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MINIREVIEW

NOD1 and NOD2 Activation by Diverse Stimuli: a Possible Role for Sensing Pathogen-Induced Endoplasmic Reticulum Stress

Sharon K. Kuss-Duerkop,[a] A. Marijke Keestra-Gounder[a]

[a]Department of Immunology and Microbiology, University of Colorado School of Medicine, Aurora, Colorado, USA

ABSTRACT Prompt recognition of microbes by cells is critical to eliminate invading pathogens. Some cell-associated pattern recognition receptors (PRRs) recognize and respond to microbial ligands. However, others can respond to cellular perturbations, such as damage-associated molecular patterns (DAMPs). Nucleotide oligomerization domains 1 and 2 (NOD1/2) are PRRs that recognize and respond to multiple stimuli of microbial and cellular origin, such as bacterial peptidoglycan, viral infections, parasitic infections, activated Rho GTPases, and endoplasmic reticulum (ER) stress. How NOD1/2 are stimulated by such diverse stimuli is not fully understood but may partly rely on cellular changes during infection that result in ER stress. NOD1/2 are ER stress sensors that facilitate proinflammatory responses for pathogen clearance; thus, NOD1/2 may help mount broad antimicrobial responses through detection of ER stress, which is often induced during a variety of infections. Some pathogens may subvert this response to promote infection through manipulation of NOD1/2 responses to ER stress that lead to apoptosis. Here, we review NOD1/2 stimuli and cellular responses. Furthermore, we discuss pathogen-induced ER stress and how it might potentiate NOD1/2 signaling.

KEYWORDS ER stress, NOD1, NOD2, pathogens

Pattern recognition receptors (PRRs) are a consortium of innate immune molecules dedicated to quickly recognizing pathogens and alerting the immune system in order to control infections or cellular abnormalities. Five major classes of PRRs exist: (i) toll/Toll-like receptors (TLRs), (ii) nucleotide-binding domain, leucine-rich repeat-containing (NBD-LRR) proteins (NLRs); (iii) retinoic acid-inducible gene (RIG)-I-like receptors (RLRs); (iv) C-type lectin receptors (CLRs); and (v) DNA sensors (1–3). PRRs that alert cells to potential invading pathogens usually recognize very specific microbial molecules known as microbe-associated molecular patterns (MAMPs), e.g., TLR5 sensing of bacterial flagellin. A few PRRs respond to damage-associated molecular patterns (DAMPs), which are endogenous cellular ligands liberated during compromised cell health that act as danger signals. DAMPs, such as heat shock proteins and high-mobility group box 1 (HMGB1), can be produced during infections and activate the immune system similarly to MAMPs (2). In addition to recognizing MAMPs and DAMPs, the host can recognize distinct pathogen-induced processes which are considered to be common infection strategies that many pathogens employ to cause disease (4–7).

The NLR family contains over 20 intracellular receptors, including NOD1 (CARD4), NOD2 (CARD15), NLRCs (NLR family CARD domain containing), NLRPs (NLR family PVD domain containing), and NAIPs (NLR family apoptosis inhibitory protein) (3). Distinguishing characteristics of the NLR family are a central NOD (also known as NACHT), a C-terminal LRR (leucine-rich repeat) and an N-terminal protein-protein interaction domain (8, 9). NLR ligands are mainly of bacterial origin, although a few NLRs, e.g.,

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Address correspondence to A. Marijke Keestra-Gounder, Marijke.Keestra-Gounder@cuanschutz.edu.

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TABLE 1 Diverse ligands stimulate NOD1 and/or NOD2 signaling

Ligand	PRR	Role during infection	Reference(s)
iE-DAP	NOD1	Activates NF-κB upon LRR ligation	12, 13, 15
MDP	NOD2	Activates NF-κB upon LRR ligation	14, 15
Respiratory syncytial virus (RSV)	NOD2	Activates type I IFN by ssRNA, requires MAVS; restricts viral replication	19
Vesicular stomatitis virus (VSV)	NOD2	Activates type I IFN by ssRNA, requires MAVS; restricts viral replication	19
Influenza A virus (IAV)	NOD2	Activates type I IFN by ssRNA, requires MAVS	19
	NOD2	Restricts viral pathogenesis	17, 18
	NOD2	Restricts viral replication	17
Human parainfluenza virus type 3 (HPIV3)	NOD2	Activates type I IFN by ssRNA, requires MAVS	19
Human cytomegalovirus (HCMV)	NOD1	Activates type I IFN, restricts viral replication	21
	NOD2	Activates type I IFN, restricts viral replication	20, 160
Murine cytomegalovirus (MCMV)	NOD1	Activates type I IFN, restricts viral replication	21
Hepatitis C virus (HCV) NS5B	NOD1	Activates type I IFN by dsRNA, MAVS independent	163
Coxsackievirus B3	NOD2	Promotes virus replication and pathogenesis	16
Foot-and-mouth-disease virus (FMDV)	NOD2	Activates type I IFN, restricts viral replication	23
Plasmodium berghei	NOD1/2	Activated but parasite replication unaffected	24
Plasmodium falciparum	NOD2	Activates NO production, hemozoin dependent	25
Trypanosoma cruzi	NOD1/2	Activated during infection	26
	NOD1	Restricts parasite replication	26
Aspergillus fumigatus	NOD1/2	Activated, promote fungal replication by inhibiting fungal killing, Dectin-1 dependent	27, 28
Activated Rho GTPases	NOD1	Constitutively active Rac1 and Cdc42, *S.* Typhimurium SopE activation of Rac1 and Cdc42	30
	NOD1	*S. flexneri*, GEF-H1 and RhoA kinase dependent	56
Endoplasmic reticulum (ER) stress	NOD1/2	Thapsigargin-mediated activation	29, 32, 42
Calcium concn alterations	NOD1/2	Thapsigargin, not tunicamycin; Ca^{2+} chelation, thapsigargin	29, 32
	NOD1	Thapsigargin; CaSR/PLC/IP3R agonists	31
	NOD1	Binds RyR and increases cytosolic Ca^{2+}	136
	NOD2	CaSR promotes MDP uptake	73

NLRP3, respond to DAMPs. Uric acid and cholesterol crystals, ATP, oxidized mitochondrial DNA, reactive oxygen species (ROS), and endoplasmic reticulum (ER) stress are examples of NLR DAMPs (2, 10, 11). The founding members of the NLR family, NOD1 and NOD2 (NOD1/2), sense both MAMPs and DAMPs. NOD1/2 were initially described as bacterial peptidoglycan fragment receptors (12–15), but mounting evidence has revealed that NOD1 and/or NOD2 is activated during infections with peptidoglycan-deficient pathogens, including viruses (16–23), parasites (24–26), and fungi (27, 28). In addition, NOD1 and/or NOD2 participates in the detection of pathogen-induced processes such as the activation of Rho GTPases, ER stress, and the unfolded protein response (UPR), autophagy and mitophagy, disruption of calcium homeostasis, and cell death (29–32) (Table 1). Here, we review the details underlying NOD1 and NOD2 activation by diverse stimuli with an emphasis on pathogen-induced ER stress.

NOD1 AND NOD2

Nod1 and *Nod2* are highly similar yet distinct vertebral genes that may have resulted from an evolutionarily early gene duplication event (33). High interspecies amino acid conservation coupled with increased conservation of critical sequences important for mediating NOD1 or NOD2 protein/ligand molecular interactions reveals the importance of NOD1 and NOD2 for immunity (33). In addition to their central NOD and C-terminal LRR domains, NOD1 contains one N-terminal caspase activation and recruitment domain (CARD), while NOD2 contains two CARDs (34). The CARDs mediate protein-protein interactions, e.g., with adaptor protein receptor-interacting serine/threonine-protein kinase 2 (RIPK2). NOD domains contain a nucleotide binding site for ATPase activity and are important for oligomerization, while the LRR domains mediate ligand recognition (35). To maintain an inactive state in the absence of ligand, the LRR domain occludes the NOD (36). NOD1 is activated with moderate affinity (~30 μM) (37) by γ-D-glutamyl-meso-diaminopimelic acid (iE-DAP) moieties, which are produced by Gram-negative and a few Gram-positive bacteria (13, 15). NOD2 is activated with strong affinity (~50 nM) (38) by muramyl dipeptide (MDP) moieties present in peptidoglycan from

both Gram-positive and -negative bacteria (14, 15, 39). Peptidoglycan detection induces the oligomerization of NOD1 and NOD2 and recruitment of RIPK2, a NOD1/2-specific adaptor protein required for facilitating their proinflammatory response (40). RIPK2 consists of an N-terminal kinase domain, a central linker region and one CARD domain. The CARD of RIPK2 interacts with the CARDs of NOD1 and NOD2 leading to RIPK2 phosphorylation by leucine-rich repeat kinase 2 (LRRK2) and ubiquitination at multiple sites by several E3 ligases, such as the inhibitor of apoptosis proteins cIAP1, cIAP2, and XIAP (41). The phosphorylation and ubiquitination events promote interactions with TNF receptor-associated factors (TRAF) 2/5/6 (42) and activate the expression of nuclear factor-κB (NF-κB)- and mitogen-activated protein kinase (MAPK)-dependent genes involved in host immunity and pathogen clearance (43, 44).

Tissue expression of *Nod1* and *Nod2* is one distinguishing feature between these molecules. *Nod1* is mostly ubiquitous throughout the body, while *Nod2* expression is confined to monocytes, dendritic cells, epithelial cells, Paneth cells and intestinal stem cells (8, 44). However, *Nod1* and *Nod2* are interferon-stimulated genes (ISGs), and therefore their expression in tissues may only be detected under particular conditions, such as viral and bacterial infections (22). Furthermore, *Nod2* mRNA expression in the murine heart was recently demonstrated during coxsackievirus B3 (CVB3) infection (16) and was also observed in vascular smooth muscle cells (45). This expanded distribution of *Nod2* gene expression requires further confirmation but may be specific to the models or conditions used in these studies.

Membrane localization. NOD1 and NOD2 are critical cytoplasmic innate immune molecules; however, significant evidence underscores a major role of membrane localization for NOD1/2 functions. NOD1/2 localizes to endosomes (46, 47) and the plasma membrane (48–53). NOD2 plasma membrane localization, which is mediated by the C-terminal end, is required for its response to MDP (48). Similarly, NOD1 localizes to the plasma membrane in an actin-dependent manner and accumulates at sites of *Shigella flexneri* attachment (49). Cell membrane localization via S-palmitoylation of NOD1 and NOD2 is required for peptidoglycan sensing (54). The signal that induces NOD1/2 to localize to membranes is unknown. Small Rho GTPases are known to regulate the actin cytoskeleton (55), and activation of Rac1, Cdc42 and RhoA by bacterial effector proteins results in NF-κB activation that is mediated by NOD1 and/or NOD2 (30, 56). Of note, bacterium-induced Rac1-mediated NF-κB activation also occurs via NOD1/2-independent mechanisms (57, 58). In addition, NOD2 bound to activated Arf GTPases (39), which are also involved in actin cytoskeletal dynamics but are distinct from Rho GTPases and associate with vesicular transport systems (59). Thus, perturbation of the actin cytoskeleton and the activation of small GTPases might be a signal for NOD1/2 to localize to membranes and initiate immune responses (30, 39, 51, 56).

Cell death. NOD1 and NOD2 were initially implicated to play a role in cell death. NOD1 and NOD2, as well as other members of the NLR family, share homology with apoptotic protease activating factor 1 (APAF-1), a major regulator of apoptosis (60–63). Upon binding to cytochrome *c* that is released from mitochondria in response to certain apoptotic stimuli, APAF-1 associates with procaspase-9 via CARD-CARD interaction, resulting in formation of the apoptosome which leads to cell death. NOD1 can bind several caspases, including caspase-9 (60). It was proposed that NOD2 can bind to caspase-1 to induce interleukin-1β (IL-1β) secretion (64). Furthermore, administration of iE-DAP induces apoptosis in murine hearts, suggesting that NOD1 activation stimulates cell death (65). However, several reports showed that *Nod1*- and/or *Nod2*-deficient cells have increased cell death, arguing for a protective role of NOD1 and NOD2 (66). In *Nod1*-deficient cells, *Shigella*-induced cell death increased, indicating that NOD1 protects nonmyeloid cells from apoptosis during *Shigella* infection (66). Recent work characterizing the role of NOD2 in vascular smooth muscle cells revealed that tunicamycin-induced endoplasmic reticulum (ER) stress was resolved in *Nod2*-sufficient cells, whereas ER stress-induced cell death was increased in *Nod2*-deficient cells (45). One ER stress-induced cell death pathway depends on caspase-12. In resting cells,

procaspase-12 is localized to the ER and bound to TRAF2. Upon ER stress, procaspase-12 is cleaved by m-calpain, which is activated by the release of calcium from the ER (67, 68). TRAF2 dissociates from procaspase-12 and is recruited to IRE1α leading to Jun N-terminal kinase (JNK) and NF-κB activation (69). Activated caspase-12 subsequently cleaves caspase-9, which in turn cleaves and activates the executioner caspase-3 to induce cell death (67). *Caspase-12*-deficient mice are resistant to ER stress-induced apoptosis, but their cells still undergo apoptosis in response to other stimuli, supporting the observation that caspase-12 activation is only mediated by ER stress (67). Interestingly, caspase-12 competes with TRAF6 binding to RIPK2 in response to *Citrobacter rodentium* infection, thereby inhibiting RIPK2 ubiquitination and NF-κB activation (70). One possible explanation for the controversial role of NOD signaling in cell death could be caspase-12-mediated control. In the event of low to moderate ER stress, the cell attempts to restore homeostasis, and caspase-12 inhibits immune responses. However, in the event of severe ER stress, caspase-12 will activate caspase-9 and caspase-3 to execute cell death. An excess in calcium flux might be the trigger that determines whether the cell will remain viable or undergo apoptosis.

Calcium homeostasis. Perturbation in calcium homeostasis is a major cause of ER stress, and infection-triggered calcium signaling can be considered a DAMP. Many pathogens can stimulate calcium influx through the plasma membrane or via release from the ER leading to changes in intracellular calcium concentrations (71). Thapsigargin is an inhibitor of the sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA), resulting in depletion of ER calcium and an increase in cytosolic calcium (72). Thapsigargin-induced ER stress resulted in NOD1/2-dependent inflammatory responses, whereas ER stress induced by tunicamycin, which inhibits protein glycosylation, resulted in NOD1/2-independent inflammatory responses, suggesting that calcium flux contributes to NOD1/2 responses to ER stress (29). It was recently proposed that increases in cytosolic and extracellular calcium concentrations induce endocytosis of trace levels of contaminating peptidoglycan found in the cell culture additive fetal calf serum (FCS), as well as in mouse serum thereby activating NOD1/2 signaling (32). Similarly, it was suggested that activation of the plasma membrane-localized calcium-sensing receptor (CaSR) increased macropinocytosis, which facilitated the uptake of extracellular MDP and activated NOD2 signaling (73). An alternative explanation is that activation of CaSR results in phospholipase C (PLC) activation which generates inositol triphosphate (IP3), the ligand for the 1,4,5-triphosphate receptor (IP3R), suggesting activation of IP3R may contribute to NOD1/2 activation by extracellular calcium stimulation. Calcium flux from the ER is mediated by IP3R and the ryanodine receptors (RyRs). Induction of the CaSR/PLC/IP3R pathway significantly contributes to NOD1-mediated immune responses (31). In mice with postmyocardial infarction, NOD1 modulated intracellular calcium mishandling. It was demonstrated that NOD1 binds RyR, thereby increasing its phosphorylation and activation, which led to increased cytosolic calcium (74). The precise mechanism of how NOD1 activation influences calcium flux and whether the increase in intracellular calcium facilitates the uptake of trace levels of peptidoglycan needs to be further elucidated.

Autophagy. Macroautophagy (referred to here as "autophagy") is a self-degradative process for balancing cellular homeostasis to promote survival. It plays an important role in the removal of damaged organelles, protein aggregates, misfolded proteins, and pathogens. The UPR and autophagy are intimately related as ER stress can directly induce autophagy. The transcription factors CHOP and ATF4, which are downstream of PERK, activate autophagy gene transcription. Furthermore, activation of JNK results in autophagosome formation. On the other hand, impaired autophagy can activate the UPR (75). Interestingly, NOD1 and NOD2 directly interact with ATG16L1 to regulate autophagy by recruiting ATG16L1 to the cell membrane at the site of bacterial invasion, which promotes autophagic killing of bacteria (50). The Crohn's disease-associated *Nod2-3020insC* mutation showed impaired autophagy and was unable to recruit ATG16L1 to the plasma membrane. Similarly, the *Atg16l1* mutation associated with

Crohn's disease was unable to induce autophagy when cells were stimulated with MDP (50). Whether NOD2 and NOD1 play important roles in autophagy induced in the absence of peptidoglycan remains to be elucidated. However, NOD2 and RIPK2 are required for mitophagy in cells infected with influenza A virus (IAV) (18). Mitophagy is a form of autophagy targeting mitochondria that have been damaged during infection or stress (76). Mice deficient for *Nod2* and *Ripk2* were hypersusceptible to IAV-induced pathogenesis due to defective mitophagy. The damaged mitochondria in *Ripk2*$^{-/-}$ bone marrow-derived dendritic cells (BMDCs) produced increased levels of ROS, leading to activation of the NLRP3 inflammasome and uncontrolled inflammation compared to wild-type BMDCs (18). These results suggest that NOD2 and RIPK2 play important roles in host defense in the absence of peptidoglycan, although microbiota-derived contaminating peptidoglycan fragments that activate NOD2 during viral infections cannot be fully excluded.

ER stress. ER stress activates NOD1/2 to mount a proinflammatory response (29, 32, 42). ER stress occurs when a cellular perturbation disrupts the ER or its capacity to properly process and fold proteins. The unfolded protein response (UPR) is initiated to help the cell restore homeostasis. Three UPR pathways exist which are activated by separate ER stress transmembrane receptors, including inositol-requiring protein 1 (IRE1α), activating transcription factor 6 (ATF6), and protein kinase R-like ER kinase (PERK) (77) (Fig. 1). Each receptor is held inactive by the master ER chaperone binding immunoglobulin protein (BIP; also known as 78-kDa glucose-regulated protein, GRP78, encoded by *Hspa5*). When ER stress occurs and misfolded proteins accumulate, BIP dissociates from IRE1α, ATF6, and PERK, initiating their activation (77). Each protein signals distinctly to influence cellular physiology in order to cope with ER stress. IRE1α dimerizes, autophosphorylates, and splices X-box binding protein-1 (*Xbp1*) mRNA to produce a functional XBP1s transcription factor, as well as initiates regulated IRE1α-dependent decay (RIDD), which degrades mRNAs in order to reduce protein burdens (78). BIP dissociation from ATF6 reveals a Golgi localization signal that targets ATF6 to the Golgi apparatus, where it is cleaved, translocates to the nucleus, and functions as a transcription factor (77). PERK, like IRE1α, dimerizes and autophosphorylates. PERK then phosphorylates eukaryotic initiation factor 2α (eIF2α) to inhibit translation of most proteins aside from activating transcription factor 4 (ATF4), which regulates C/EBP homologous protein (CHOP; also known as GADD34). CHOP is a major regulator of apoptosis in response to ER stress (79). As a whole, these three pathways lead to ER chaperone and immune gene regulation, ER-associated degradation (ERAD), survival versus apoptotic responses depending on the magnitude of ER stress, lipid synthesis, autophagy, and redox regulation (77).

ER stress promotes inflammation and is thus often considered a DAMP (80) since ER stress is linked to PRR-associated immune responses (81). Some NLRs sense and respond to ER stress (29, 31, 32, 82). NLRP3 senses tunicamycin-induced ER stress through an IRE1α-dependent mechanism that initiates mitochondrial production of ROS. It was proposed that ROS production leads to recruitment of NLRP3 to mitochondrial membranes, the release of mitochondrial contents, and activation of the canonical NLRP3 inflammasome (82). Receptor interacting protein 1 (RIP1) is required for NLRP3 sensing of ER stress (83). Similarly, using both *Nod1/2*$^{-/-}$ and *Ripk2*$^{-/-}$ mice/cells compared to the wild type, NOD1/2 required RIPK2 to sense and respond to ER stress (29, 32, 42). Upon ER stress, NOD1/2 were selectively activated downstream of IRE1α (29). Thus, NOD1 and NOD2 can sense the DAMP ER stress and elicit immune gene expression; however, the exact mechanism of NOD1/2 sensing of ER stress remains to be elucidated. A possible mechanism might involve ER stress-mediated sampling of the extracellular environment for peptidoglycan fragments, and NOD1/2-dependent antimicrobial responses may be a result of ER stress-induced uptake of peptidoglycan (32). This mechanism assumes that peptidoglycan is present in the extracellular milieu, and it was found in trace levels in both mouse serum and cell culture FCS tested in this study; however, the

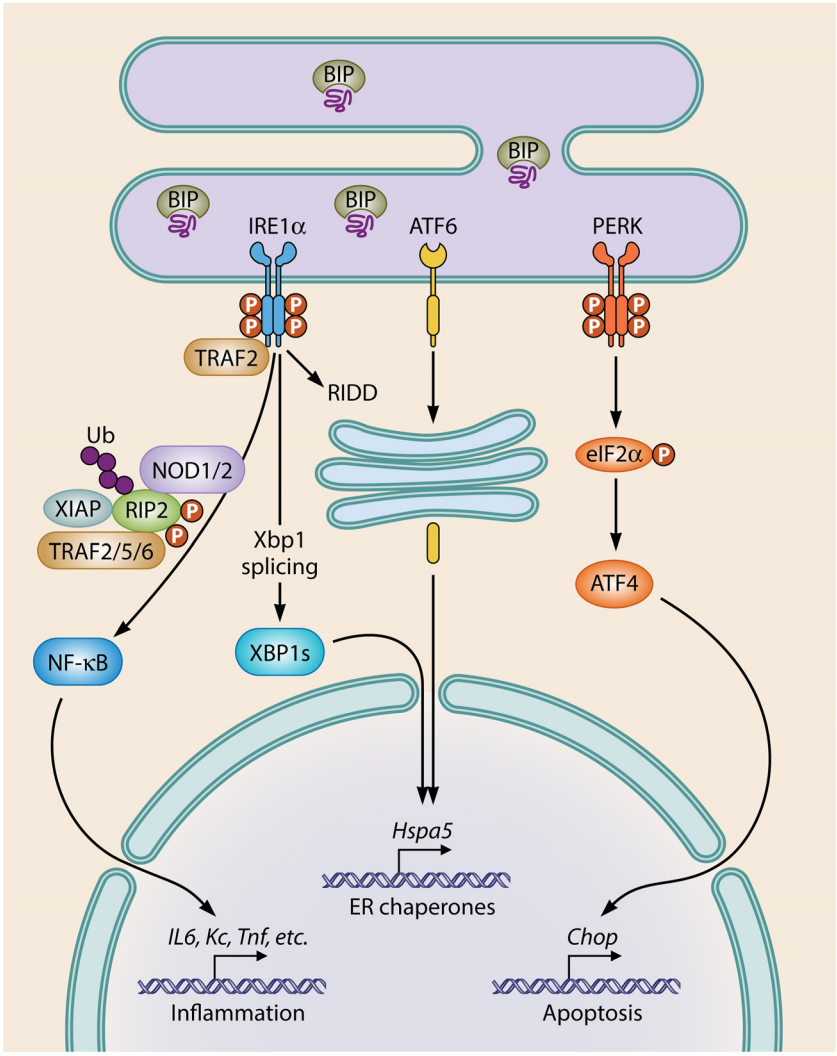

FIG 1 ER stress induces the UPR. Transmembrane ER stress sensors IRE1α, ATF6, and PERK are activated upon dissociation of BIP, an ER chaperone that binds to misfolded proteins. UPR promotes restoration of homeostasis through upregulation of genes involved in multiple pathways related to global cellular physiology. If unresolvable, UPR induces apoptosis mediated via PERK. NOD1/2 are activated downstream of IRE1α resulting in proinflammatory cytokine production.

authors of that study did not assess whether the concentrations of trace peptidoglycan detected in sera were sufficient to activate NOD1/2 (32). Thus, additional research is needed to determine whether potential contaminating peptidoglycan taken up during times of ER stress is responsible for NOD1/2 activation, and caution should be taken when making conclusions about mechanisms underlying peptidoglycan-independent NOD1/2 activation. An alternative, peptidoglycan-independent mechanism of ER stress-mediated NOD1/2 activation is that NOD1 and NOD2 are recruited to the ER stress-activated IRE1α receptor in complex with TRAF2 at the ER membrane, which is mediated by the major TRAF2-binding motifs present in NOD1 and NOD2 to initiate their signaling and antimicrobial responses (84).

PATHOGEN-INDUCED ER STRESS SENSING AND NOD1/2

Intracellular pathogens, including bacteria, protozoan parasites, and viruses, are well known to elicit ER stress (81, 85). ER stress can be a result of increased protein translation due to replication of the invading pathogen or modification of ER membranes, e.g., to establish viral replication complexes, as is the case for many RNA viruses (85, 86). Moreover, extracellular bacteria that attach to mammalian cells also induce ER

stress through the introduction of toxins or effector proteins into the host cytosol via bacterial secretion systems (85, 87). Whether pathogens specifically activate single arms of the UPR or if pathogen-induced cellular disruptions cause ER stress differs among pathogens. Detecting ER stress during microbially induced pathogenesis is a good strategy for cells to initiate early, broad antimicrobial immune responses that allow cells to combat infections.

Bacteria. As sensors of peptidoglycan fragments, NOD1 and NOD2 are activated by many pathogenic bacteria (44, 88). NOD1 promotes immune clearance of *Pseudomonas aeruginosa* (89), *Campylobacter jejuni* (90), *Clostridium difficile* (91), *Legionella pneumophila* (92–94), *Helicobacter pylori* (95, 96), *Chlamydia pneumoniae* (97), *Citrobacter rodentium* (98), *Haemophilus influenzae* (99), *Listeria monocytogenes* (100–102), *Salmonella enterica* Typhimurium (103–105), *Shigella flexneri* (50), and *Streptococcus pneumoniae* (106). NOD2 protects against infections with *Citrobacter rodentium* (22, 98), *Legionella pneumophila* (92), *Listeria monocytogenes* (100–102, 107), *Salmonella enterica* Typhimurium (103–105), and *Staphylococcus aureus* (108). Peptidoglycan recognition by NOD1 and/or NOD2 during bacterial infection initiates NF-κB-dependent proinflammatory responses; however, whether bacterium-induced ER stress is also sensed by NOD1/2 during infection is beginning to be explored. Indeed, NF-κB activation during *Brucella abortus* infection was increased in wild-type versus *Nod1/2*$^{-/-}$ mice (29), which required the *B. abortus* effector VceC that induces ER stress (109). In addition, *S.* Typhimurium exploits the UPR to promote intracellular replication, and ER stress enhanced NOD1-dependent NF-κB activation (31, 110). ER stress mediated by bacterial infections is increasingly appreciated as a commonality during infection; some bacteria produce toxins or inject effectors into host cells that impact ER stability, and others induce rearrangements of ER membranes for replicative purposes (85, 87). Thus, NOD1/2 sensing of ER stress as a pathogen-induced process may promote UPR-dependent innate immune responses that can influence bacterial infections (Fig. 2).

To establish intracellular replicative compartments, *Brucella* significantly alters ER structure (85, 87) using its TcpB protein, which stabilizes microtubules, localizes to the ER, and also induces UPR (111, 112). Furthermore, *Brucella abortus* effector VceC triggers ER stress by inducing inflammatory cytokines in an IRE1α-dependent manner (109). VceC localizes to the ER and binds to host BIP, suggesting that VceC sequesters BIP from ER stress receptors, leading to activation of the UPR (109). Furthermore, the UPR is critical for *B. abortus* replication (113–116). Proinflammatory gene expression following UPR activation by *B. abortus* infection required VceC and NOD1/2, which exacerbated infection and disease outcomes. Furthermore, this effect was independent of peptidoglycan sensing by NOD1/2 and unveiled a novel role for NOD1/2 in detecting and responding to ER stress in an IRE1α-dependent manner (29). Therefore, *B. abortus* exploits the UPR and NOD1/2 to establish a successful infection.

Like *Brucella* spp., *Legionella* and *Chlamydia* spp. establish intracellular replication compartments that either are derived from the ER or come in contact with it, respectively (117, 118). *Legionella pneumophila* encodes translation elongation inhibitors to block host translation, which are required to inhibit IRE1α-mediated splicing of *Xbp1* in a MyD88-dependent manner (119). Given that *L. pneumophila* inhibits the IRE1α/ER stress pathway, it might be preventing NOD1/2 stimulation via IRE1α, since NOD1/2 restrict *L. pneumophila* infection (92–94). In one report, *Chlamydia pneumoniae* upregulated *Hspa5* and activated PERK, but IRE1α and ATF6 pathways were unaffected (120). However, a different study showed that *Xbp1* splicing and *Chop* expression increased during *Chlamydia trachomatis* infection (121). *Chlamydia muridarum* infection induced *Il6* gene expression, which was reduced when IRE1α was inhibited; this effect was dependent on RIPK2 (29). The differences in UPR activation may lie in the *Chlamydia* species used or timing of infection. Overall, ER stress is evident during infection with *Chlamydia*, and *Chlamydia* is known to stimulate NOD1 and/or NOD2 during infection (122, 123).

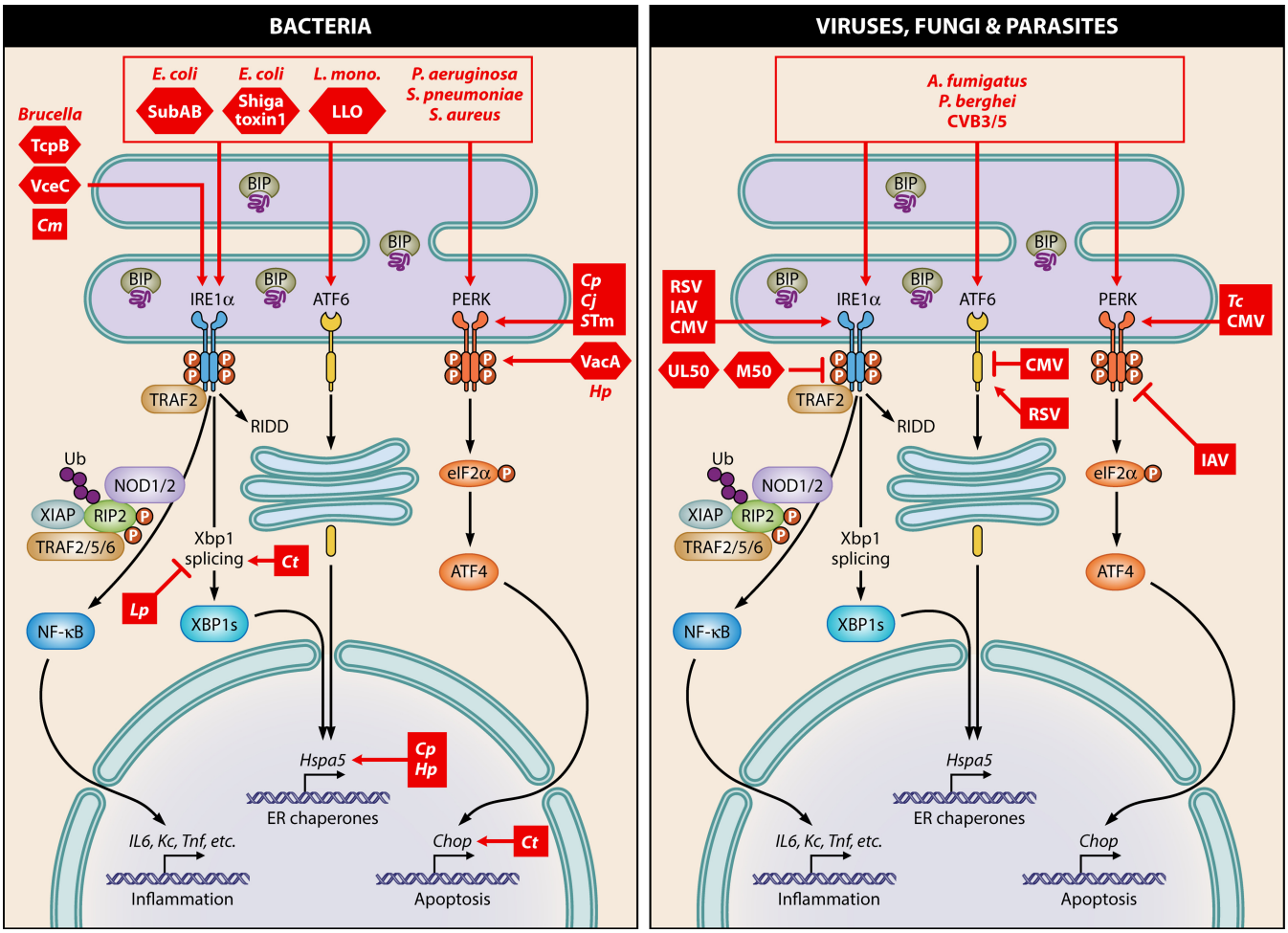

FIG 2 Pathogen-induced ER stress and the convergence with NOD1/2 signaling. Bacteria (left panel) and viruses, fungi, and parasites (right panel) differentially induce ER stress, which may be sensed by NOD1/2. Pathogens or pathogen-encoded proteins are depicted in red. RSV, respiratory syncytial virus; IAV, influenza A virus; CMV, cytomegalovirus (proteins UL50 and M50); CVB, coxsackievirus B; *Cm*, *Chlamydia muridarum*; *Lp*, *Legionella pneumophila*; *Ct*, *Chlamydia trachomatis*; *Cp*, *Chlamydia pneumoniae*; *Hp*, *Helicobacter pylori*; *Cj*, *Campylobacter jejuni*; STm, *Salmonella* Typhimurium; *Tc*, *Trypanosoma cruzi*; *L. mono.*, *Listeria monocytogenes*; LLO, listeriolysin O; SubAB, subtilase toxin AB.

NOD1 is also stimulated during infection with extracellular bacteria, including *Helicobacter pylori* (96, 124), a result of peptidoglycan delivery to host cell cytosol mediated by the type IV secretion system of *H. pylori*. Moreover, mice deficient for *Nod1* are more susceptible to *H. pylori* stomach colonization (96). To help protect against *H. pylori* infection, NOD1 promotes anti-bacterial type I interferon (IFN) signaling (9). *Helicobacter* induces ER stress to various degrees for all three UPR pathways in mice and humans (125). *H. pylori* effector VacA activated PERK, which increased *Chop* expression and ultimately apoptosis (126) or autophagic cell death (127) in human gastric cell lines. No changes in the IRE1α or ATF6 pathways were observed, but *Hspa5* was upregulated (126). In addition, increased ER stress induced by thapsigargin in VacA-expressing cells further enhanced VacA-mediated autophagic cell death (127). Since *Helicobacter* upregulates ER stress and NOD1 is activated by *H. pylori*, then NOD1 may act as a sensor for *H. pylori*-induced ER stress to limit infection. If so, this would likely occur through a mechanism independent of VacA since IRE1α stimulation was not observed by introduction of this effector alone (126). Another possibility is that NOD1 signaling may rely on other ER stress receptors independently of IRE1α during *H. pylori* infection.

Bacterial pore-forming toxins can have potent effects on targeted host cells, and UPRs elicited by bacterial pore-forming toxins are protective in mice (128). *Escherichia coli* subtilase toxin SubAB activated all three arms of the UPR (129) by cleavage of BIP

(130, 131), which led to apoptosis (131). However, proinflammatory responses to SubAB appear unaffected by NOD1/2 (32). Another *E. coli* cytotoxin, Shiga toxin 1, caused calcium release from the ER, which resulted in apoptosis in monocytes (132). Similarly, *Listeria monocytogenes* toxin listeriolysin O induced all three UPR arms, and the ER stressors tunicamycin and thapsigargin reduced *L. monocytogenes* loads (133), which indicates that the UPR facilitates antibacterial effects. UPR stimulation by *L. monocytogenes* also likely occurs through depletion of ER calcium (134, 135). Since ER stress responses to pore-forming toxins ameliorate toxin-induced damage (128) and NOD1 senses calcium fluxes (31, 32, 136), perhaps this occurs through the IRE1α/NOD1/NF-κB axis. *Clostridium difficile*, which encodes a pore-forming toxin, is restricted by NOD1 and also induces ER stress (137–139). Thus, NOD1 might sense pore-forming toxin-mediated ER stress to mount protective immune responses, which would aid in alleviation of the potent effects of intracellular toxins.

Several other bacteria restricted by NOD1 and/or NOD2 signaling induce ER stress during infections. *Campylobacter jejuni* activated the PERK pathway and led to an upregulation of CHOP, but XBP1s and ATF6 upregulation was not observed. In addition, siRNA depletion of *Ire1α*, *Atf6*, or *Perk* increased intracellular *C. jejuni* loads. Furthermore, *C. jejuni* invasion was inhibited by the UPR induced by thapsigargin and tunicamycin treatment (140). Altogether, these data indicate that the UPR inhibits *C. jejuni* infection. NOD1 (but not NOD2) restricts *C. jejuni* infection in intestinal epithelial cells (90) and therefore may be involved in ER stress-mediated restriction of *C. jejuni* infection. Other bacteria that induce ER stress and are also inhibited by NOD1 or NOD2 include *P. aeruginosa* (141–145), *Staphylococcus aureus* (146, 147), *S.* Typhimurium (148), and *S. pneumoniae* (149). Additional studies are necessary to determine a link between bacterium-induced ER stress and NOD1/2 antibacterial effects.

Fungi. NOD1 senses and elicits proinflammatory responses during *Aspergillus fumigatus* infection of corneal epithelial cells (150) and promotes invasive aspergillosis, a disease induced by *A. fumigatus* (27). Similarly, NOD2 promotes *A. fumigatus* pathogenicity (28). *Nod1*$^{-/-}$ mice were less susceptible to *A. fumigatus*, and bone marrow-derived macrophages (BMDMs) from *Nod1*$^{-/-}$ mice killed *A. fumigatus* more efficiently in an ROS-dependent manner. A similar, yet distinct, mechanism for NOD2 enhancement of invasive aspergillosis occurs. Peripheral blood mononuclear cells (PBMCs) from human donors with the *Nod2* polymorphism 1007insC and *Nod2*-deficient PBMCs had decreased proinflammatory cytokines yet increased fungal killing in an ROS-independent manner during *A. fumigatus* infection. Like *Nod1*, during *A. fumigatus* infection (27), *Nod2* deficiency led to an upregulation of Dectin-1 (28), which is a CLR that promotes uptake of *A. fumigatus* (151), thereby enhancing phagocytosis of *A. fumigatus* (27, 28). Therefore, *A. fumigatus* exploits the PRR Dectin-1 to gain access to host cells in a NOD1/2-dependent fashion.

A. fumigatus activates all three UPR axes (Fig. 2), which required mitochondrial ROS production (152, 153). Interestingly, ER stress inhibition using 4-phenylbutyric acid (4-PBA) during *A. fumigatus* infection in an asthma mouse model reduced pulmonary inflammation, ROS generation, ER calcium depletion, and NLRP3 inflammasome activation (153). Thus, ER stress mediated by *A. fumigatus* infection leads to damaging inflammatory responses. This may involve NOD1/2 sensing of *A. fumigatus*-induced ER stress directly or possibly by regulating *A. fumigatus*-induced mitophagy.

Parasites. Little is known regarding the role of NOD1/2 during infections with protozoan parasites; however, NOD1 and/or NOD2 is activated by a few parasites. *Plasmodium berghei* infection activated NOD1/2, but parasite replication or disease outcome was unaffected by NOD1/2 signaling (24). A related malarial parasite, *Plasmodium falciparum*, induced nitric oxide, which required NOD2, RIPK2, and the *P. falciparum* toxin hemozoin (25). Both NOD1 and NOD2 are required for NF-κB-dependent cytokine responses during *Trypanosoma cruzi* infection; however, NOD1, but not NOD2, restricted *T. cruzi* infection in mice (26). ER stress sensing by NOD1/2 may be a plausible mode of sensing and responding to parasitic infections. Indeed, *P.*

berghei infection in the liver and brain activates and requires the IRE1α/JNK, ATF6, and PERK branches of the UPR (Fig. 2) (154–156). Proapoptotic factors, proinflammatory cytokines, and neuronal cell death were decreased in *P. berghei*-infected mice that were administered a JNK inhibitor (157). Thus, *P. berghei* induction of ER stress likely activates NOD1/2 proinflammatory pathways in both the liver and the brain. ER stress is critical for establishing infection in the liver, and NOD1/2 may therefore benefit *P. berghei* infection in the liver. ER stress is linked with inflammation at both infection sites (154, 157); however, potential NOD1/2 sensing of *P. berghei*-induced ER stress may lead to detrimental inflammatory effects in the brain, resulting in neuronal cell death. Indeed, NOD1/2 proinflammatory responses have been associated with hyperinflammation that can have adverse effects on cells (85). Whether NOD1/2 sense *Plasmodium*-induced ER stress and whether NOD1/2 may have organ-specific effects that result in differential disease outcomes warrant more investigation.

T. cruzi also causes ER stress as measured by assessing the PERK pathway. Inhibition of ER stress in *T. cruzi*-infected mice relieves cardiomyopathy and Chagas disease sequelae, which is consistent with decreased apoptosis and cardiac inflammation. Furthermore, *T. cruzi* infection reduced mitochondrial antioxidant gene expression, which was reversed with an ER stress inhibitor (158). NOD1/2 activation may respond to parasite-induced ER stress during *T. cruzi* infection and contribute to inflammation, leading to cardiomyopathy and the development of Chagas disease. However, early recognition of ER stress during *T. cruzi* infection by NOD1 may control parasite replication prior to disease onset (26).

Altogether, ER stress mostly promotes cell death during parasite infections suggesting that if NOD1/2 sense parasite-induced ER stress, then they likely contribute to a hyper-inflammatory response that could have detrimental effects by inducing killing of infected cells. Since NOD1 protects mice against *T. cruzi* infection (26), then perhaps early sensing and responses by NOD1/2 restrict parasite replication prior to later stages in disease in which NOD1/2 might contribute to cell death and adverse inflammatory effects.

Viruses. NOD1 and/or NOD2 is activated during some viral infections and is mostly antiviral. NOD2 protects mice/cells against respiratory syncytial virus (RSV) (19), vesicular stomatitis virus (VSV) (19), IAV (17, 18, 159) and foot-and-mouth-disease virus (FMDV) (23) in a type I IFN-dependent manner (17, 19, 23, 159). Furthermore, both NOD1 and NOD2 are upregulated by and restrictive to human and mouse cytomegalovirus (HCMV and MCMV, respectively), which required type I IFN as well (20, 21, 160). Interestingly, single nucleotide polymorphisms in *Nod1* correlated with the prevalence of HCMV infection in humans (21), further indicating its antiviral effects. A few viruses have countermeasures to inhibit NOD1/2 signaling, including FMDV and human immunodeficiency virus 1 (HIV-1). Although NOD2 transcription increased during FMDV infection, the virus strongly inhibited protein expression (23). HIV-1 cleaves and inactivates RIPK2 (161), suggesting that NOD1/2 signaling may be antiviral to HIV-1; yet, this is undetermined.

NOD1/2 significantly impact viral infections through their interplay with the antiviral type I IFN pathway. NOD1/2 and type I IFN signaling have significant overlap and can regulate each other (11, 162). Indeed, *Nod1* (163), *Nod2* and *Ripk2* are ISGs (22) and are required for strong induction of type I IFN signaling (9, 19, 164). Introduction of single-stranded RNA (ssRNA) into cells to mimic viral infection led to NOD2-dependent, not NOD1, type I IFN responses (19). Sabbah et al. (19) revealed that mitochondrial antiviral signaling protein (MAVS) was required for the NOD2-mediated type I IFN response to ssRNA. Ectopically expressed NOD2 and MAVS interacted, and NOD2 localization to mitochondrial membranes increased upon RSV infection (19). Furthermore, NOD2 enhanced type I IFN and proinflammatory responses during infection with CMV by an unclear mechanism (20), since the DNA virus CMV does not have an RNA intermediate. NOD2 interacted with antiviral dsRNA-activated 2′-5′-oligoadenylate synthetase type 2 (OAS2), which enhances RNase L activity (165). RNase L is an endoribo-

nuclease whose cleavage products initiate type I IFN signaling during viral infection (166). Hepatitis C virus (HCV) RNA-dependent RNA polymerase NS5B induced NOD1 expression in hepatocytes and IFN-β was decreased upon NOD1 inhibition (163). In contrast, NOD2 inhibited type I IFN signaling by directly interacting with RIG-I to negatively regulate RIG-I-induced type I IFN expression (167). Thus, NOD1/2 are intimately linked to type I IFN signaling, and yet how they regulate each other is largely unclear.

The mechanisms underlying NOD1/2 sensing of viruses are mostly elusive. NOD2 may interact with ssRNA (19). However, additional biochemical analyses are required to determine whether the interaction of NOD2 with ssRNA is direct or indirect to help understand the mechanism of NOD2 stimulation by ssRNA. Moreover, the double-stranded RNA mimetic poly(I·C) elicited strong inflammatory cytokine expression (*Il8*, *Tnf*α, and *Ifn*β), which was reduced using a dominant negative *Nod1* or cells depleted of *Nod1* or *Ripk2*. NOD1 bound directly to poly(I·C), which was independent of the NOD1 LRR domain (163). Therefore, these studies indicate that NOD1/2 could be involved in direct sensing of viral single-stranded or double-stranded RNA, but more research is necessary to fully confirm these possibilities.

An alternative hypothesis for NOD1/2 sensing of viral infection could be that NOD1/2 are broadly sensing ER stress induced during viral infections or are involved in ER stress-mediated cellular processes such as autophagy and mitophagy (18, 29, 47, 50, 168). ER stress induction by viruses is a well-known phenomenon and usually occurs by ER membrane rearrangements induced by several viruses that establish replication complexes on the ER, disruption of ER-Golgi trafficking and/or by the large influx of viral proteins that need to be processed and folded (85, 86). Of the viruses known to be restricted by NOD1/2, RSV, IAV, and CMV stimulate ER stress (Fig. 2). FMDV is a member of the *Picornaviridae* family; other members of this family induce ER stress (169), but this has not been shown for FMDV specifically. RSV, IAV, and CMV uniquely affect ER stress pathways, but the IRE1α pathway that was implicated in NOD1/2 signaling (29) is activated by all three (170–175).

RSV infection causes ER stress as evidenced by ATF6 and IRE1α activation, and IRE1α inhibits RSV replication independent of *Xbp1* (170). IRE1α-dependent restriction of RSV replication may occur by viral mRNA degradation via the RIDD pathway downstream of IRE1α (176), which has not been evaluated. Alternatively, NOD1/2 acting downstream of IRE1α may be responsible for restricting RSV replication.

HCMV differentially regulates the UPR (175). PERK and IRE1α were activated during CMV infection, whereas ATF6 was suppressed, and ER stress-inducing drugs inhibit CMV infection (173, 175, 177). PERK is critical for HCMV replication (178). HCMV inhibited IRE1α (177), and MCMV inhibited *Xbp1* splicing by IRE1α (179). In addition, XBP1s target EDEM was downregulated by HCMV (175), further suggesting that CMV actively inhibits the IRE1α pathway. Indeed, cytomegalovirus (CMV) proteins M50 and UL50 downregulate IRE1α (180). However, XBP1 is important for CMV gene expression (173). It is likely that IRE1α signaling at different stages of CMV infection can lead to various effects on CMV replication. Therefore, ER stress induced by CMV likely activates IRE1α signaling early, but CMV then inhibits IRE1α signaling later in infection once enough M50 and UL50 have been generated. Thus, CMV may block ER stress-activated IRE1α signaling to inhibit antiviral NOD1/2 signaling.

ER stress induction by IAV has been studied rather extensively but may vary based on cell types and timing of infection. IRE1α is activated during IAV infection (171, 172, 174, 181), but the effects of IRE1α on IAV infection are unclear. Inhibition of IRE1α blocks IAV protein synthesis and replication (171), suggesting that ER stress is critical for IAV replication. In addition, knockdown of the ER stress chaperone ERp57 (also known as Grp58), critical for proper folding of IAV hemagglutinin (HA) protein, reduced IAV replication (172, 182). IRE1α is activated by HA, which upregulates ERAD and restricts IAV replication (174). However, this indicates that ER stress can restrict IAV infection. In addition, poorly glycosylated HA from pandemic-like IAVs, compared to commonly circulating human-adapted strains, causes significant ER stress and a heightened

proinflammatory immune response which correlated with increased IAV pathogenesis. The IRE1α and PERK pathways were upregulated by a pandemic IAV strain, and ER stress inhibition reduced the production of proinflammatory cytokines (183). IAV replication was unaffected by ER stress in this study; however, pathogenesis induced by IAV increases with more ER stress. Lastly, IAV inhibits PERK phosphorylation, and chemical activation of PERK is antiviral (184). Overall, ER stress pathways are differentially regulated by IAV and result in various outcomes. One common theme is the induction of IRE1α, which can lead to NOD1/2 activation (29). Since NOD2 and RIPK2 have been shown to inhibit IAV infection (17, 18, 159), early detection of virus-induced ER stress by NOD1/2 could reduce IAV pathogenesis through upregulation of immune responses. Analysis of NOD1 and further analyses of NOD2 during IAV infection would be helpful to distinguish whether there is a role for IAV-induced ER stress in activating NOD1/2.

Despite its previously described antiviral role, NOD2 enhanced CVB3 replication and myocarditis in a CVB3-induced myocarditis mouse model. CVB3-induced apoptosis and NLRP3 activation were reduced in the absence of *Nod2*, which correlated with reduced myocarditis and production of proinflammatory mediators (16). NLRP3 was previously shown to contribute to CVB3 myocarditis (185), and it appears to be regulated by NOD2 in this infection model (16). How NOD2 promotes CVB3 replication and pathogenesis is unknown when it generally inhibits other viruses. Interestingly, CVB induces all three arms of UPR, which are important for CVB replication (186–188). Knockdown of each ER stress pathway modestly reduced CVB3 replication, indicating that ER stress response proteins are required for efficient CVB3 replication (187). CHOP was critical for CVB3 to establish myocarditis and replicate efficiently, and proinflammatory cytokine expression was significantly reduced with an ER stress inhibitor in CVB3-infected mice (186). CVB5 activated IRE1α and PERK in pancreatic β cells, which enhanced CVB5 replication. Inhibition of JNK, which is downstream of IRE1α, reduced CVB5-induced apoptosis and replication (188). Furthermore, a soluble factor produced by CVB3-infected cardiomyocytes induced ER stress in cardiac infiltrating macrophages leading to enhanced CVB3 pathogenesis, but replication was not assessed. In this study, inhibition of ER stress reduced cardiac macrophage production of proinflammatory cytokines and alleviated CVB3-induced myocarditis (189). CVB3 also induced *Nod2* expression, which is important for viral infection (16). Therefore, CVB likely activates NOD2, and possibly NOD1, signaling by inducing ER stress, and this benefits CVB through promotion of infection by an unknown mechanism.

CONCLUDING REMARKS

The ER is a highly dynamic organelle that plays a major role in coordinating signaling pathways to ensure cellular homeostasis. Whether or not ER stress results in cell survival, inflammation, or cell death is determined by multiple different factors, such as the duration of ER stress, cell type, environmental and/or genetic factors, and infection with a variety of pathogens. NOD1 and NOD2 have been implicated in ER stress-induced inflammation either directly, by sensing the disruption in ER homeostasis, or indirectly, via ER stress-mediated processes such as autophagy, mitophagy and increases in intracellular calcium concentration. Are the functions of NOD1 and NOD2 solely to sense peptidoglycan, or do they have broader functions in the detection of pathogens? In this regard, it is of great interest to elucidate the underlying mechanisms of NOD1/2 activation by peptidoglycan-deficient pathogens. It is increasingly apparent that NOD1 and/or NOD2 is activated during parasitic, fungal, and viral infections, but whether sensing of ER stress by NOD1 and/or NOD2 is a common strategy to combat these infections remains to be elucidated.

Interestingly, evidence is accumulating for a role of ER stress-mediated inflammation and NOD1/2 signaling in a variety of chronic inflammatory disorders, such as inflammatory bowel disease, obesity, diabetes, rheumatoid arthritis, ankylosing spondylitis, and cardiovascular disease (190–197). What exactly are the roles of NOD1 and NOD2 in chronic inflammatory diseases? Do they recognize circulating peptidoglycan fragments

which may be increased during chronic inflammation, is there an increase in intestinal microbiota translocation to various tissues, or can NOD1 and NOD2 sense ER stress and/or ER stress-mediated processes in the absence of peptidoglycan (198–200)? Targeting ER stress and the UPR pathways might offer opportunities for treating infectious diseases and chronic inflammatory diseases. However, a clearer understanding of the mechanisms that orchestrate ER stress-induced pathologies, whether activated by environmental and/or genetic factors or during infections, and a link with NOD1/2 signaling is required to safely modulate this process for the development of future therapeutics.

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Sharon K. Kuss-Duerkop received her B.S. in Biology from Angelo State University. Under the advisement of Dr. Julie Pfeiffer, Sharon completed her Ph.D. in Molecular Microbiology at the University of Texas Southwestern Medical Center in which she studied gastrointestinal influences on poliovirus infection. Her postdoctoral research characterizing the role of mTORC1 and mTORC2 during influenza virus infection was performed in Dr. Beatriz Fontoura's laboratory at the University of Texas Southwestern Medical Center. Sharon became a Research Instructor at the University of Colorado Denver School of Medicine initially in the laboratory of Dr. Dohun Pyeon studying host restriction factors during human papillomavirus infection. She is currently a Research Instructor in the Keestra-Gounder laboratory, and her research over the last two years has focused on understanding how NOD1 and NOD2 respond to and influence viral infections.

A. Marijke Keestra-Gounder is an Assistant Professor at the University of Colorado Denver School of Medicine. She received her Ph.D. in microbiology and immunology at the Department of Infectious Diseases and Immunology, Utrecht University in the Netherlands, under the supervision of Dr. Jos van Putten. Her Ph.D. thesis project focused on the elucidation of the functions of Toll-like receptors (TLRs) of chicken to determine their ligand specificity and (dis)similarities with mammalian TLRs. During her postdoctoral training in the laboratory of Dr. Andreas Bäumler at the University of California at Davis, she investigated pathways of the innate immune system in response to *Salmonella* Typhimurium and *Brucella abortus*. Her research continues to focus on the activation of the host innate immune system and the roles of NOD1 and NOD2 during bacterial and viral infections.