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Review article

NOD1 and NOD2 in inflammation, immunity and disease

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A B S T R A C T

NOD1 and NOD2 are related intracellular sensors of bacterial peptidoglycan and belong to the Nod-like receptor (NLR) family of innate immune proteins that play fundamental and pleiotropic roles in host defense against infection and in the control of inflammation. The importance of these proteins is also highlighted by the genetic association between single nucleotide polymorphisms in *NOD2* and susceptibility to Crohn's disease, an inflammatory bowel disease. At the cellular level, recent efforts have delineated the signaling pathways triggered following activation of NOD1 and NOD2, and the interplay with various cellular processes, such as autophagy. *In vivo* studies have revealed the importance of NOD-dependent host defense in models of infection, and a crucial area of investigation focuses on understanding the role of NOD1 and NOD2 at the intestinal mucosa, as this is of prime importance for understanding the etiology of Crohn's disease.

1. Introduction

Innate immunity is an evolutionary conserved system of defense against infection and toxic threats that is found in all metazoans. While innate immunity in the nematode *Caenorhabditis elegans* does not seem to rely on the detection of microbial or danger signals by specific receptors (also known as pattern recognition molecules or PRMs) and instead relies on the cellular response to stress and toxins [1,2], PRMs are widely used in other branches of animal evolution to detect infection and danger signals. Because PRMs are encoded in the germline and are invariant among individuals of the same species, these molecules have been selected to detect microbial motifs and danger signals that are widely conserved. In mammals, several families of PRMs have been identified. The Toll-like receptors (TLRs) are transmembrane proteins expressed at the plasma membrane or at the surface of endosomes, which detect various microbial motifs, including bacterial lipopolysaccharide (TLR4), lipopeptides, lipoproteins and lipoteichoic acid (TLR2 with TLR1 or TLR6), flagellin (TLR5), CpG DNA (TLR9), as well as viral nucleic acids, double-stranded RNA (TLR3) and single-stranded RNA (TLR7/8) [3]. Since the discovery of TLRs, several families of intracellular sensors of microbes and danger signals have been identified, including the Nod-like receptors (NLRs) [4,5], Rig-I-like receptors (RLRs) [6] and Aim2-like receptors (ALRs) [7]. In addition, intracellular detection of DNA by the cGAS/STING pathway is emerging as a crucial pathway in innate immunity, with implications for cancer and cellular senescence control [8].

As for NLRs, this family is comprised of approximately 20 members (this number varies between species in vertebrates because of gene duplications or deletions) which have in common the juxtaposition of a central NACHT domain (NACHT is an acronym standing for NAIP (neuronal apoptosis inhibitor protein), C2TA (MHC class II transcription activator), HET-E (incompatibility locus protein from *Podospora anserina*) and TP1 (telomerase-associated protein), proteins that share this domain organization), flanked with a leucine-rich repeat (LRR) domain. Interestingly, a similar domain organization is encoded in plant Resistance (or R) genes that play central roles in host defense against phyto-pathogens [9,10]. Among the most studied NLRs are proteins that are crucial for the formation of caspase-1 activation complexes, known as inflammasomes. NLR proteins such as NLRP3, NLRP1 and NLRC4 detect microbial and danger signals to trigger assembly of caspase-1 inflammasomes that lead to the processing and secretion of interleukin (IL)-1β and IL-18 [11]. The other well-studied NLR proteins are the related proteins NOD1 and NOD2, which are the focus of this review article. NOD1 and NOD2 are intracellular sensors of bacterial peptidoglycan that play critical roles in the control of host defense and inflammation as reviewed here.

2. Detection of peptidoglycan by NOD1 and NOD2

Peptidoglycan is a polymer comprised of amino acids and sugars with a backbone made of alternating *N*-acetylglucosamine and *N*-acetylmuramic acid residues (MurNAc). A peptide chain is linked to MurNAc to create a muramyl peptide, which can be crosslinked to form the lattice structure of peptidoglycan [12]. Early studies had identified a role for TLR2 in the extracellular detection of peptidoglycan, but this was likely caused by the presence of contaminating molecules, such as

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lipoteichoic acid or lipoproteins, in commercial preparations of peptidoglycan [13], and it is now widely recognized that peptidoglycan is detected intracellularly by NOD1 and NOD2. While NOD1 recognizes γ-D-glutamyl-*meso*-diaminopimelic acid found predominantly in Gram-negative bacteria [14–16], NOD2 detects muramyl dipeptide found in peptidoglycans of most bacteria [17,18]. Although the MurNac group is dispensable for NOD1 activation, NOD2 can only be activated by muramyl dipeptides that have an intact MurNAc ring structure, and the sugar must be attached to a dipeptide (L-Ala-D-Glu or L-Ala-D-iso Gln) or tripeptide (L-Ala-D-Glu-Lys or L-Ala-D-iso Gln-Lys) moiety [15]. Although murine and human NOD1 are highly homologous, it was nonetheless identified that murine NOD1 is optimally activated by *meso* diaminopimeic acid (*meso* DAP)-type peptidoglycan with a peptide stem made of four amino acids while human NOD1 preferentially detects tripeptide stems with the *meso* DAP amino acid in terminal position [19,20]. Importantly, studies have shown that NOD2 can directly bind to MDP in the nanomolar concentration range, strongly suggesting that NOD1 and NOD2 are *bona fide* cytoplasmic receptors [21,22].

NOD1 and NOD2 have a similar domain organization with a single N-terminal CARD domain (caspase activation recruitment domain) in NOD1, whereas two are found in NOD2, followed by a NACHT domain and a C-terminal LRR domain with differing sizes between NOD1 and NOD2 [23,24] (Fig. 1). The CARD domain interacts with downstream adaptor proteins, which is a prerequisite for pro-inflammatory signaling pathways [25,26], the NACHT domain mediates interactions required for homo-oligomer formation and the LRR domain is involved in the recognition of peptidoglycan [20,27,28]. The importance of the LRR domain in ligand binding is illustrated by the conservation of key residues from zebrafish to humans in both NOD1 and NOD2 LRR domains [29]. Importantly, mutations in the LRR domain of NOD2 are also correlated with disease in humans [30,31], although the exact underlying mechanisms for this link have not been fully elucidated at the molecular level.

NOD1 and NOD2 are typically associated with endosomal membranes, which are thought to represent the site where complex formation occurs [32–34]. In line with these observations, studies have shown that efficient NOD1- and NOD2-dependent responses require delivery of ligands into the cytosol by endosomal peptide transporters of the SLC15 family [35–37]. Chemicals which disrupt the acidic nature of endosomes inhibit NOD1 induced nuclear factor-kappaB (NF-κB) activation, presumably because of the reliance on the proton gradient as

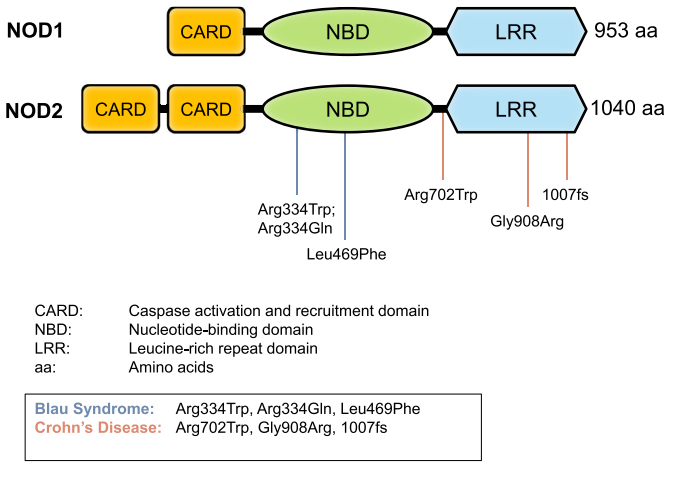

Fig. 1. Schematic representation of the structures of NOD1 and NOD2.
The NOD1 protein comprises of one N-terminal caspase activation and recruitment domain (CARD), whereas NOD2 has two in tandem. Both proteins contain a nucleotide-binding domain (NBD), and a C-terminal leucine-rich repeat domain (LRR). Important single nucleotide polymorphisms of NOD2 associated with Crohn's disease and Blau syndrome have been indicated on the structure as referenced in Refs. [30,31,128,156].

an energy source for transport [35]. In addition to endocytosis, uptake of NOD2 muramyl peptide ligands may also occur by macropinocytosis. Macrophages, which normally undergo constitutive macropinocytosis in a G-protein-coupled calcium-sensing receptor (CaSR) dependent manner, can deliver NOD ligands in this way [38]. In contrast, the internalization of polymeric peptidoglycan by macrophages occurs by phagocytosis and requires an initial step of peptidoglycan digestion by lysozyme in lysosomes [39], likely allowing formation of monomeric peptidoglycan fragments that can then access the cytosol through the action of specific transporters, such as those discussed above.

3. NOD1 and NOD2 signaling circuitry

Under steady-state conditions, NOD1 and NOD2 likely exist in an autoinhibited monomeric state in the cytosol. Upon recognition of their respective cognate ligands, both NOD1 and NOD2 self-oligomerize via the NACHT domain and undergo a conformational change. Subsequently, NOD1 and NOD2 recruit the scaffolding kinase protein, receptor-interacting serine-threonine kinase 2 (RIPK2, also known as RIP2 or RICK), through a homotypic CARD-CARD interaction [40]. RIPK2 activity and its association with NOD1 and NOD2 is kept in check by MEKK4 at homeostasis [41]. Recently, two-independent groups have revealed that RIPK2, via its CARD, can spontaneously form slender helical filaments, which are nucleated from one end by activated NOD2 [42,43]. Interestingly, another report demonstrated that RIPK2 kinase activity is dispensable for NOD2 inflammatory signaling. Further, RIPK2 acts as a scaffolding protein providing an interface for interaction of downstream signaling mediators [44]. RIPK2 filamentation triggers receptor proximal events that lead to hierarchical recruitment of the inhibitor of apoptosis protein (IAP) E3-ligase family members, including X-linked IAP (XIAP) [45], cellular IAP1 (cIAP1) and cIAP2 [46] as well as TNF-receptor associated factors (TRAF2, TRAF5 and/or TRAF6) [47]. XIAP and cIAP-TRAF complexes facilitate poly-ubiquitination of RIPK2, which is essential for recruitment of the linear ubiquitin assembly complex (LUBAC) [48,49]. RIPK2 then mediates the recruitment of transforming growth factor β-activated kinase 1 (TAK1) and TAK1 binding protein 1 (TAB1), TAB2 or TAB3 [50,51]. These events facilitate the formation of the multi-protein signaling complex termed “nodosome”, which activates downstream NF-κB and mitogen-associated protein kinase (MAPK) signaling pathways [25,52,53].

Activation of the NF-κB signaling pathway requires RIPK2 and TAK1-mediated polyubiquitylation of NF-κB essential modulator kinase (NEMO, also known as IKKγ) and phosphorylation of the inhibitor of kappaB kinase (IKK)-complex comprised of NEMO, IKKα and IKKβ [54]. The IKK-complex drives phosphorylation of signal responsive serine residues of inhibitors of kappaB (IκBs) bound to the NF-κB dimers in the cytosol. Phosphorylated IκBs are then targeted for lysine 48 (K48)-polyubiquitination-dependent proteosomal degradation. NF-κB dimers subsequently translocate into the nucleus and bind to kappaB (κB)- elements, activating pro-inflammatory and anti-microbial peptide (AMP) gene expressions (Fig. 2).

Alternatively, nodosome complex formation also triggers activation of p38, extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) MAPK pathways [26,55]. These kinases then translocate into the nucleus and phosphorylate AP-1 transcription factors, including ATF, c-fos, c-Jun and JDP family members. These transcription factors then bind to TPA DNA-response elements (TRE) and mediate expression of pro-inflammatory cytokines/chemokines and AMPs (Fig. 2).

In addition to NF-κB and MAPK pathways, it was recently demonstrated that NOD1 and NOD2 are involved in the activation of interferon (IFN) signaling. Upon infection with single-stranded RNA virus, NOD2, unlike NOD1, was reported to oligomerize and interact with the mitochondrial anti-viral signaling (MAVS) protein. MAVS was shown to activate interferon regulatory transcription factor 3 (IRF3) in a TRAF3-

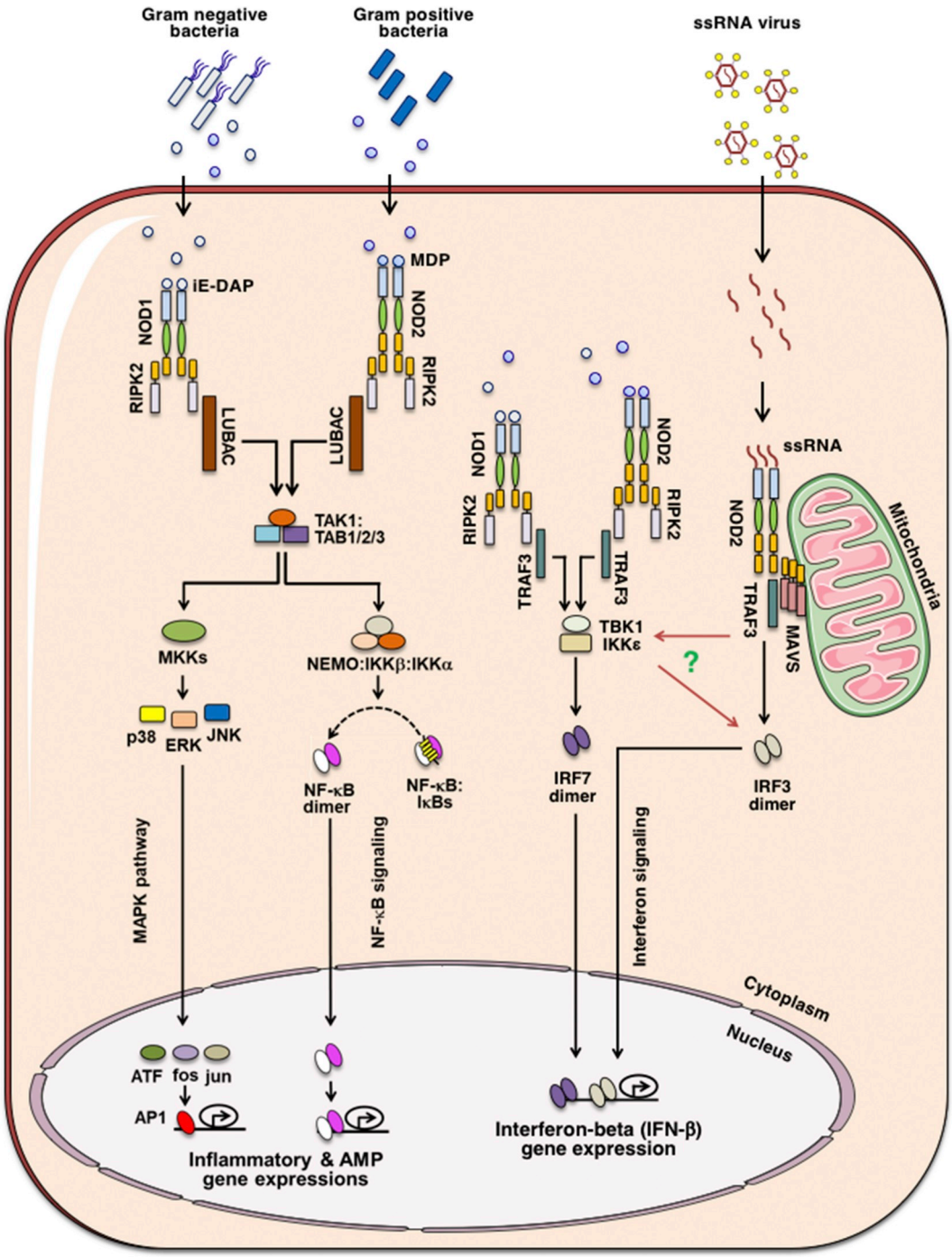

Fig. 2. NOD1 and NOD2 induced NF-κB, MAPK and IFN signaling pathways.
Recognition of γ-D-glutamyl-meso-diaminopimelic acid (iE-DAP) and muramyl dipeptide (MDP) through the leucine-rich repeat (LRR) domains activates the NOD (nucleotide-binding oligomerization domain) proteins NOD1 and NOD2, respectively. Activation of NODs facilitates recruitment of receptor-interacting serine/threonine kinase (RIPK2). Subsequently, RIPK2 interacts with LUBAC and TAK1-TAB kinase complex leading to formation of the "nodosome" complex, which either triggers NF-κB or MAPK pathway. During NF-κB signaling, the TAK1-TAB complex activates the scaffold of the inhibitor of NF-κB (IκB)-kinase complex (IKK complex), composed of NEMO, IKKβ and IKKα. The IKK complex triggers phosphorylation dependent degradation of IκBs, leading to nuclear translocation of NF-κB dimers. In addition to NF-κB signaling, NOD1 and NOD2 activate mitogen-activated protein kinases (MAPKs) such as p38 MAPK, extracellular-signal-regulated kinase (ERK) and JUN amino-terminal kinase (JNK) through MAPK kinases (MKKs), ultimately triggering transcription factor activator protein 1 (AP1). The NF-κB and MAPK pathways, together stimulate the expression of inflammatory and anti-microbial peptide (AMP) genes.
Alternatively, NOD1 and NOD2 signaling also activates the interferon pathway. NOD-RIPK2 complex was shown to recruit TRAF3-TBK1-IKKε kinase complex and to induce IRF7-mediated interferon signaling, upon bacterial infection. Moreover, recognition of virus-derived single strand RNA (ssRNA) by NOD2-dependent signaling leads to interferon induction. NOD2 in association with mitochondrial antiviral signaling (MAVS) protein and TRAF3 induces IRF3-dependent interferon-beta (IFNβ) production. However, involvement of TBK-IKKε in the activation of IRF3 remains unclear.

dependent manner [56–58]. Subsequently, IRF3 translocates into the nucleus and induces expression of type-1 IFN genes (IFNα/β). Interestingly, bacterial infection was also shown to trigger NOD1-and NOD2-dependent type I IFN responses, potentiating formation of the RIPK2-TRAF3 complex and recruitment of TANK-binding kinase 1 (TBK1) and IKKε. The TBK-IKKε complex further drives IRF7-dependent expression of IFNβ and type-I IFN target genes, which are critical and necessary for bacterial clearance [59] (Fig. 2).

Interestingly, recent studies have proposed that endoplasmic reticulum (ER) stress causes inositol-requiring enzyme 1α (IREα) kinase mediated recruitment of TRAF2 to the ER membrane, which initiates an inflammatory response in a NOD2/RIPK2 dependent manner [60]. Lastly, NODs were shown to bind procaspase-1 through homophilic CARD interaction, and promote procaspase-1 oligomerization and conversion into active caspase-1. This led to caspase-1-dependent processing of pro-IL-1β to mature IL-1β and its secretion [61]. However, the physiological relevance of NOD2-dependent induction of IL-1β secretion remains unexplored.

4. Regulation of NOD1 and NOD2 signaling

The NOD1 and NOD2 signaling cascade is tightly controlled by various molecular regulators. Yeast-two-hybrid screening, co-immunoprecipitation assays, *in vitro* protein over-expression and/or knockdown cell-culture based assays and *in vivo* mice studies have been used to uncover potential regulators of the pathway. Moreover, post-translation modifications (PTMs) including ubiquitination, phosphorylation and glycosylation were identified to regulate conformational changes, interactions, activation, localization and turnover of the NOD-signaling pathway proteins (Table 1).

Ubiquitination events fine-tune initiation, activation and termination of the NOD signaling cascade. Following NOD1 and/or NOD2 activation, RIPK2 undergoes XIAP-mediated methionine 1 (M1)-linked linear poly-ubiquitination [45]. Additionally, cIAPs facilitate lysine 63 (K63)-linked poly-ubiquitination of RIPK2 at the position lysine 209 (K209) [47]. These events of RIPK2 ubiquitination are essential for the recruitment of downstream molecular regulators and nodosome complex formation. RIPK2 and TAK1-mediate (K63)-linked poly-ubiquitynation of NEMO at lysine 285 (K285) [62]. Moreover, LUBAC, containing the E3 ligase RNF31 (also known as HOIP), potentiates direct linear polyubiquitination of NEMO, which is necessary for the activation of NOD2-induced NF-κB signaling [48]. E3 ubiquitin ligases, including TRAF2, TRAF5, TRAF6 [47] and Pellino3 [63] were shown to positively regulate NOD-mediated NF-κB and MAPK activation. Conversely, TRAF4 [64] and TRIM27 [65,66] were shown to facilitate lysine 48 (K48)-linked polyubiquitination mediated negative regulation of NOD2 signaling. Likewise, interaction of RNF34 inhibited NOD1 signaling [67]. Another E3 ubiquitin ligase, ITCH is speculated to act as a molecular switch in dictating the fate of NOD1 and NOD2 signaling to NF-κB and MAPK activation [68]. A20, a deubiquitinase (DUB) was shown to play a role in the termination of NOD2 signaling [69]. Furthermore, recent studies have demonstrated that cylindromatosis protein (CYLD) deubiquitinates M1-linked linear and K63-linked branched polyubiquitination of RIPK2, limiting NOD2-induced TNFα and IL-6 production [70,71]. Similarly, ovarian tumor (OTU) family deubiquitinase (OTULIN) disassembles M1-linked linear ubiquitination of RIPK2, dampening NOD signaling [72]. MYSM1 was also identified as a central negative regulator restricting polyubiquitination of RIPK2, thus preventing excessive NOD2-mediated inflammation [73].

Further, phosphorylation and dephosphorylation of cellular proteins were indicated to be critical for NOD signaling. NOD1 was shown to sense cytosolic microbial products by monitoring the activation state of small Rho GTPases, including Rac1, Cdc42 and RhoA. This triggered NOD1-mediated nodosome phosphorylation and NF-κB activation [74]. Alongside, cofilin phosphatase slingshot homolog 1 (SSH1), which is known to mediate actin dephosphorylation, was reported to form a complex with NOD1 and regulate CXCL-8 production [75]. Guanine nucleotide exchange factor H1 (GEF-H1) was also demonstrated to co-localize and phosphorylate RIPK2 at serine 176 (S176), leading to enhanced NF-κB signaling [76]. Moreover, inhibition studies suggested that RIPK2 autokinase activity might be required for the recruitment of IAPs, downstream of NOD signaling [77].

Interestingly, ubiquitination and glycosylation-associated PTMs have been demonstrated to play a crucial role in the stability and activity of NOD proteins. The evolutionary conserved molecular chaperones, heat shock protein 90 (HSP90) and HSP70 were indicated to be essential for NOD1 and NOD2 stabilization [78,79]. It was proposed that HSP90 prevented K48 polyubiquitination-dependent NOD2

Table 1
Molecular interactors regulating NOD1 and NOD2 signaling.

Molecule(s)	Function(s)	Impact	Pathway(s) regulated	Reference(s)
XIAP	M1-linked linear poly-ubiquitination of RIPK2	positive	NOD1 and NOD2	[45]
cIAPs	K63 poly-ubiquitination of RIPK2	positive	NOD1 and NOD2	[47]
TRAF2/5/6	facilitates K63 ubiquitination along with cIAPs	positive	NOD1 and NOD2	[47]
Pellino3	K-63 poly-ubiquitination of RIPK2	positive	NOD2	[63]
TRAF4	K48 poly-ubiquitination of RIPK2	negative	NOD2	[64]
RNF31	K48 poly-ubiquitination of RIPK2	negative	NOD2	[48]
TRIM27	K48 poly-ubiquitination of RIPK2	negative	NOD1	[65,66]
RNF34	K48 poly-ubiquitination of RIPK2	negative	NOD1	[67]
ITCH	skews NOD signaling towards MAPK pathway	fine-tunes	NOD1 and NOD2	[68]
A20	deubiquitination of RIPK2 complex	negative	NOD1 and NOD2	[69]
CYLD	deubiquitination of M1-linked linear and K63-linked branched poly-ubiquitination of RIPK2	negative	NOD2	[70,71]
OTULIN	deubiquitination of M1-linked linear poly-ubiquitination of RIPK2	negative	NOD2	[72]
MYSM1	deubiquitination of RIPK2 complex	negative	NOD2	[73]
RhoGTPases	interacts with NOD1 and phosphorylates nodosome complex	positive	NOD1	[74]
SSH1	interacts with NOD1 and regulates cofilin phosphorylation	positive	NOD1	[75]
GEF-H1	phosphorylation of RIPK2	positive	NOD1	[76]
HSP90	NOD1 and NOD2 stabilization	positive	NOD1 and NOD2	[78]
HSP70	NOD2 stabilization	positive	NOD2	[79]
p62	promotes oligomerization of NOD2 and prevents its degradation	positive	NOD2	[80]
SOCS3	NOD2 degradation	negative	NOD2	[65]
Erbin	directly interacts with NOD2	negative	NOD2	[82]
Centaurin-β	directly interacts with NOD2	negative	NOD2	[83]
Caspase12	removes TRAF6 from nodosome complex	negative	NOD1 and NOD2	[84]
ATG16L1	interferes with NOD oligomerization	negative	NOD1 and NOD2	[85]
GRIM19	enhances NOD induced NF-κB signaling	positive	NOD2	[86]

degradation. Moreover, the interaction of NOD2 with autophagy-associated scaffolding protein p62 (also known as sequestome-1, SQSTM1) triggered oligomerization of NOD2 and inhibited 26S proteasome-dependent NOD2 degradation [80]. In contrast, suppressor of cytokine signaling 3 (SOCS3) promoted NOD2 degradation at steady-state conditions [65]. Recently, the addition of N-acetylglucosamine (GlcNAc) to serine/threonine residues mediated by O-GluNAc transferase (OGT), a process known as O-GlcNAcylation, was proposed to enhance half-life and function of NOD2 [81].

Additionally, NOD1 and NOD2 signaling have also been reported to be directly regulated by several interacting molecules. Erbin, an LRR- and PDZ domain-containing family member was identified to interact with NOD2 and negatively influence NF-κB activation [82]. Centaurin beta1 (CENTB1), a GTPase-activating protein, as well as a member of the ADP-ribosylation factor family, was demonstrated to interact with endogenous NOD1 and NOD2. CENTB1 was shown to downregulate NOD-induced NF-κB responses [83]. Caspase-12 was reported to bind to RIPK2, displacing TRAF6 from the nodosome complex and blunting NF-κB induced TNFα, IL-1β, MCP-1, MIP-2 and β-defensin expression [84]. Surprisingly, autophagy-related protein 16 like-1 (ATG16L1) negatively regulates NOD-driven inflammatory responses by interfering with polyubiquitination of the RIPK2 adaptor and preventing nodosome formation [85]. Finally, it has been shown that optimal activation of NF-κB by NOD2 requires an intracellular molecule gene associated with retinoid-IFN-induced mortality 19 (GRIM19), although the mechanism remains unknown [86].

5. Role of NOD1 and NOD2 in the host response to infection

The importance of NOD1 and NOD2 in host defense against pathogens has been demonstrated using cellular systems *in vitro*, murine *in vivo* models as well as genetic susceptibility studies in humans (Table 2) and has been extensively reviewed [52,87–89]. Human and murine cell lines transfected with silencing RNA directed against NOD1 or NOD2 have predominantly been used to study the role of these receptors in the recognition of pathogens. This revealed NOD-induced NF-κB activation following cellular infection with *Campylobacter jejuni* [90], *Pseudomonas aeruginosa* [91], *Shigella flexneri* [26], *Helicobacter pylori* [92] and *Acinetobacter baumannii* [93], among others. Besides activating NF-κB, recognition of bacteria by NOD1 and NOD2 is also important for bacterial clearance by autophagy. Following invasion of *S. flexneri*, NOD1 and NOD2 recruit ATG16L1 to the plasma membrane to promote the formation of an autophagosome to remove this pathogen [88,94]. The overexpression of NOD1 or NOD2 in cells that do not naturally express these receptors is also a commonly used tool to study these sensors. This has, for example, revealed a role for NOD2 in the antiviral response mediated by the IRF-3-dependent production of IFNβ against respiratory syncytial virus [56]. More recently, CRISPR-cas9 has emerged as a tool to knock-out the NOD receptors. This implicated activation of NOD1, by its association with single-stranded viral RNA, in the innate immune response against hepatitis C virus [95]. Alternatively, primary cells isolated from patients that have natural occurring mutations in either *NOD2* or *NOD1* can be used. This revealed a role for NOD2 in the host response, indicated by cytokine production, against *Borrelia burgdorferi* [96]. The *in vivo* importance of NOD1 and NOD2 during infection is shown using *Nod1*$^{-/-}$ and *Nod2*$^{-/-}$ mice, as well as double knock-out mutant mice. *Nod1*$^{-/-}$ mice were shown to be more susceptible to infection with a variety of pathogens including *H. pylori* [97,98], *Clostridium difficile* [99] and *Trypanosoma cruzi* [100]. Whereas *Nod2*$^{-/-}$ mice displayed increased susceptibility to, among others, *Listeria monocytogenes* [55,101], *Chlamydophila pneumoniae* [102], *Toxoplasma gondii* [103] and *Staphylococcus aureus* [104] infection. An increased susceptibility to infection with for example *Bacillus anthracis* [105] and *Salmonella* spp. [106] was only evident in double knock-out mutant mice indicating the cooperation of both NOD receptors. Using these double knock-out mutant mice, NOD1 and NOD2 were furthermore shown to be crucial for the induction of enteric T helper 17 (Th17) responses following *Citrobacter rodentium and Salmonella typhimurium* infection [107]. Interestingly, single nucleotide polymorphisms (SNPs) of *NOD2* in humans have been associated with the development of leprosy [108], susceptibility to tuberculosis disease [109], *H. pylori* associated gastric lymphoma [110], as well as with a decreased risk of invasive aspergillosis after hematopoietic stem cell transplantation [111]. Additionally, *NOD1* SNPs in humans were shown to be associated with the risk of infection with human Cytomegalovirus [112] and an increased risk of peptic ulceration following *H. pylori* infection [113]. This together with the wide variety of pathogens experimentally shown to be recognized by NOD1 and/or NOD2 (Table 2) highlights the importance of these sensors in the host immune response. Consequently, many pathogens have evolved immune evasion strategies to overcome this recognition. The protein YopJ produced by *Yersinia* spp. directly inhibits NOD signaling by acetylating NOD2 mediators [114]. Moreover, most pathogens modulate the release or composition of peptidoglycan to escape these sensors [115–118].

6. NOD1 and NOD2 in adaptive immunity

In addition to the role of NOD1 and NOD2 proteins in innate immune responses to bacterial and viral infections, several reports have implicated their function in priming adaptive immune responses. Earlier, bacterial peptidoglycan derivatives have been identified to mount an adaptive immune response by acting as an adjuvant for antigen-specific immunoglobulin G (IgG) production [55]. In this line, NOD2 stimulation by MDP was demonstrated to trigger an antigen-specific Th2 immune response and IgG1 production. This NOD2-mediated Th2 polarization profile was characterized by IL-4 and IL-5 cytokine production [119]. Likewise, other studies demonstrated that stimulation of NOD1 with its agonist alone was sufficient to drive a Th2 antigen-specific immune polarization [120]. Additionally, NOD1 and NOD2 stimulation-dependent production of lymphopoietin from the thymic stromal cells and induction of the co-stimulatory molecule, OX40 ligand on dendritic cells (DCs) was crucial for Th2-cell-oriented acquired immunity [121]. Interestingly, NOD1 activation was reported to synergize with TLR signaling in priming Th1, Th2 as well as Th17 immune responses [120].

In vivo infection studies have further elucidated the pivotal role of NOD1 and NOD2 in mounting appropriate expression of pro-inflammatory cytokines, including TNFα, IL-1α, IL-1β, CCL5, IL-6 and KC and T cell responses to restrict *Mycobacterium tuberculosis* and *B. anthracis* infection [105,122]. NOD1 and NOD2 were also shown to contribute to IL-6-dependent induction of mucosal Th17 responses during early stages of intestinal infection with *C. rodentium* and *S. typhimurium* [107]. Besides, a NOD2-driven Th1 response was proposed to provide protection against *T. gondii* and *Leishmania infatum* pathogenesis [103,123].

Recently, lack of both NOD1 and NOD2 was shown to prime T cells for activation-induced cell death upon encountering alloantigens [124]. Moreover, T cell-intrinsic functions of NOD1 and NOD2 were implicated in potentiating TCR-mediated ERK signaling, thymic selection of $CD8^+$ T cells [125] and limiting Th17 responses associated with autoimmune arthritis [126]. Taken together, these studies outline the requirement of NOD1 and NOD2 for optimal humoral and cell-mediated adaptive responses in the context of pathophysiology. However, future studies are needed to unravel the plausible contribution of NOD1 and NOD2 in defining immune tolerance and memory functions.

7. The role of NOD1 and NOD2 at the intestinal homeostasis and disease

The lower gastrointestinal tract is colonized by a high abundance of microbial organisms, estimated in humans to be 10^3 to 10^8 and 10^{11} bacteria per milliliter small intestinal and colonic content, respectively

Table 2
NOD1 and NOD2-dependent host immune responses to pathogens.

Microorganism	NOD1 and/or NOD2 (experimental model)	Human Genetic Susceptibility	Evasion	Reference(s)
Bacteria				
Bacillus anthracis	NOD1 and NOD2 are important for the induction of an adequate adaptive immune response (*Nod1*$^{-/-}$*Nod2*$^{-/-}$ mice); NOD2 is involved in IL-1β secretion by peritoneal macrophages (*Nod2*$^{-/-}$ mice)	–	N-deacetylation of peptidoglycan	[105,165,166]
Borrelia burgdorferi	NOD2 is important for cytokine secretion following infection (primary cells from homozygous 3020insC *NOD2* mutation patients and peritoneal macrophages from *Ripk2*$^{-/-}$ mice)	–	L-ornithine instead of meso-DAP in peptidoglycan	[14,96]
Campylobacter jejuni	Infection results in NOD1 activation (siRNA in human Caco-2 cells); NOD2 is involved in the regulation of the innate and adaptive immune response following infection (*Nod2*$^{-/-}$ mice)	–	Pgp1, a peptidoglycan DL-carboxypeptidase, decreases NOD1 activation.	[90,118,167]
Chlamydia trachomatis	NOD1 is involved in bacterial recognition (siRNA in human HeLa cells); NOD1 is important for mediating IL-1β secretion (human trophoblast cells)	*NOD1* +32656 GG insertion is associated with protection from disease	–	[168–170]
Chlamydophila pneumoniae	NOD1 and NOD2 are involved in bacterial clearance (*Nod1*$^{-/-}$ and *Nod2*$^{-/-}$ mice)	*NOD1* G796A associated with increased risk of ischemic stroke following infection	–	[102,171]
Citrobacter rodentium	NOD1 and NOD2 are involved in mounting an IL-6 dependent Th17 response necessary for bacterial clearance (*Nod1*$^{-/-}$ and *Nod2*$^{-/-}$ mice) and NOD2 is involved in the recruitment of monocytes (*Nod2*$^{-/-}$ mice)	–	–	[107,172]
Clostridium difficile	NOD1 is involved in neutrophil recruitment for bacterial clearance (*Nod1*$^{-/-}$ mice)	–	–	[99]
Escherichia coli	NOD1 is involved in bacterial recognition (dominant-negative NOD1 overexpression in human Caco-2 cells); NOD2 mediates bacterial clearance in the lung by neutrophils (*Nod2*$^{-/-}$ mice)	–	–	[173,174]
Haemophilus influenzae	NOD1 is necessary for bacterial clearance by neutrophils (*Nod1*$^{-/-}$ mice); NOD2 is involved in the induction of inflammation following infection (siRNA in human middle ear epithelial cells)	–	–	[175,176]
Helicobacter pylori	NOD1 involved in bacterial clearance (*Nod1*$^{-/-}$ mice) and IL-8 production (gastric epithelial cells); NOD2 is required for the induction of pro-IL-1β and NLRP3 (*Nod2*$^{-/-}$ BMDCs)	*NOD2* R702W associated with an increased risk of development of gastric lymphoma; *NOD1* E266K associated with an increased risk of peptic ulceration	–	[97,110,113,177,178]
Legionella pneumophila	NOD1 and NOD2 are involved in bacterial clearance by neutrophils (*Nod1*$^{-/-}$ and *Nod2*$^{-/-}$ mice)	–	EnhC decreases anhydro-disaccharide-tetrapeptide by interfering with soluble lytic transglycosylase thus evading NOD1 signaling	[179–181]
Listeria monocytogenes	NOD1 is necessary for bacterial clearance *in vitro* (*Nod1*$^{-/-}$ BMDMs and fibroblasts); NOD1 and NOD2 are crucial for bacterial clearance *in vivo* especially following LPS priming (*Nod1*$^{-/-}$ and *Nod2*$^{-/-}$ mice)	–	Pdga, a peptidoglycan deacetylase, decreases NOD1 stimulation	[101,116,182]
Mycobacterium tuberculosis	NOD1 and NOD2 induce an immune response following infection (*Nod1*$^{-/-}$ *Nod2*$^{-/-}$ BMDMs and mononuclear cells from individuals homozygous for the 3010insC *NOD2* mutation); NOD2 is important for the initial bacterial control in the lungs (human alveolar macrophages); NOD2 is involved in the induction of a type 1 IFN response (*Nod2*$^{-/-}$ BMDMs)	*NOD2* P268S and R702W associated with protection from disease; *NOD2* A725G associated with susceptibility to disease	Peptidoglycan containing amidated residues decreasing NOD1 stimulation	[14,183–185]
Mycobacterium leprae	NOD2 is involved in the induction of IL-23 production (human peripheral blood monocytes)	*NOD2* polymorphisms rs2287185, rs8044554, rs8043770, rs13339578, rs4785225 and rs751217 are associated with an increased susceptibility to leprosy	Peptidoglycan containing amidated and glycine residues decreasing NOD1 stimulation	[108,186,187]
Pseudomonas aeruginosa	NOD1 is involved in the innate immune response following bacterial infection (*Nod1*$^{-/-}$ MEFs, overexpression in human HEK293T cells)	–	–	[91]

(*continued on next page*)

Table 2 (*continued*)

Microorganism	NOD1 and/or NOD2 (experimental model)	Human Genetic Susceptibility	Evasion	Reference(s)
Salmonella enterica	NOD1 and NOD2 are involved in mounting an IL-6 dependent Th17 response necessary for bacterial clearance (*Nod1*$^{-/-}$ and *Nod2*$^{-/-}$ mice); NOD1 controls bacterial infection in the intestinal lamina propria (*Nod1*$^{-/-}$ mice and BMDCs)	–	–	[106,107,188,189]
Shigella flexneri	NOD1 and NOD2, activated following infection, are important for bacterial clearance following autophagy (overexpression in human HeLa cells, *Nod2*$^{-/-}$ and *Nod1*$^{-/-}$ mouse embryonic fibroblasts)	–	–	[26,94]
Staphylococcus aureus	NOD2 is involved in bacterial clearance in the skin by inducing IL-6 secretion and neutrophil activation (*Nod2*$^{-/-}$ mice, neutrophils and BMDMs)	–	–	[104]
Streptococcus pneumoniae	NOD1 and NOD2 contribute to bacterial recognition (overexpression in human HEK293 cells, human bronchial epithelial cell line BEAS-2B); NOD1 is important in priming innate defenses to this bacterium *in vivo* (*Nod1*$^{-/-}$ mice)	–	–	[190,191]
Yersinia pseudotuberculosis	NOD2 is involved in the host response following bacterial infection (*Nod2*$^{-/-}$ mice)	–	YopJ acetylates NOD2 mediators RICK and TAK1 kinases resulting in intestinal barrier dysfunction	[114,192]
Protozoa				
Toxoplasma gondii	NOD2 signaling has been reported to either be or not be important for Th1 cell differentiation and parasitic clearance (*Nod2*$^{-/-}$ mice)	–	–	[103,193]
Trypanosoma cruzi	NOD1, but not NOD2, is involved in parasitic clearance (*Nod1*$^{-/-}$ mice and BMDMs, *Nod2*$^{-/-}$ mice)	–	–	[100]
Leishmania infantum	NOD2 is important for the induction of a Th1 response necessary for parasitic clearance (*Nod2*$^{-/-}$ mice and BMDCs, human peripheral blood)	–	–	[123]
Virus				
Cytomegalovirus	NOD1 and NOD2 activation restricts viral replication (overexpression and shRNA in human HFF and U373 cells)	*NOD1* polymorphisms rs2284358, rs2970500, rs10267377 are associated with an increased susceptibility to infection	–	[112,194]
Hepatitis C virus	NOD1 is involved in the anti-viral immune response (CRISPR-cas9 of human HepaRG cells)	–	–	[95]
Respiratory syncytial virus	NOD2 mediates the antiviral response via IRF3-dependent production of IFN-β (siRNA of human lung epithelial A549 cells, *Nod2*$^{-/-}$ mice, MEFs and BMDCs)	–	–	[56,195]
Fungi				
Aspergillus	NOD1 has an inhibitory role in the fungal clearance (*Nod1*$^{-/-}$ mice and BMDMs, splenocytes, siRNA of human monocyte derived macrophages)	*NOD2* polymorphism rs2066842 confers resistance to invasive aspergillosis	–	[111,196]

BMDCs: bone marrow derived dendritic cells; BMDMs: bone marrow derived macrophages; IRF3: interferon regulatory factor-3; MEFs: mouse embryonic fibroblasts; shRNA: short hairpin RNA; siRNA: silencing RNA; Th: T helper.

[127]. This potential for peptidoglycan sensing, along with the identification of *NOD2* risk polymorphisms (Fig. 1) in the development of the gastrointestinal disease, Crohn's disease (CD), have influenced research interests into delineating the role of NOD1 and NOD2 at the intestinal mucosa [30,31,128]. Both *NOD1* and *NOD2* are expressed throughout the intestinal epithelium, as well as in various intestinal immune cells [103,129–133].

How NOD1 and NOD2 affect intestinal homeostasis is not yet well understood. At baseline without experimental manipulation, NOD2-deficient mice do not develop spontaneous symptoms of colitis [55]. Within the intestinal epithelial compartment, early studies showed an effect of NOD2 on AMP expressions in murine and human crypt Paneth cells [55,134], important orchestrators of small intestinal innate immunity; however, these findings have not been supported by additional studies [135–138]. More recently, MDP detection by murine $Lgr5^+$ stem cells promoted stem cell survival and epithelial reconstitution after injury, pointing at a role for peptidoglycan sensing in maintaining the epithelial barrier [139]. In contrast, within an acute model of T cell mediated enteropathy in mice, loss of *Nod2* expression in the epithelial compartment did not exacerbate the disease phenotype, while the full-body and macrophage-specific knockouts did [140].

The effects of both NOD proteins in different mouse models of colitis appear to be context and cell-type dependent. Loss of NOD2 does not affect susceptibility to dextran sodium sulfate (DSS) induced colitis in the acute phase [55] or in a chronic model [141]. Additionally, neither NOD1 nor NOD2 affected intestinal inflammation in a chronic infectious model of colitis [142]. However, simultaneous loss of both NOD proteins does increase susceptibility to DSS colitis and intestinal barrier permeability, but these differences depended on intestinal microbial colonization [136]. Furthermore, NOD2 signaling in intestinal DCs and macrophages has been shown to maintain intraepithelial lymphocytes (IELs); the loss of *Nod2* led to a decrease in IELs which in turn predisposed mice to non-DSS chemically-induced colitis [143]. On the other hand, NOD2 deficiency in T cells did not affect T cell transfer mediated colitis [133], nor immunity to infection with the parasite, *T. gondii* [103]. Strikingly, *Nod2* deletion ameliorated disease in a spontaneous model of intestinal pathology [144]. Together, these studies highlight the complexity of NOD signaling in the maintenance of intestinal homeostasis under different conditions. Suffice it to say, while roles for NOD1-and NOD2-mediated peptidoglycan sensing have been established at the intestinal mucosa, downstream effects depend on the context in which NOD1 and NOD2 are functioning, pointing to a necessity for well-controlled and well-selected models of perturbation of intestinal homeostasis. Finally, NOD1 and NOD2 have been shown not to affect microbial community composition as evidenced by studies of mouse models deficient in NOD1 or NOD2 that controlled for familial and cage effects of microbiota transmission [136–138]. A recent study of the microbiota of human CD patients and their first-degree relatives also failed to identify an effect of NOD2 on microbiota composition [145].

SNPs of *NOD2* were the first genetic susceptibility factors discovered to be associated with risk of developing CD, and these also confer the highest genetic risk [30,31,128]. CD is an inflammatory disorder that may affect any part of the gastrointestinal tract. Yet, it is commonly localized to the terminal ileum and colon. The etiology is currently not well understood, but it has been hypothesized that genetic susceptibility, in conjunction with environmental risk factors, may lead to a breakdown of the intestinal barrier, resulting in an aberrant inflammatory response to the intestinal microbiota [146]. The three most prevalent SNPs in the *NOD2* gene are the insertion mutation 1007fs which leads to a frameshift and premature stop codon, and two missense mutations Arg702Trp and Gly908Arg; all three SNPs result in alteration of the LRR domain or adjacent region [30,31]. Ultimately, signaling through the LRR is diminished and NF-κB activity is decreased [17,18]. Mutations in *NOD2* have been strongly linked to disease localization to the ileum [147–150]. While conferring less risk and not consistently confirmed, polymorphisms of *NOD1* have also been associated with IBD [151–155]. Beyond IBD, additional *NOD2* polymorphisms have been associated with other autoinflammatory conditions, e.g. Blau syndrome; herein the mutation occurs in the nucleotide-binding domain which, in contrast to the CD associated mutations, results in an augmentation of signaling through NOD2 [156].

8. Interplay between NODs and autophagy proteins

Recent studies have elucidated an interplay between NODs and autophagy proteins in the intestinal epithelium, which might contribute in regulating the balance between homeostasis and disease in the gut. It was shown that NOD2 activation by MDP induced autophagic vacuole formation in fibroblasts, epithelial cells, macrophages and DCs, in an ATG16L1-dependent manner [94,157,158]. Likewise, NOD1 and NOD2 were required for sensing of cyto-invasive bacteria-induced autophagy. NOD2 but not CD-associated NOD2 variant, recruits ATG16L1 to the plasma membrane at the bacterial entry site. NOD2 acts as a scaffold for autophagic machinery. It directs bacteria to the autophagosome and facilitates fusion with the lysosome to form the autophagolysosome, allowing efficient clearance of pathogens such as *S. typhimurium*, entero-adherent invasive *E. coli* (AIEC) [157,159] as well as *S. flexneri* [94]. Further, this study also suggested that NOD2-dependent autophagy was unimpaired in RIPK2-deficient mouse embryonic fibroblasts (MEFs) [94]. However, the involvement of RIPK2 remains unclear as another independent study revealed a role of RIPK2 in NOD2-mediated autophagy in human DCs. Therefore, future investigations are required to identify the exact molecular mechanism [157].

Additionally, NOD2 has been shown to affect autophagy-mediated antigen presentation, known as cross-presentation in DCs [157]. It was demonstrated that NOD2 influences the autophagy-dependent trafficking and surface expression of major histocompatibility class II (MHC II), but not MHC class I. Consequently, this led to impaired induction of $CD4^+$ T cell-dependent immunity towards a bacterial antigen. Similarly, DCs expressing CD-associated NOD2 or ATG16L1 risk variants also displayed altered antigen cross-presentation [157].

Intriguingly, ATG16L1 was suggested to suppress inflammatory cytokine expression downstream of NOD1 and NOD2 signaling. Mechanistically, ATG16L1 negatively regulated RIPK2-dependent NOD signaling by preventing nodosome complex formation, which was molecularly decoupled from autophagy. Besides, the CD-associated ATG16L1 allele was also reported to be defective in regulating NOD1 and NOD2 signaling [85].

Moreover, polymorphisms of *ATG16L1* have also been associated with IBD. Interestingly, CD-associated NOD2 and ATG16L1 variants trigger similar phenotypes such as elevated inflammatory IL-1β production as well as Paneth cell dysfunction with impaired granule biogenesis and decreased lysozyme secretion [55,160–162]. In sum, these studies highlight the importance of the NODs and autophagic pathways in the maintenance of intestinal homeostasis and immune response [163,164].

9. Concluding remarks

Since the discovery of NOD1 and NOD2 two decades ago, and the publication of over 3000 studies on these innate immune sensors, significant advances have been made towards elucidating their function and mode of action. The discovery of *NOD2* as the first susceptibility gene for CD has also pushed the field forward dramatically by providing a strong impulse to delineate the role of these peptidoglycan sensors at the intestinal mucosa. Disappointingly, and despite all the significant advances made, the exact mechanisms underlying disease susceptibility in CD patients carrying *NOD2* mutations remain poorly understood, and this challenge will undoubtedly be the next frontier in the NOD research field. Of prime importance will be to delineate if defective detection and control of (i) the intestinal microbiota, (ii) intestinal

pathogens, or (iii) both, is associated with CD-associated polymorphisms in *NOD2*. More generally, a better characterization of NOD1 and NOD2 biology will have a significant impact on our understanding of the underlying mechanisms of host defense against infection, inflammation and the priming and control of adaptive immunity.

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