional inhibition of NOD2[300]. This type of crosstalk is envisioned to expand the NLR regulatory network and their impact.

Finally, a common theme that emerges for NLR proteins (NLRX1, NLRC3, NLRP3, NLRP6, NLRP1) is the potential for binding to nucleic acid PAMPs and DAMPs. This flexibility would allow a single NLR to function both in host responses against pathogens as well as in host stress responses. Whether this is a shared function among many NLRs and what the divergent functional consequences and downstream signalling consequences of this may be will be of great interest to explore.

Obviously, there are numerous other areas of NLR biology that deserve further investigation, such as their therapeutic targeting and their precise roles in disease. We trust that the next decades of research on the NLR family will be just as exhilarating as the first two.

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Glossary

MHC class II transactivator (CIITA)
The master transcriptional regulator of MHC class II expression.

NACHT domain
NAIP, CIITA, HET-E (incompatibility locus protein from the fungus Podospora anserina) and TEP1 (telomerase-associated protein 1). The NACHT domain is a subgroup of the STAND class of P-loop NTPases, and is composed of four subdomains (NBD, HD1, WHD, and HD2). This domain allows for nucleotide-binding dependent conformational changes and oligomerization to influence diverse biological outcomes such as transcriptional activation, cytokine signalling, and pyroptosis.

Apaf-1
Apoptotic protease-activating factor 1. A protein of the STAND class of P-loop ATPases that is central to initiating apoptosis upon mitochondrial cytochrome C release into the cytosol. In addition to the STAND ATPase module, Apaf-1 contains an N-terminal CARD and C-terminal WD-40 repeats. The formation of the apoptosome and activation of caspase 9 upon cytochrome C binding was a biochemical model that significantly influenced early NLR studies.

ASC
Apoptosis-associated speck-like protein containing a CARD. Also called PYCARD and TMS1. Adaptor protein that contains a PYD and CARD allowing for inflammasome recruitment of pro-caspase 1.

STAND
A subgroup of the AAA+ ATPase superfamily that includes both apoptotic (AP)-ATPases as well as NACHT ATPases. The model for STAND protein function involves ADP binding stabilizing a closed, inactive state, and exchange for ATP triggers a conformational change to the open, active state.

SXY cis-elements
A regulatory module comprising four elements: S or W box, X1 box, X2 box and the Y box. When bound by their cognate transcription factors, these sites allow for assembly of the MHC enhanceosome.

cryopyrin-induced autoinflammatory syndromes (CAPS)
Autoinflammatory diseases caused by gain-of-function mutations in NLRP3 (cryopyrin).

AIM2
Absent in melanoma 2. An innate immune sensor that detects cytosolic dsDNA resulting in inflammasome formation. AIM2 is composed of an N-terminal PYD and a C-terminal dsDNA-binding HIN domain distinguishing it from NLR inflammasome proteins.

NR100

N-terminal domain of rodent Nlrp1 proteins, approximately 100 amino acids. Whereas human NLRP1 possesses an N-terminal PYD, mouse Nlrp1 proteins contain this sequence of unknown function. Alphafold predicts this region to be mostly disordered.

T3SS
Type III secretion system. A multiprotein membrane apparatus present in gram-negative bacteria used to inject proteins into host cytosol. Components of this nanomachine trigger NAIP/NLRC4 inflammasome assembly.

Inflammasomopathies
Autoinflammatory diseases resulting from gain-of-function mutations in inflammasome-forming NLRs.

Anakinra
A short-acting human recombinant IL-1receptor (IL-1R) antagonist that can competitively inhibit the binding of IL-1β and IL-1α to IL-1R and block IL-1 signal transduction.

imprinting disorder
Diseases caused by genetic defects or epigenetic mutations affecting imprinted chromosomal regions or genes that are expressed in a parent-of-origin specific manner.

hydatidiform moles
A hydatifiform mole is a rare condition in which tissue around a fertilized egg that would normally have developed into the placenta instead develops as an abnormal mass of cells.

M2-like macrophages
M1' and 'M2' are classifications historically used to define macrophages activated in vitro as pro-inflammatory (when 'classically' activated with IFNγ and LPS) or anti-inflammatory (when 'alternatively' activated with IL-4 or IL-10), respectively. However, in vivo macrophages are highly specialized, transcriptomically dynamic and extremely heterogeneous with regards to their phenotypes and functions, which are continuously shaped by their tissue microenvironment. Therefore, the M1 or M2 classification is too simplistic to explain the true nature of in vivo macrophages, although these terms are still often used to indicate whether the macrophages in question are more pro- or anti-inflammatory.

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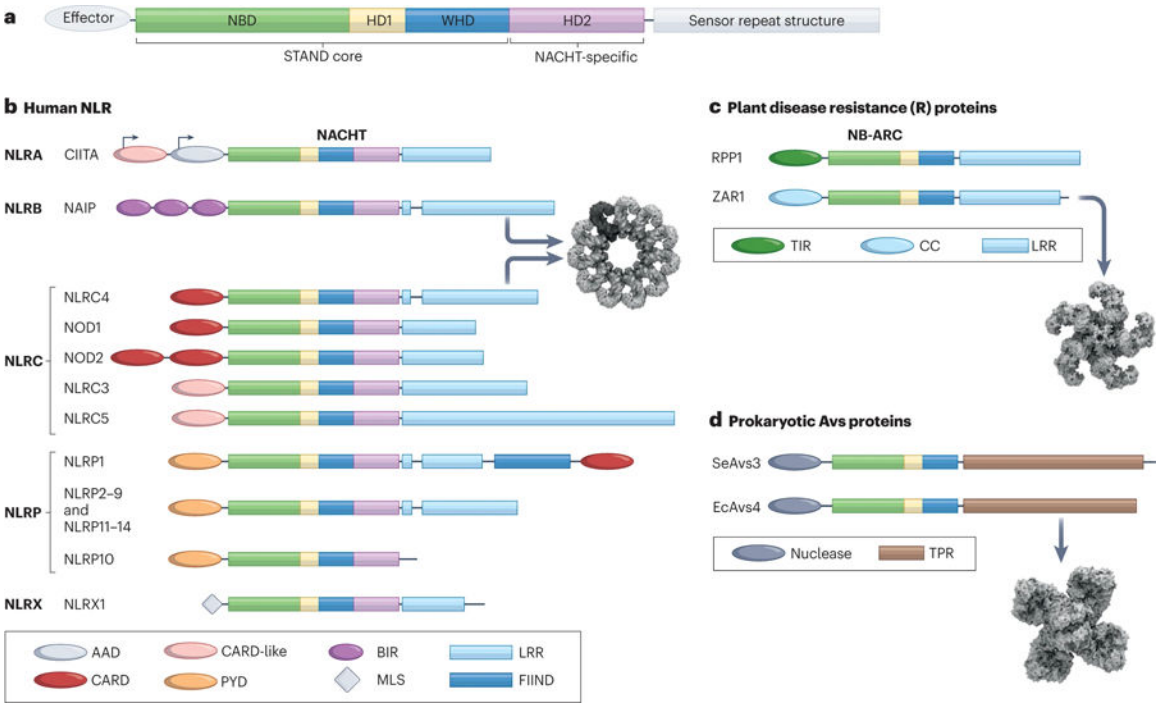

Figure 1: Nucleotide-binding and oligomerizing sensors as a universal strategy for cellular defense.

(A) The STAND ATPase module consisting of NBD, helical domain 1 (HD1), and winged helix domain (WHD) is utilized for cellular defense from prokaryotes to eukaryotes. An additional helical domain 2 (HD2) is present in many STAND proteins including a NACHT-specific domain used in the NLR family of proteins. (B) The primary structural organization of human NLRs. Here, NLRs are grouped according to subfamily which is determined by the effector domain at the N-terminus. The variable domains associated with the NACHT domain are color coded and indicated in the domain legend below. CIITA exhibits cell-type specific alternative promoter usage, and this is designated with arrows. The oligomerized inflammasome for NAIP/NLRC4 is shown (PDB:3JBL)[288]. (C) Two representative members of the plant disease resistance proteins with either TIR or CC domains are shown. The NB-ARC module lacks the HD2 domain. The C-terminal sensor is an LRR domain for these proteins as well. The oligomerized resistosome for ZAR1 is shown (PDB:6J5T)[327]. (D) Two representative members of the recently described prokaryotic Avs protein family are shown. The effector domain in these proteins is a nuclease instead of a protein-recruitment domain, and the sensor domain is composed of tetratricopeptide repeats (TPR). The oligomerized complex for EcAvs4 is shown (PDB:8DGF)[27]. Cryo-EM structure representations in this figure were created with BioRender.com.

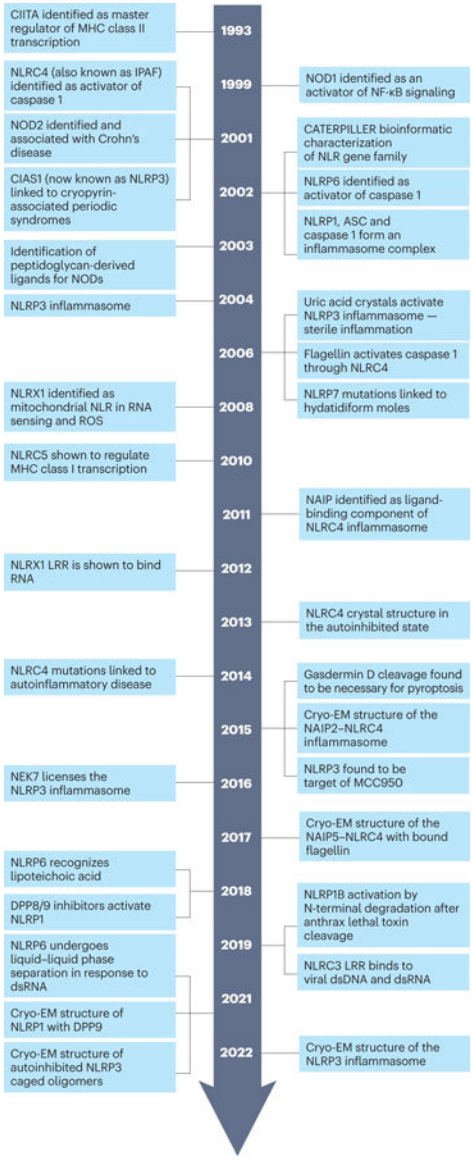

Figure 2: Key historical events in the NLR field

The timeline highlights some of the key discoveries and conceptual advances that have influenced the field over the last two decades. There are clearly many important contributions to the field which are not included here, and we apologize to those who have been left out due to spatial constraints.

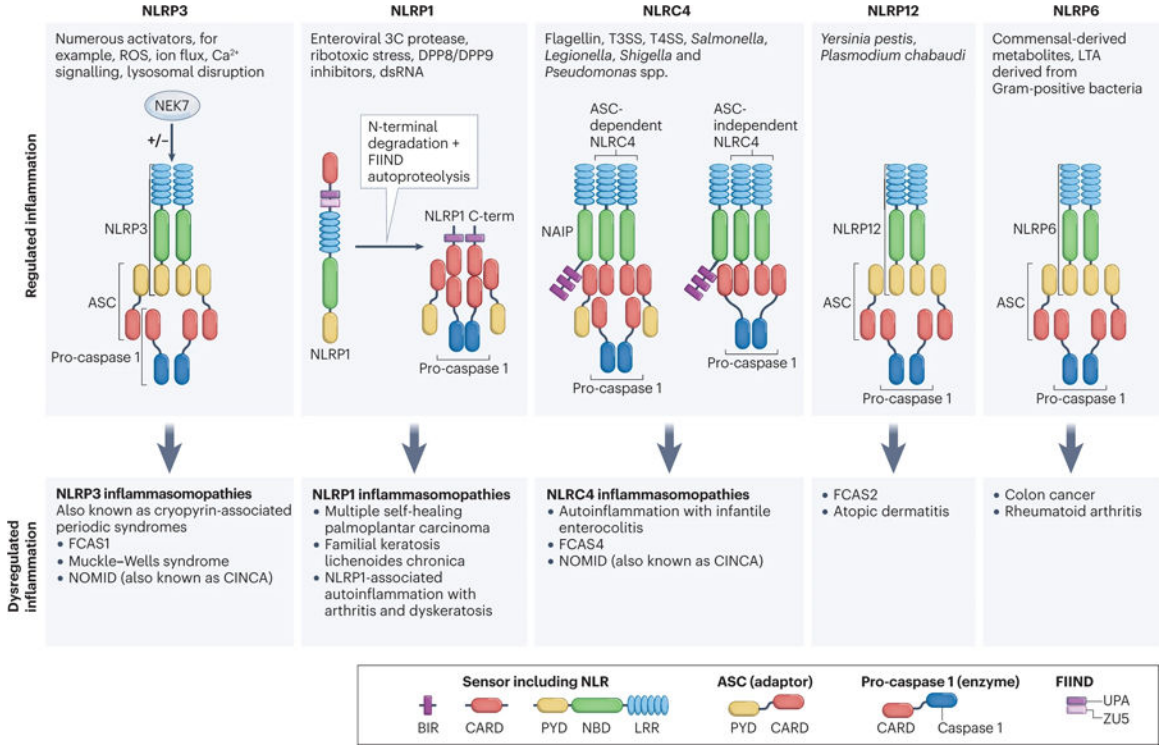

Figure 3: Inflammasome activators and related disorders

The NLRP3, NLRP1, NLRC4, NLRP12 and NLRP6 inflammasomes with their intracellular mediators involved in activation are summarised. Dysregulated or chronically activated inflammasomes may lead to inflammatory diseases. NLRP3 is a sensor for numerous PAMPs and DAMPs responding to intracellular damage induced by pathogenic or sterile insults. NLRP1 is a sensor for ribotoxic stress and dsRNA. DPP8/9 inhibitors are activators of the NLRP1 inflammasome. The current model for NLRP1 inflammasome activation involves ASC-dependent recruitment of pro-caspase 1 by the UPA-CARD C-terminal fragment of NLRP1. The NLRC4 inflammasome detects T3SS bacterial proteins via NAIPs and can assemble an inflammasome with or without ASC. NLRP12 inflammasome is assembled in response to Yersinia pestis and Plasmodium chabaudi. NLRP6 inflammasome detects commensal-derived metabolites, LTA derived from Gram-positive bacteria. Abbreviations used: CINCA, chronic neurologic cutaneous and articular syndrome; NLRP3, NLR family pyrin domain containing 3; NEK7, NIMA related kinase 7; LRR, leucine rich repeats; NBD, nucleotide-binding domain; PYD, pyrin domain; ASC, Apoptosis-associated speck-like protein containing a CARD; CARD, caspase recruitment domain; ROS, reactive oxygen species; FIIND, function to find domain; UPA, conserved in UNC5, the death-domain-containing protein PIDD and proteins of the ankyrin family; NLRC4, NLR family CARD domain containing 4; T3SS, type 3 secretory system, NAIP; neuronal apoptosis inhibitory protein.

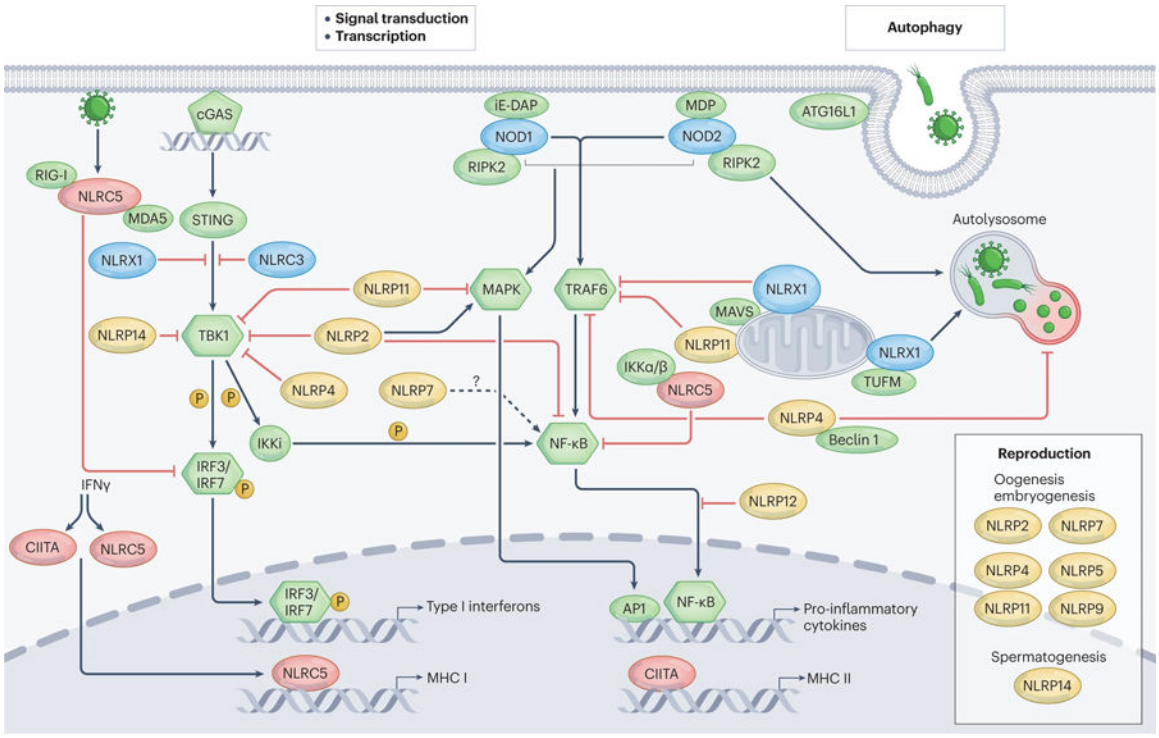

Figure 4: Regulatory Functions of NLRs

Different NLRs act as either positive or negative regulators in transcription, MAPK, NF-κB, and type I IFN signalling pathways and in autophagy. CIITA and NLRC5 induced by IFNγ acts as transactivators of MHC genes. NLRC5 also negatively regulates the NF-κB and type I IFN signalling pathways. In addition to NLRC5, several NLRs reduce either NF-κB or type I IFN signalling pathways or both. These NLRs are NLRC3, NLRX1, NLRP2, 4, 11, 12, and 14. On the other hand, NLRP7 may positively regulate NF-κB pathway, and NLRP2 promotes MAPK signalling. Likewise, NOD1 and NOD2 recognizes iE-DAP and MDP separately and interact with RIP2 to activate NF-κB and MAPK signalling pathway. Additionally, NOD2 recognizes MDP and recruits ATG16L1 to the plasma membrane to induce autophagy[328]. The right shows that NLRX1 interacts with TUFM to induce autophagy while NLRP4 interacts with Beclin-1 to inhibit autophagy. The right box shows NLRs that regulate development in the reproductive system. NLRP14 is the only NLRP molecule that contributes to spermatogenesis while other NLRPs including NLRP2,4,5,7,9,11 may regulate oogenesis and embryogenesis. NLR, NOD-like receptors; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; TRAF6, tumor necrosis factor (TNF) receptor-associated factor 6; MHC, major histocompatibility complexes; STING, Stimulator of interferon genes; TBK1, TANK-binding kinase 1; IRF3, Interferon Regulatory Factor 3; iE-DAP, γ-D-glutamyl-meso-diaminopimelic acid; MDP, muramyl dipeptide; RIP2, receptor interacting protein 2; TUFM, Tu translation elongation factor of mitochondria.

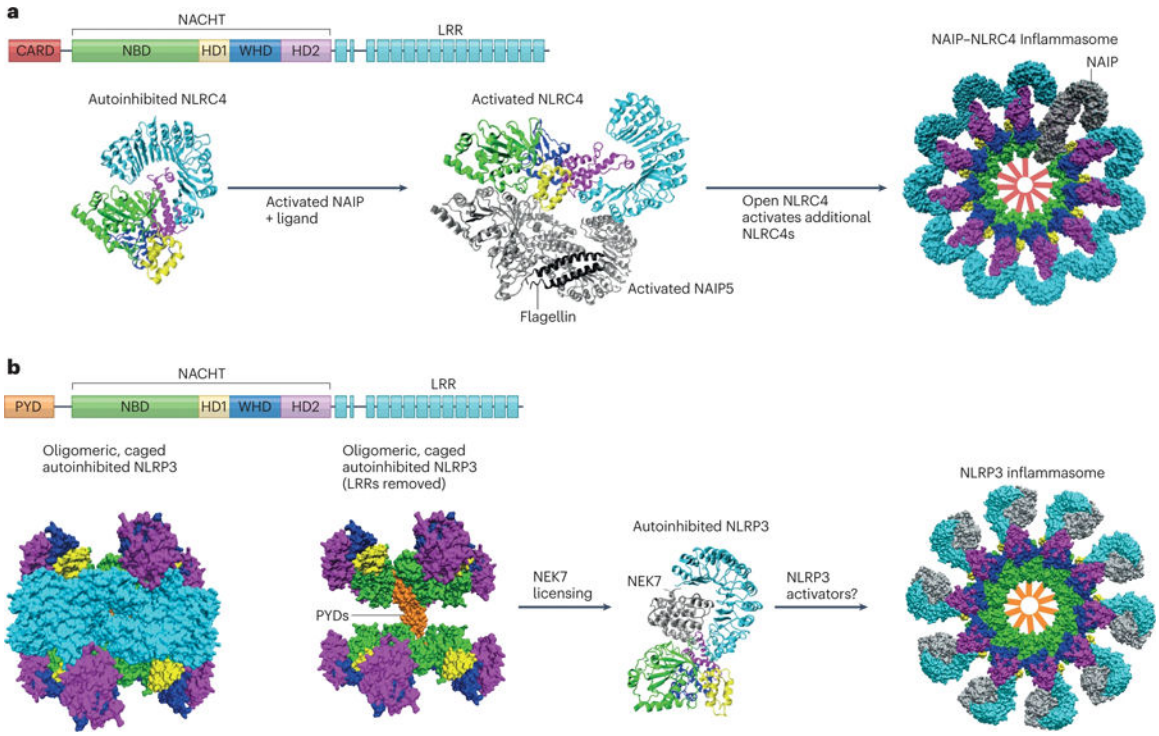

Figure 5: Structural Insights into NLR Activation

(A) Assembly of the NAIP/NLRC4 Inflammasome. The primary structure of NLRC4 is shown, and color coding for domains is replicated in the structural depictions. The crystal structure of closed, autoinhibited NLRC4 is adapted from PDB:4kxf[286]. Interactions between the HD2 and LRR domains stabilize the closed conformation. The cryo-EM structure of activated NLRC4 and NAIP5 is adapted from PDB:6b5b[290]. Activated NAIP5 (silver) with bound flagellin (black) initiates a conformational change in NLRC4 to an open, activated form which can activate downstream NLRC4 molecules. Finally, the cryo-EM structure of the assembled NAIP/NLRC4 inflammasome is adapted from PDB:3jbl[288]. A top view of the surface representation shows a single NAIP (gray) present in the complex with ten NLRC4 molecules. Red bars are added in the center of the complex to show the location of the NLRC4 CARDs which will recruit pro-caspase 1. (B) NLRP3 structural regulation preceding inflammasome assembly. The primary structure of NLRP3 is shown, and color coding is replicated in the structural depictions. The cryo-EM structure for autoinhibited NLRP3 alone is adapted from PDB:7pzc[292]. The left panel shows a surface representation of an oligomeric complex consisting of ten NLRP3 molecules. When the LRR domains are excluded from the image, the position of the PYDs within the “cage” shows how they are sequestered and prevented from initiating spurious inflammation. The cryo-EM structure of NLRP3 with bound NEK7 is adapted from PDB:6npy[70]. NEK7 interaction with the LRR domain of NLRP3 prevents NLRP3 from forming caged oligomers. All NLRP3 structures shown here show NLRP3 in a closed, autoinhibited conformation bound to ADP. Presumably, NEK7 licenses NLRP3 to freely interact with activating signals or ligands to form an inflammasome. Upon activation, NLRP3 assembles into an inflammasome disc with

10–11 NLRP3 molecules[329]. A cartoon representation is shown as the PDB file is currently unavailable. Structural representations were created using VMD[330].

Table 1:
NLR Functions and Human Disease Associations

The table shows the 22 human NLRs with the first column indicating their principal function and the second column showing the best-characterized pathways by which they mediate their function (transcription, inflammasome, signalling pathway, etc.). Finally, the last column shows human diseases that have been linked to mutations in human NLRs. This list includes a spectrum of affected states ranging from polymorphisms that increase disease susceptibility to severe gain-of-function inflammasomopathies. We have attempted to be thorough, but we are aware that there may be some research that is not cited here.

NLR	Function	Pathway	Diseases
CIITA	MHC-II transcriptional regulator	Regulation of MHC-II expression	Bare lymphocyte syndrome, Primary mediastinal B-cell lymphoma and Classical Hodgkin lymphoma, Multiple Sclerosis
NAIP	Flagellin sensing, pyroptosis, inhibition of apoptosis	TAK1-dependent JNK1 activation, inflammasome assembly	Increased susceptibility to legionella, spinal muscular atrophy
NOD1	PRR for DAP	RIP2-dependent NF-κB and MAPK activation	Asthma, inflammatory bowel disease
NOD2	PRR for MDP and viral ssRNA, autophagy	RIP2-dependent NF-κB and MAPK activation	Crohn's disease, Blau syndrome, atopic eczema, atopic dermatitis, susceptibility to leprosy and tuberculosis
NLRC3	Negative regulation of T cell activation and TLR response	Interaction with STING to reduce STING-TBK1 association	Prevents colorectal cancer and hepatocellular carcinoma, M. tuberculosis infection, and attenuates lymphocytic choriomeningitis virus infection and experimental autoimmune encephalomyelitis (EAE).
NLRC4	PRR for flagellin and rod protein, pyroptosis, phagosome maturation	Inflammasome formation	Increased susceptibility to bacterial infection, Multiple Sclerosis, autoinflammation with infantile enterocolitis (AIFEC), NOMID and FCAS4, stroke, colitis and colitis-induced colon cancer.
NLRC5	MHC-I upregulation, regulates innate immune response	MHC-I regulation, type I interferon response	hepatocellular carcinoma, liver inflammatory injury, hepatic steatosis, Liver ischemia/reperfusion injury, lymphoid cancers, CNS infection, cerebral ischemia/reperfusion injury, glioma, multiple sclerosis, and epilepsy
NLRP1	PRR for MDP, anthrax lethal toxin	Inflammasome formation	Vitiligo, Alzheimer's disease, celiac disease, Addison's disease, type 1 diabetes, autoimmune thyroid disorders, systemic lupus erythematosus, systemic sclerosis, giant cell arteritis, congenital toxoplasmosis, rheumatoid arthritis, corneal intraepithelial dyskeratosis
NLRP2	Negative regulation of NF-κB, embryonic development	Inflammasome formation	Beckwith-Wiedemann syndrome, Female infertility, hepatic steatosis
NLRP3	PRR for PAMPs, DAMPs, and irritants	Inflammasome formation	Cryopyrin-associated periodic fever syndrome, gout, type 1 diabetes, celiac disease, psoriasis, Multiple Sclerosis, increased susceptibility to HIV-1 infections, Inflammatory bowel diseases, type 2 diabetes
NLRP4	Negative regulation of type I interferon signaling by dsRNA, DNA, or viral infection. Reduces autophagy in response to bacterial infection	DTX4-dependent TBK1 degradation, beclin-1 dependent autophagy	*Streptococcus* infection, viral infection, Asthma
NLRP5	Embryogenesis	Mitochondrial function, ROS	Female Infertility
NLRP6	Negative regulation of NF-κB	Inflammasome formation	Colitis and colon cancer, non-alcoholic fatty liver disease, alcoholic hepatitis, hepatocarcinoma
NLRP7	PRR for lipopeptide	Inflammasome formation	Recurrent hydatidiform moles, testicular seminoma, endometrial cancer, colon cancer
NLRP8	Unknown	Unknown	Expressed in ovaries, testes and preimplantation embryos

NLR	Function	Pathway	Diseases
NLRP9	Unknown	Unknown	Expressed in ovaries, testes and preimplantation embryos
NLRP10	Adaptive immunity by dendritic cells	Unknown	Increased susceptibility to bacterial infection, candida albicans, atopic dermatitis, Asthma, EAE
NLRP11	Association with MAVS during viral infection, inhibits type I interferon signaling	NLRP3 Licenses NLRP11 for inflammasome activation	Cryopyrin-associated periodic syndrome (CAPS)
NLRP12	Negative regulation of NF-κB	Inflammasome formation	FCAS2, Atopic dermatitis, Glioblastoma
NLRP13	Unknown	Unknown	Unknown
NLRP14	Spermatogenesis	Unknown	Spermatogenic failure
NLRX1	ROS generation, autophagy and mitophagy	blocks STING-TBK-mediated antiviral responses, negatively regulates NF-κB pathway through TRAF6	Increased susceptibility to chronic hepatitis B, Viral infections, *Listeria monocytogenes* infection, tumor suppressor in cancer, negatively regulates Group A Streptococcus (GAS) infection