Trends in Immunology

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Review

Redefining nucleotide-binding oligomerization domain-like receptors: from immune sentinels to multifunctional regulators

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Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are a large family of intracellular pattern recognition receptors primarily involved in innate immunity. Although canonical inflammasome-forming NLRs, such as NLRP3 and NLRC4, and microbial sensors, including NOD1 and NOD2, are well-characterized, the functions of many other NLRs remain poorly understood. This review article addresses this gap by highlighting the critical, context-dependent roles of these less-characterized NLRs beyond pathogen sensing. We classify these NLRs as immune modulators, regulators of autophagy and mitophagy, tissue-specific effectors, and reproductive mediators, expanding the traditional view of NLR functions. Understanding the diverse, context-dependent roles of NLRs across biological systems is essential to fully understand their complex regulatory networks and therapeutic potential, which extends beyond classical inflammasome functions.

Highlights

Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) have traditionally been recognized as intracellular immune sensors involved in pathogen detection and inflammasome assembly.

Emerging evidence reveals noncanonical NLR functions beyond immune sensing, positioning them as broader regulators of signaling pathways, cellular and tissue homeostasis, reproduction, and disease.

Recent findings highlight functional interactions among NLR family members that fine-tune inflammatory outcomes, emphasizing regulatory networks rather than isolated inflammasome pathways.

Despite expanding insights, NLR functions remain highly context-dependent, and how their activities are coordinated across tissues and physiological settings remains poorly defined, underscoring the need to better understand NLR functions outside canonical immune sensing.

Significance

Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) exhibit diverse, context- and tissue-specific functions that extend beyond classical pathogen sensing. These noncanonical roles contribute to immune regulation, tissue homeostasis, and broader physiological processes, varying with cellular context, expression patterns, and molecular features. Recognizing and understanding this functional diversity will be essential for interpreting NLR activity across different conditions and for applying insights from NLR biology to varied physiological and disease-relevant contexts.

Redefining nucleotide-binding oligomerization domain-like receptors: beyond immune sentinels

Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) represent one of the largest and most diverse families of intracellular **pattern recognition receptors (PRRs)** (see Glossary). These receptors are known to detect **pathogen-associated molecular patterns (PAMPs)** and **damage-associated molecular patterns (DAMPs)**, thereby triggering a rapid innate immune response characterized by the activation of key signaling pathways, such as **nuclear factor-κB (NF-κB)** and mitogen-activated protein kinases (MAPKs), which leads to the upregulation of proinflammatory **cytokines** and other defense-related genes [5].

Canonical members such as NOD-like receptor family pyrin domain containing 3 (NLRP3) and NOD-like receptor family CARD (caspase-activation and recruitment domain) domain containing 4 (NLRC4) are well-established **inflammasome** sensors [6,7]. Following the detection of PAMPs and DAMPs, inflammasome formation canonically mediates caspase-1-dependent pyroptosis and the subsequent release of proinflammatory cytokines [8–12], although cytokine secretion can occur without cell death in certain contexts [13,14]. Additionally, members such as NOD1 and NOD2 function as cytosolic detectors of bacterial peptidoglycan fragments, further contributing to the detection of microbial components and the activation of inflammatory signaling pathways [15,16]. Collectively, their functions have shaped our understanding of NLRs as central mediators of innate immunity, inflammation, and pathogen sensing (Box 1).

Recent advances have expanded our understanding of NLR biology, showing that these receptors are not limited to classical immune functions but also perform diverse noncanonical roles across

Box 1. The canonical role of NLRs

NLRs are a key family of PRRs that detect pathogens and cellular stress. Mammalian NLRs share two conserved domains: the central NACHT domain and the C-terminal LRRs. The NACHT domain is responsible for ATP-dependent oligomerization, while the LRRs are primarily involved in protein–protein interactions, such as ligand sensing. NLRs are further classified into five different subfamilies—NLRA, NLRB, NLRC, NLRP, and NLRX—based on their variable N-terminal domains, including the acidic domain, baculovirus inhibitor repeats domain, CARD, and the pyrin domain, which determine their interaction partners and downstream signaling [5,17].

Upon the detection of PAMPs and DAMPs, NLRs such as NLRP3 and NLRC4 undergo conformational changes that allow oligomerization and recruitment of the adaptor protein ASC. ASC then binds effector proteases such as caspase-1, forming the inflammasome complex. These complexes process pro-IL-1β and pro-IL-18 into their mature forms and trigger pyroptosis, initiating a rapid inflammatory response [18].

Beyond inflammasome formation, some NLRs, such as NOD1 and NOD2, act as intracellular PRRs that detect specific bacterial peptidoglycan fragments, with NOD1 recognizing γ-D-glutamyl-meso-diaminopimelic acid and NOD2 detecting muramyl dipeptide. Upon recognition of these bacterial components, both NOD1 and NOD2 interact with RIPK2/RICK via homophilic CARD–CARD interactions, activating NF-κB signaling pathways and shaping innate immune responses [15,16].

Together, inflammasome activation and NF-κB signaling represent the canonical functions of NLRs; they serve as intracellular sentinels that sense microbial or danger cues and coordinate appropriate inflammatory and protective responses.

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biological processes. These include modulation of immune signaling pathways independent of direct ligand binding, regulation of cellular metabolism and mitochondrial function, maintenance of tissue-specific **homeostasis**, and critical roles in reproductive biology (Figure 1). Importantly, disruptions in these noncanonical NLR functions are linked to a range of diseases, including autoinflammatory disorders, cancer, metabolic syndromes, and infertility. These emerging functions redefine NLR biology and emphasize the need for a comprehensive review that integrates these noncanonical roles.

Despite these insights, the noncanonical functions of NLRs remain less recognized than their classical immune roles. Their functional diversity, context-dependent activities, and tissue-specific expression underscore the need to understand how these alternative roles influence physiological homeostasis and contribute to pathogenesis. Addressing this gap is crucial for a more complete understanding of NLR biology and its implications for health and disease.

In this review article, we systematically categorize these understudied roles of NLRs into emerging functional groups and discuss how they challenge the traditional models of NLR biology. By highlighting their roles in immune regulation and homeostatic signaling, we propose that these less-characterized functions of NLRs represent a promising and largely unexplored frontier in immunology.

Regulatory NLRs: context-dependent modulators of cellular signaling

While traditionally associated with inflammasome formation, a subset of NLRs has emerged as potent regulators of diverse cellular signaling pathways. Independent of pathogen recognition, these NLRs fine-tune key cellular responses by modulating signaling hubs such as NF-κB, **type I interferons (IFNs)**, and MAPKs (Figure 2). Their context-dependent functions influence inflammation, infection, cancer, and tissue homeostasis, underscoring their importance beyond canonical inflammasome activity.

Regulatory NLRs in the modulation of NF-κB signaling

While canonical NLRs, including NOD1 and NOD2, directly activate NF-κB upon recognition of microbial ligands [15,16], several regulatory NLRs function primarily as modulators rather than initiators of NF-κB signaling. These regulatory NLRs employ diverse mechanisms to modulate

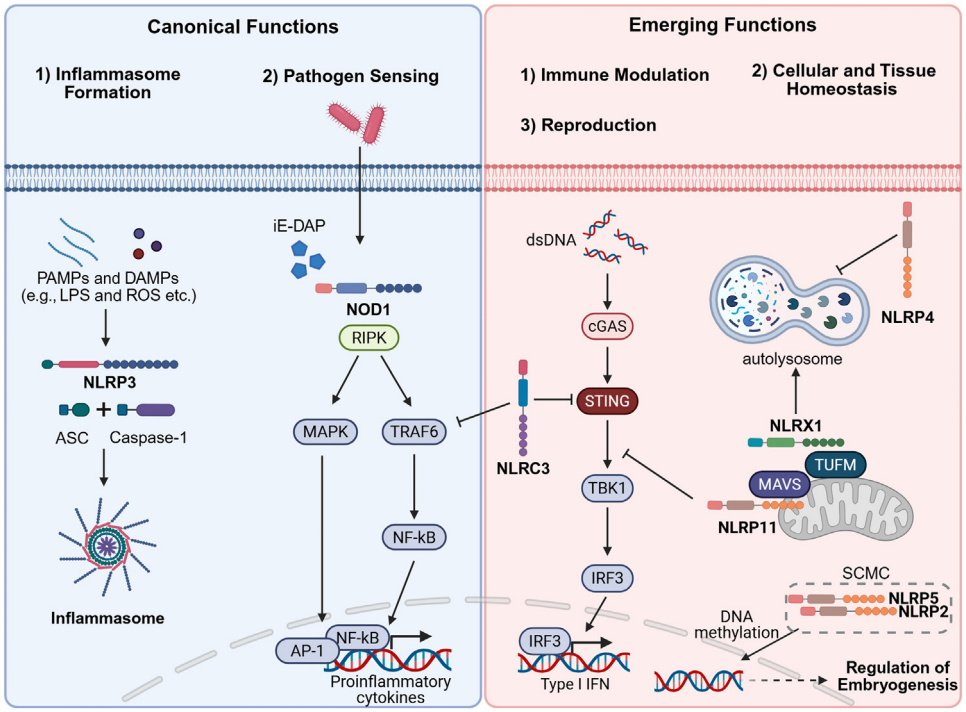

Figure 1. Beyond inflammasomes: canonical and emerging functions of nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs). Canonically, NLRs are well-characterized for their role in inflammasome assembly following the detection of PAMPs and DAMPs, and in innate immune sensing of pathogens, leading to the activation of inflammatory signaling cascades and cytokine production. However, emerging functions extend past their established roles as sensors to include immune modulation, cellular and tissue homeostasis, and reproduction, reflecting a broader spectrum of roles beyond classical inflammation. AP-1: activator protein-1; ASC: apoptosis-associated speck-like protein containing a CARD; PAMPs: pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; LPS: lipopolysaccharide; ROS: reactive oxygen species; iE-DAP: γ-D-glutamyl-meso-diaminopimelic acid; RIPK1: receptor-interacting serine/threonine-protein kinase 1; MAPK: mitogen-activated protein kinase; TRAF6: TNF receptor-associated factor 6; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; STING: stimulator of interferon genes; TBK1: TANKbinding kinase 1; IRF3: interferon regulatory factor 3; dsDNA: double-stranded DNA; cGAS: cyclic GMP-AMP synthase; MAVS: mitochondrial antiviral-signaling protein; TUFM: Tu translation elongation factor, mitochondrial; SCMC: subcortical maternal complex; IFN: interferon. The figure was created by using BioRender.

inflammatory and homeostatic processes. A common strategy involves regulating ubiquitination events. For example, NLRC3, which is highly expressed in T cells [19], attenuates NF-κB activation by inhibiting K63-linked ubiquitination of tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6). Consequently, IFN-γ and TNF production, as well as T cell proliferation, are reduced in murine $CD4^+$ T cells *in vitro* and *in vivo* during lymphocytic choriomeningitis virus infection, autoimmune disorders [20], and *Mycobacterium tuberculosis* infection [21]. Similarly, NLRP11, a primate-restricted NLR family member highly expressed in monocytes, B cells, testes, ovaries, and lung tissue, recruits the E3 ligase RNF19A to promote TRAF6 degradation via K48-linked ubiquitination. This process suppresses NF-κB and MAPK signaling pathways and restricts proinflammatory cytokine production in human myeloid cells [22].

Contrastingly, NLRP12, prominently expressed in myeloid cells such as granulocytes and dendritic cells, modulates both canonical and noncanonical NF-κB pathways through interactions with signaling kinases and adaptor molecules. In the canonical pathway, NLRP12 blocks the activation of interleukin (IL)-1 receptor-associated kinase 1 and the phosphorylation of inhibitor of

Glossary

Autophagy: a conserved lysosome-dependent pathway that degrades and recycles cytosolic material, such as proteins, damaged organelles, and intracellular microbes, to maintain cellular quality control and contribute to host defense and tissue homeostasis.
Beckwith–Wiedemann syndrome: a congenital growth disorder characterized by somatic overgrowth and increased predisposition to embryonal tumors. It is caused by various epigenetic and/or genetic alterations that dysregulate imprinted genes on chromosome 11p15.5.
Cytokine: secreted signaling proteins produced by immune and nonimmune cells, including interleukins, interferons, chemokines, and tumor necrosis factors, that coordinate inflammation, cell recruitment, differentiation, and effector functions.
Damage-associated molecular patterns (DAMPs): endogenous molecules released by damaged cells (e.g., ATP, HMGB1, and mitochondrial DNA) that are recognized by pattern recognition receptors (PRRs) to drive sterile inflammation and recruit innate immune cells.
Homeostasis: the regulation of internal conditions, such as temperature, pH, and ion concentrations, to maintain a stable and balanced physiological state despite external changes. In immunology, homeostasis refers to the balance between tolerance and appropriate immune responses.
Inflammasomes: cytosolic multiprotein complexes that assemble in response to PAMPs and DAMPs, recruit ASC, and activate caspase-1 to process pro-IL-1β and pro-IL-18; inflammasome activation also cleaves gasdermin D to induce pyroptosis.
Maternal effect gene: a gene in the maternal genome whose products are deposited into the oocyte and regulate the early stages of embryogenesis before the activation of the zygotic genome.
Mitochondrial antiviral signaling protein (MAVS): a signaling adaptor on the mitochondrial outer membrane that transmits signals from viral RNA sensors to transcription factors, driving type I interferon and proinflammatory cytokine expression during antiviral responses.
Mitophagy: the selective autophagic removal of damaged or dysfunctional mitochondria. Mitophagy preserves

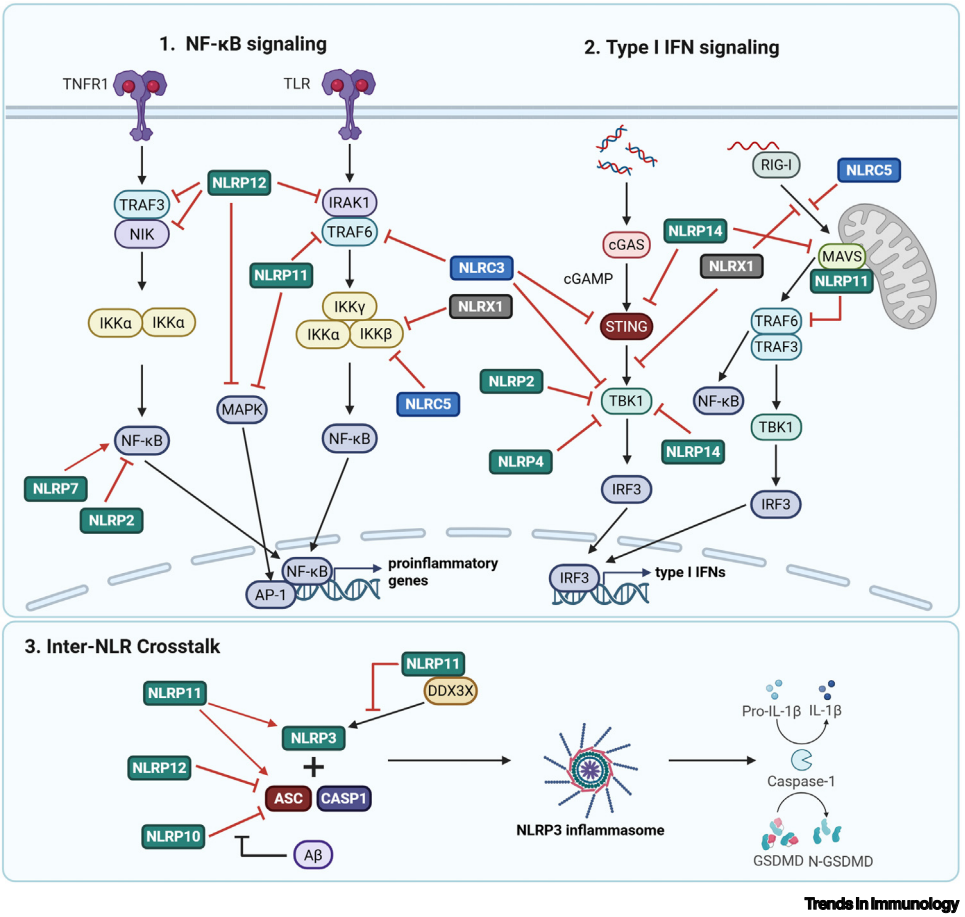

Figure 2. Immunoregulatory functions of nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs): signal transduction and inter-NLR interactions. Certain NLRs regulate immune signaling pathways such as NF-κB, type I interferons, and MAPK through distinct molecular mechanisms, independent of direct pathogen sensing. In addition, several NLRs modulate the function of other NLR family members through inter-NLR interactions. These regulatory activities are context-dependent and contribute to the modulation of immune responses. TNFR1: tumor necrosis factor receptor 1; TLR: toll-like receptor; TRAF: TNF receptor-associated factor; NIK: NF-κB-inducing kinase; IKK: IκB kinase; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon genes; TBK1: TANK-binding kinase 1; IRF: interferon regulatory factor; MAVS: mitochondrial antiviral signaling protein; RIG-I: retinoic acid-inducible gene I; IFN: interferon; AP-1: activator protein 1; ASC: apoptosis-associated speck-like protein containing a CARD; DDX3X: DEAD-box helicase 3 X-linked; GSDMD: gasdermin D; IL-1β: interleukin-1 beta; CASP1: caspase-1; Aβ: amyloid-beta. The figure was created by using BioRender.

kappa B alpha following Toll-like receptor (TLR) stimulation; this prevents excessive activation of NF-κB during infections such as *Mycobacterium tuberculosis* in THP-1 cells [23] and *Salmonella* in murine bone marrow-derived macrophages (BMDMs) [24]. In the noncanonical pathway, NLRP12 interacts with TRAF3 and NF-κB-inducing kinase (NIK), promoting NIK degradation and attenuating prolonged NF-κB signaling in inflammation-driven colon tumorigenesis in mice [25]. Variants of NLRP12 (e.g., p.Arg284X and c.2072 + 3insT) impair NF-κB inhibition, leading to recurrent systemic inflammation in hereditary periodic fever syndromes [26].

Another mechanism involves direct modulation of the IκB kinase (IKK) complex. NLRX1, which is ubiquitously expressed in mammals with particularly high levels in the human mammary gland,

mitochondrial quality, prevents the release of mitochondrial DAMPs, and limits inflammasome activation and inflammation.

Nuclear factor-κB (NF-κB): a family of transcription factors that regulate genes controlling inflammation, immunity, cell survival, and proliferation. NF-κB is activated downstream of PRRs and many cytokine receptors via canonical and noncanonical signaling cascades.

Pathogen-associated molecular patterns (PAMPs): conserved microbial molecules, such as LPS, flagellin, and viral dsRNA, are recognized by PRRs to trigger innate immune responses.

Pattern recognition receptor (PRR): germline-encoded receptors (including TLRs, RLRs, NLRs, and cGAS) that detect PAMPs and DAMPs and initiate signaling cascades, shaping early host defenses.

Stimulator of interferon genes (STING): an adaptor protein located on the endoplasmic reticulum that mediates immune signaling in response to cytosolic DNA. Activation of STING promotes type I interferon and proinflammatory cytokine production.

Type I interferons: a family of antiviral cytokines, including IFN-α and IFN-β, that induce interferon-stimulated genes (ISGs) to establish an antiviral state, enhance antigen presentation, and modulate immune responses.

heart, and muscle [27], disassociates from TRAF6 through K63-linked polyubiquitination upon TLR stimulation with lipopolysaccharide and binds directly to the IKK complex, attenuating the downstream NF-κB activation and proinflammatory cytokine secretion in murine macrophages [28,29]. Notably, overexpression of human NLRX1 has also been linked to increased reactive oxygen species (ROS) production triggered by various stimuli, including TNF-α, *Shigella*, and poly(I:C). This activates NF-κB and c-Jun N-terminal kinase (JNK) signaling pathways, illustrating the context-dependent roles of NLRX1 [27]. Similarly, NLRC5, predominantly expressed in immune cells of myeloid and lymphoid lineages [30], interacts with IKKα/β when overexpressed in HEK293T cells. Both human NLRC5 and its mouse homolog suppress the NF-κB pathway while simultaneously modulating type I IFN responses via retinoic acid-inducible gene I (RIG-I) during viral infections [31].

NLRs in the regulation of type I IFN responses

Beyond NF-κB, several NLRs also modulate type I IFN signaling pathways by targeting central signaling nodes such as the **stimulator of interferon genes (STING)**-TANK-binding kinase 1 (TBK1) axis, **mitochondrial antiviral signaling protein (MAVS)**-dependent RIG-I-like receptor (RLR) pathways, and ubiquitin-mediated regulation of key kinases.

NLRC3 exemplifies this by associating with STING and TBK1 and disrupting their interactions, thereby inhibiting downstream innate immune responses to cytosolic DNA, cyclic di-GMP, and DNA viruses, such as Herpes simplex virus-1 (HSV-1) in mouse embryonic fibroblasts and BMDMs [32]. Notably, viral double-stranded DNA binding to the leucine-rich repeat (LRR) domain of NLRC3 also enhances its ATPase activity, thereby disrupting the interaction of NLRC3 with STING and promoting type I IFN production [33]. NLRP4, widely expressed across the lung, liver, thymus, pancreas, placenta, testis, and spleen [34,35], also targets the same axis via a distinct mechanism. Overexpression of human NLRP4 revealed that the NACHT domain of NLRP4 recruits the E3 ubiquitin ligase DTX4 to activated TBK1, promoting K48-linked ubiquitination and subsequent proteasomal degradation of TBK1 upon viral infection or TLR stimulation. This inhibits interferon regulatory factor 3 (IRF3) phosphorylation and dampens the downstream type I IFN response [35]. Likewise, NLRP2, expressed in oocytes and ovaries [36], directly interacts with TBK1 when transfected into HEK293T cells, blocking its interaction with IRF3 and negatively regulating IFN-induced antiviral responses [37]. Contrastingly, NLRP11 is transcriptionally induced by type I IFNs or upon poly(I:C) treatment and Sendai virus infection and translocates to mitochondria. At the mitochondria, NLRP11 interacts with MAVS and promotes TRAF6 degradation, indirectly constraining MAVS-dependent TBK1 activation in 293 T and THP-1 cells [38].

Furthermore, NLRX1 demonstrates context-dependent, opposing roles in the regulation of type I IFN signaling. Located in the outer mitochondrial membrane, human NLRX1 interacts with the CARD domain of MAVS, disrupting the virus-induced RLR–MAVS interaction through its LRR domain, and plays an inhibitory role in MAVS-mediated IRF3 activation [29,39]. In human and murine monocytic cells, NLRX1 also sequesters the DNA-sensing adaptor STING and interferes with the interaction between STING and TBK1, attenuating antiviral responses against DNA viruses such as HSV-1 [40]. Crystal structures reveal that C-terminus oligomerization of human NLRX1 leads to direct interaction with RNA, supporting its role in viral RNA recognition [41]; however, it also competes with double-stranded RNA (dsRNA)-activated protein kinase R (PKR) for viral RNA binding, preventing PKR-mediated translational shutdown in human hepatocytes. This competition allows for the post-transcriptional maintenance of NF-κB-mediated IRF1 protein expression, ultimately promoting antiviral responses against hepatocyte-targeted viral infections [42].

Notably, unlike other NLRs that primarily shape virus-induced type I IFN responses, NLRP14, found exclusively in the testes and ovaries [43], negatively regulates cytosolic nucleic acid detection in germ cells, supporting successful fertilization. In human NLRP14-overexpressing HEK293T cells, NLRP14 interacts with TBK1 through its NACHT domain, inhibiting TBK1-mediated type I IFN production and thus preventing inappropriate immune responses during human fertilization. NLRP14 also binds to MAVS and STING via its LRR domain to inhibit nucleic acid recognition. Notably, this interaction also results in the breakdown of NLRP14, preventing excessive immunosuppression [44].

Inter-NLR regulation and inflammasome crosstalk

In addition to their roles in regulating canonical signaling pathways, several regulatory NLRs modulate the activity of other inflammasome-forming NLRs. For instance, in HEK293T cells, human NLRP12 suppresses NLRP3 inflammasome activation by limiting apoptosis-associated speck-like protein containing a CARD (ASC) polymerization, whereas disease-associated NLRP12 variants (e.g., P210L, R284*, H304Y, and V635ThrfsX12) lose this inhibitory function. Peripheral blood mononuclear cells from patients carrying these variants exhibit excessive IL-1β release, contributing to Cryopyrin-associated periodic syndromes (CAPS)-like autoinflammatory responses [45]. NLRP11 exhibits both positive and negative regulatory roles. One study reported that NLRP11 acts as a scaffold for NLRP3 inflammasome assembly in human macrophages by interacting with ASC via homotypic PYD–PYD interactions, and with NLRP3 via its LRR and NACHT domains. Due to its interaction with NLRP3, NLRP11 contributes to enhanced immune responses driven by mutant NLRP3-associated CAPS [46]. However, another study reported that in HEK293T cells, NLRP11 negatively regulates DDX3X [47], an ATP-dependent RNA helicase known for its involvement in the activation of the NLRP3 inflammasome and type I IFN signaling [48]. Similarly, NLRP10 has been found to interact with ASC in rat primary glia at resting states, while amyloid-beta disrupts this interaction, leading to cathepsin-dependent NLRP10 degradation and subsequent NLRP3 inflammasome activation, suggesting that NLRP10 also acts as a negative regulator of NLRP3 inflammasome formation [49]. Collectively, these findings highlight a complex network of inter-NLR interactions that modulate inflammasome activation and downstream immune responses.

NLRs in disease contexts

The context-dependent regulatory roles of NLRs are increasingly recognized as contributing factors in various disease states. In human hepatocellular carcinoma (HCC), reduced NLRC3 expression correlates with poor prognosis, as its silencing enhances IL-6-induced Janus kinase 2-signal transducers and activators of transcription 3 (STAT3) signaling and tumor progression [50]. In enterocytes, NLRC3 suppresses PI3K-AKT-mTOR signaling, restraining epithelial proliferation and protecting against colitis and colorectal cancer (CRC) in mice [51].

NLRP12 also plays an important role in tumor biology. In glioblastoma, NLRP12 deficiency is linked to reduced cell proliferation, whereas elevated NLRP12 expression is observed in human glioblastoma tissues, indicating its role in tumor growth regulation [4]. Contrastingly, in mouse HCC models, NLRP12 negatively regulates the JNK pathway; suppresses the production of IL-6, TNF-α, and chemokines such as CXCL1, CXCL2, and CCL2; and downregulates oncogenes including c-Jun and c-Myc, thereby mitigating inflammation and cancer progression [52]. Similarly, NLRX1 exhibits tumor-suppressive features. In mouse models of colitis-associated and sporadic colon cancer and in patients with human colon cancer, reduced NLRX1 expression correlates with the activation of multiple signaling pathways, such as NF-κB, MAPK, STAT3, and IL-6, all of which contribute to tumorigenesis [53]. NLRX1 also influences the balance between extrinsic and intrinsic apoptosis in mouse SV40-transformed cells, highlighting its context-

dependent role in cancer cell survival [54]. In the context of TNF-α exposure in human cancer cell lines overexpressing NLRX1, NLRX1 and activated caspase-8 localize to the mitochondria, where they regulate ROS generation and maintain ATP levels through the modulation of mitochondrial Complex I and III activities, ultimately suppressing tumorigenesis [55].

NLRP7 is a primate-specific NLR, broadly expressed across tissues except for skeletal muscle, heart, and brain [56], and has been implicated in tumor development. In human CRC, it activates the NF-κB pathway, resulting in the polarization of M2-like macrophages and increased secretion of the chemokine CCL2, which supports tumor growth and metastasis. Protein levels of NLRP7 are upregulated in human CRC tissues [57]. In contrast, NLRP2-mediated NF-κB inhibition reduces epithelial-to-mesenchymal transition and cytoskeletal reorganization in human lung adenocarcinoma cells, thereby reducing cell migration and proliferation [58]. It also serves a protective function outside of tumor biology by controlling inflammation in hepatic steatosis observed in high-fat diet (HFD)-fed mice [59].

In summary, regulatory NLRs exert nuanced control over key immune signaling pathways such as NF-κB and type I IFN responses. By employing diverse mechanisms, these NLRs regulate inflammatory and antiviral responses, contributing to immune homeostasis and impacting disease processes such as infection, autoimmunity, and cancer.

NLR-mediated control of autophagy, mitophagy, and tissue-specific immunity

Expanding beyond their canonical roles in immunity, NLRs regulate key cellular processes such as **autophagy** and **mitophagy** to maintain cellular and mitochondrial stability. Furthermore, certain NLRs show tissue-specific roles, shaping localized immune responses and preserving organ homeostasis.

NLRs regulating autophagy and mitophagy

Autophagy and mitophagy maintain organelle integrity and support metabolic homeostasis. NLRX1, a unique NLR notable for its N-terminal mitochondrial-targeting sequence, forms a complex with Tu Translational Elongation Factor, mitochondrial (TUFM). This complex inhibits RLR-induced type I IFN signaling while enhancing autophagy to facilitate viral replication in mouse embryonic fibroblasts [60]. In head and neck squamous cell carcinoma cells, this NLRX1-TUFM complex also interacts with Beclin-1 in the mitochondria, facilitating its polyubiquitination and inducing autophagy [61]. Additionally, upon mitochondrial protein import stress, NLRX1 translocates to the cytosol and interacts with RRBP1, a protein associated with the endoplasmic reticulum. This interaction facilitates the migration of RRBP1 to the mitochondria, where it promotes mitophagy by regulating the lipidation of LC3 in HEK293T cells [62]. Furthermore, during *Listeria monocytogenes* (*L. monocytogenes*) infection in mouse peritoneal macrophages, NLRX1 functions as a mitophagy receptor by interacting with LC3 through its LC3-interacting region [63].

Conversely, NLRP4 contributes to autophagy during bacterial infections. The NACHT domain mediates its interaction with Beclin1, a key autophagy regulator. During group A streptococcus (GAS) infection in various human cell lines, NLRP4 is recruited to the phagosome, where it dissociates from Beclin1, facilitating the initiation of autophagy. Additionally, NLRP4 negatively regulates autophagosome maturation by interacting with class C vacuolar protein-sorting complexes [64]. Human NLRP4 also binds to Rho GDP dissociation inhibitor α, which plays a critical role in Rho GTPase signaling, promoting actin-mediated antibacterial autophagy in response to GAS infection [65]. Furthermore, in human pancreatic ductal adenocarcinoma cells, NLRP4 enhances resistance to olaparib, a therapeutic agent for pancreatic cancer, by promoting DNA

repair and inducing NLRP4-mediated autophagy, thereby positioning NLRP4 as a promising target in cancer therapy [66].

Tissue-specific immune regulatory roles of NLRs

Some NLRs extend their regulatory influence to specific tissues, where they coordinate localized immune responses and aid in the maintenance of tissue homeostasis (Figure 3). For instance, NLRP6, highly expressed in colonic myofibroblasts and epithelial cells [67], is a key regulator of intestinal homeostasis. The NLRP6 inflammasome protects against dextran sodium sulfate-induced colitis in mouse models by promoting IL-18 secretion and maintaining epithelial integrity. It also suppresses colorectal tumorigenesis by inhibiting proliferative signaling pathways, including SMARCC1, p53, WNT, and Notch [67,68]. Furthermore, in both human colonic epithelial cell lines and DSS-induced colitis mouse models, estrogen receptor β enhances NLRP6 expression and induces autophagic flux through interactions with NLRP6 and recruitment of autophagy-related proteins such as ULK1, BECN1, ATG16L1, LC3B, and p62. This process inhibits excessive inflammation by promoting K48-linked polyubiquitination and degradation of inflammasome components, proinflammatory cytokines, and damaged mitochondria [69]. *In vivo* mouse studies further demonstrate that NLRP6-inflammasome-dependent autophagy in goblet cells supports mucus secretion, reinforcing the epithelial barrier and sustaining intestinal host–microbial homeostasis [70].

Beyond its role in barrier maintenance, NLRP6 also contributes to the regulation of infection biology within the intestine. Microbiota-derived metabolites, such as taurine, histamine, and spermine, modulate NLRP6 inflammasome activity to induce IL-18 production and antimicrobial peptide expression, stabilizing gut homeostasis in mice [71]. Additionally, during enteric viral infection in mice, NLRP6 is required for intestinal antiviral innate immunity, forming a complex with viral RNA via the RNA helicase DHX15 to engage MAVS and induce type I and III IFNs and IFN-stimulated genes [72]. In parallel, viral dsRNA can also drive liquid–liquid phase separation of NLRP6 through a disordered polylysine motif (K350–354), thereby promoting inflammasome activation and reinforcing epithelial barrier immunity [73]. Recent findings further indicate that NLRP6, beyond sensing microbial ligands [74], detects endolysosomal damage from bacterial pathogens such as *L. monocytogenes* or by sterile insults in human intestinal epithelial cells, triggering inflammasome-mediated pyroptosis and IL-1β release [75]. Clinically, reduced NLRP6 expression has been observed in the jejunum of patients with obesity-associated type 2 diabetes, coinciding with elevated intestinal damage markers, suggesting impaired epithelial sensing and barrier function [76].

Other NLRs also contribute to gut immune balance. Under HFD conditions, NLRP12 supports barrier microbiota homeostasis by sustaining short-chain fatty acid-producing Lachnospiraceae while limiting the expansion of obesity-associated Erysipelotrichaceae in mice. Consistently, reduced adipose NLRP12 expression correlates with obesity in humans [3]. Notably, reduced NLRP12 expression has also been reported in patients with ulcerative colitis, linking NLRP12 to intestinal inflammatory disorders [77]. Recent evidence further shows that NLRP10, expressed in multiple tissues with high levels in the heart, skeletal muscle, brain, and skin [78], can form an ASC-dependent inflammasome in mouse intestinal epithelial cells under mitochondrial stress. This leads to caspase-1 activation and IL-18 secretion, supporting mucosal repair and immune regulation [79].

Beyond the intestine, NLRP10 also exerts important functions on the skin, regulating cutaneous homeostasis. It stabilizes p63 to promote human keratinocyte differentiation and reinforces epidermal barrier integrity, while limiting cell death by preventing caspase-8 recruitment to the

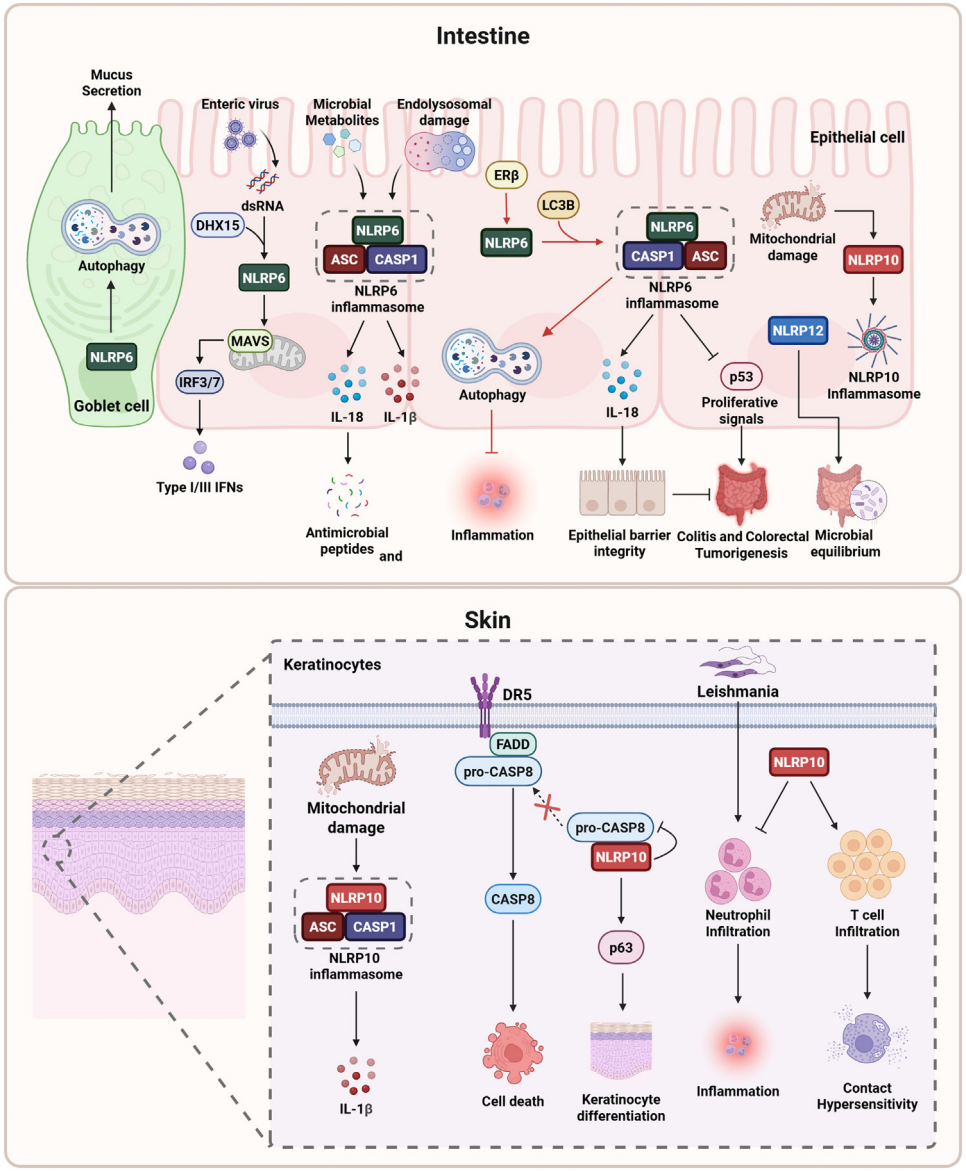

Figure 3. Tissue-specific roles of nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) in gut and skin homeostasis and immunity. NLRs such as NLRP6, NLRP12, and NLRP10 regulate localized immune responses and maintain tissue homeostasis in the intestine and skin. In the gut, NLRP6 promotes IL-18 secretion, induces autophagy, and contributes to antiviral and microbial balance, thereby protecting barrier integrity. NLRP12 helps sustain a healthy microbiota, while NLRP10 forms inflammasomes upon cellular stress to aid mucosal repair. In the skin, NLRP10 stabilizes keratinocyte differentiation, reinforces the epidermal barrier, and shows context-dependent effects by suppressing or promoting inflammation depending on the stimulus. Together, these examples highlight the tissue-specific roles of NLRs in barrier maintenance, immune regulation, and disease outcomes. ASC: apoptosis-associated speck-like protein containing a CARD; CASP1: caspase-1; IL-18: interleukin-18; ERβ: estrogen receptor β; DR5: death receptor 5; FADD: Fas-associated death domain. The figure was created by using BioRender.

death-inducing signaling complex [80]. Mitochondrial damage can also trigger NLRP10 inflammasome formation in human keratinocytes, suggesting a protective role in detecting environmental and microbial stressors that can lead to mitochondrial dysfunction [79]. Context-

dependent functions have also been reported in mice, where NLRP10 can suppress cutaneous inflammatory responses during *Leishmania major* infection [81] but has also been implicated in promoting contact hypersensitivity [82].

By modulating autophagy, mitophagy, and associated signaling pathways, NLRs influence cellular homeostasis and thereby shape host responses to infections and pathogenesis. Additionally, some NLRs mediate tissue-specific immune responses, preserving barrier integrity and maintaining tissue homeostasis, with significant implications for diseases as well.

Immune-independent functions of NLRs in reproductive biology

While NLRs are traditionally recognized for their immune functions, their roles further extend to the reproductive system. The NLR proteins, including NLRP2, 4, 5, 7, 8, 11, 13, and 14, are implicated in reproduction and are highly expressed in germline cells, such as oocytes and preimplantation embryos [83], contributing to a range of reproductive outcomes.

Maternal NLRs in early development

NLRP5, known in mice as maternal antigen that embryos require (MATER), is a well-characterized **maternal effect gene** essential for early embryonic development beyond the two-cell stage [84]. In mice, deficiency of MATER impairs mitochondrial function, increases ROS, and ultimately disrupts early embryonic development [85]. MATER is also a component of the subcortical maternal complex (SCMC), which regulates symmetric zygote division and supports early embryogenesis [86]. In humans, NLRP5 is expressed in oocytes and follicular cells within the SCMC [87]. Genetic variants, including missense and nonsense mutations, as well as duplications affecting conserved domains such as NACHT and LRR, have been linked to early embryonic arrest, infertility, and imprinting disorders such as **Beckwith–Wiedemann syndrome** [88]. Similarly, NLRP2 acts as a maternal effect gene in both mice and humans, forming part of the SCMC [89]. In mice, it has been implicated in preserving oocyte quality, contributing to maternal age-related fertility decline [90], and regulating DNA methylation during early embryogenesis [89]. Germline frameshift mutations in exon 6 of NLRP2 have also been associated with Beckwith–Wiedemann syndrome [91].

Reproductive functions of NLRs

Beyond NLRP2 and NLRP5, additional members of the NLR family have been implicated in reproductive function. NLRP7, phylogenetically related to NLRP2, is highly expressed in oocytes and ovaries [36] and harbors genetic variants such as splice site (IVS3 + 1 G > A, IVS7 + 1 G > A) and missense (R693W, R693P, and N913S) variants. These variants are linked to reproductive failure in women, including recurrent hydatidiform moles, abnormal embryogenesis, and spontaneous abortion [92]. NLRP9 exhibits differential genetic organization between humans and mice, with humans having a single gene and mice possessing three paralogs (*Nlrp9a*, *Nlrp9b*, and *Nlrp9c*) [36]. NLRP9 is highly expressed in mammalian oocytes, notably in human primordial and primary follicles, while mouse NLRP9b is present in germinal vesicles, metaphase II oocytes, and zygotes [93]. Specifically, mouse NLRP9b localizes to the cytoplasm of two-cell embryos, and its knockdown causes developmental arrest at the two- to four-cell stages. Although mice lacking all three *Nlrp9* paralogs remain fertile, they exhibit delayed blastocyst development and increased preimplantation lethality, indicating its role in embryogenesis, though it is not essential for fertility [94].

Distinct from other NLRs, NLRP14 has been implicated in both male and female fertility, where multiple genetic variants, including p.K108X, p.D86V, p.A375T, p.D522Q, and p.M1091I, have been identified in patients with spermatogenic failure [95,96]. In addition, compound

heterozygous variants c.1282_1283delTG and c.2660delinsGCTA have been linked to abnormal reproduction in females [97]. In mice, NLRP14 promotes spermatogenesis by stabilizing HSPA2 through BAG2 interaction, supporting the differentiation of primordial germ cell-like cells and spermatogonial stem cells [96]. Furthermore, NLRP14-deficient mice exhibit defective oocyte maturation and embryonic arrest, underscoring its critical role in reproduction [97]. NLRP14 also interacts with UHRF1, a key epigenetic regulator, protecting it from degradation; however, mutations in NLRP14 identified in early embryonic arrest patients disrupt this interaction, reducing UHRF1 levels and impairing oocyte maturation and early embryonic development [97].

Collectively, several NLRs are essential maternal-effect genes or regulators of germ cell development, playing crucial roles in early embryogenesis and fertility. Mutations in these NLRs have been linked to infertility, early embryonic arrest, and reproductive disorders, highlighting their significance beyond immunity.

Therapeutic modulation of NLRs: balancing activation and homeostasis

NLRs function as critical regulators of immune and cellular homeostasis, and their dysregulation contributes to a broad spectrum of inflammatory, metabolic, and tumor-associated diseases. Although therapeutic strategies have primarily focused on NLRP3, other NLRs have gained attention as potential tractable targets because of their conserved regulatory mechanisms.

A common structural feature among NLRs is the NACHT domain, which acts as a molecular switch controlling transitions between autoinhibited and signaling-competent states. Structural and biochemical studies indicate that many NLRs are maintained in restrained conformations under basal conditions, stabilized by nucleotide binding, interdomain interactions, or accessory inhibitory proteins (e.g., DPP9 for NLRP1) [98–100]. This molecular structure suggests that NLRs are generally inducible rather than constitutively active, requiring specific cellular cues, such as ligand recognition, stress responses, or post-translational modifications, to initiate signaling.

Therapeutic inhibition of NLRs has been most clearly demonstrated for NLRP3, where small-molecule inhibitors such as MCC950 stabilize the NACHT domain in its inactive state and suppress pathogenic inflammasome activation [1,2]. Notably, structural studies show that NOD2 and NLRC4, like NLRP3, require ATP binding to the NACHT domain for activation [98,99]. Dysregulation of these receptors has been implicated in human diseases, including Blau syndrome (NOD2) [101] and autoinflammation with infantile enterocolitis (NLRC4) [102]. Together, these observations suggest that NACHT-targeted inhibitors could represent a broadly applicable therapeutic strategy across multiple NLRs. Moreover, beyond ATP-dependent activation, the variety of autoinhibitory and regulatory mechanisms within NLRs offers additional opportunities for therapeutic intervention.

Therapeutic strategies may also target the homeostatic functions of NLRs. For instance, activation of NLRX1 by NX-13, which selectively targets NLRX1 in the gut, has been shown to attenuate immune activation and mitigate inflammatory bowel disease in mouse models [103]. In cancer, NLRC3 is frequently downregulated in HCC, correlating with enhanced tumor-promoting inflammatory signaling [50]; restoring NLRC3 activity may help rebalance immune homeostasis and restrain oncogenic pathways. Additionally, certain NLRs regulate autophagy and mitophagy—pathways increasingly implicated in human diseases such as Alzheimer's disease, where impaired clearance of damaged mitochondria and protein aggregates promotes oxidative stress and chronic inflammation [104]. Modulating NLR activity to restore autophagic and mitophagic function, therefore, represents a promising strategy to reinforce cellular homeostasis and limit persistent pathological signaling.

Clinician's corner

Targeting NLRP3 (nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain containing 3) has been extensively investigated for therapeutic purposes, primarily through modulation of its canonical inflammasome activity via inhibition of the conserved NACHT domain [1,2]. However, many NLR family members regulate immune signaling, cellular metabolism, epithelial barrier integrity, and reproductive processes independently of inflammasome activation. These noncanonical functions are increasingly linked to disease progression and may provide additional therapeutic opportunities.

The functional diversity of NLRs has important clinical implications. NLR activity is highly tissue- and context-dependent. The same NLR can exert protective or pathological effects depending on the cellular environment. For example, NLRP12 contributes to maintaining gut microbial homeostasis and intestinal health [3]. In contrast, it has been associated with enhanced tumor cell proliferation in certain experimental settings [4]. Such contrasting roles highlight the complexity of nucleotide-binding oligomerization domain-like receptor biology.

Given this context dependence, therapeutic targeting of NLRs requires careful consideration. Broad inhibition could disrupt physiological homeostasis or impair beneficial regulatory functions, whereas pathway- or tissue-specific modulation may improve therapeutic precision. Effective strategies should consider the specific NLR involved, its cellular and tissue distribution, and its integration within local signaling networks.

Clinicians and translational researchers should recognize that NLR biology extends beyond inflammasome activation. A deeper understanding of tissue-specific and context-dependent NLR functions will be critical for developing selective interventions that maximize therapeutic benefits while minimizing unintended effects.

Altogether, these findings highlight key principles for NLR-targeted therapy. NLR activation is tightly regulated and largely inducible, with ATP binding to the NACHT domain serving as a central mechanism. Additional autoinhibitory or regulatory pathways may provide complementary opportunities for therapeutic modulation. Importantly, strategies can be tailored to the disease context, either to suppress excessive activation or to enhance homeostatic functions.

These insights provide a framework for extending therapeutic approaches beyond NLRP3 to both canonical and noncanonical NLRs across inflammatory, degenerative, and tumor-associated diseases.

Concluding remarks

NLRs are well-established intracellular sensors, forming the first line of defense against invading pathogens, intracellular damage, and sterile inflammation. However, increasing evidence suggests that NLRs have functions beyond their canonical roles as innate immune sentinels. NLRs regulate diverse signaling pathways, including NF-κB, MAPK, and the type I IFN axis, as well as processes such as autophagy and mitophagy. They also contribute to tissue homeostasis, barrier integrity, and reproductive processes. Moreover, members such as the class II major histocompatibility complex transactivator and NLRC5 act as transcriptional activators of major histocompatibility complex class II and class I genes, respectively. This highlights their roles in adaptive immunity and underscores their functional diversity beyond the mechanisms discussed in this review [105,106].

From an evolutionary perspective, the NLR family likely expanded and diversified through host–pathogen coevolution, analogous to plant nucleotide-binding site (NBS)–LRR resistance genes that underwent gene expansion and diversification under pathogen pressure [107,108]. Such pressures may have driven the divergence of ancestral multifunctional proteins into specialized, yet partially redundant, functions. Conserved domains, including NACHT, LRR, and N-terminal variable regions, further provide a shared structural framework supporting diverse regulatory activities.

Mechanistic studies have largely focused on NLRP3, NOD1, and NOD2 because of their central roles in inflammasome formation and host defense. In contrast, other NLRs frequently act in complementary or modulatory capacities, functioning as negative regulators, transcriptional modulators, or metabolic sensors. Through these interactions, a relatively restricted receptor repertoire can respond to a broad spectrum of perturbations, ranging from pathogen-derived ligands to endogenous cellular changes, while maintaining appropriately balanced immune and homeostatic responses. Together, these features underscore the integrated and coordinated nature of NLR-mediated regulation.

To fully understand the biology of NLRs, several key aspects warrant further investigation. NLRs exhibit highly context- and tissue-specific functions that shape outcomes during infections, cancer, and other diseases, yet many of these roles remain incompletely defined. Elucidating these noncanonical functions could explain their variable effects across different settings and uncover new mechanisms relevant to disease progression. Furthermore, functional redundancy or compensatory activities within the family may limit our ability to define the roles of individual receptors; however, emerging evidence indicates that NLRs can influence one another, raising the possibility that higher-order regulatory networks are important. Additionally, investigating expression patterns, subcellular localization, and structural differences will be essential to understand their functional diversity (see Outstanding questions).

Outstanding questions

How do context- and tissue-specific functions of NLRs shape immune responses, tissue homeostasis, and disease outcomes such as infection, cancer, or sterile inflammation?

What molecular features (e.g., post-translational modifications, isoforms, and subcellular localization) determine whether NLRs act as inflammasome sensors, transcriptional regulators, or modulators of processes such as autophagy?

How do the expression patterns of NLRs across different tissues, cell types, and developmental stages influence their functional roles in immunity, homeostasis, and disease?

Why does functional redundancy occur among NLR family members? Is it primarily an evolutionary diversification maintained through tissue- or context-specific expression or shaped by integration within complex immune regulatory networks?

Given the multifunctional and context-dependent nature of NLRs, how can targeted therapies be designed to selectively modulate one function without inadvertently disrupting other essential roles?

In summary, the NLR family functions as a versatile regulatory system across immune and other physiological contexts. Integrating their context-dependent and noncanonical activities will be essential to fully appreciate their biological significance and therapeutic potential, including for lesser-studied family members.

Author contributions

S.K., S.P., and S.L. were responsible for conceptualizing the study, preparing the manuscript, critically reviewing, and revising the final version. All authors contributed to the manuscript and approved the final version submitted. S.L. secured funding and provided overall supervision.

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Declaration of interests

The authors declare no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to enhance clarity, grammar, and overall readability. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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