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REVIEW

The complex interplay between endoplasmic reticulum stress and the NLRP3 inflammasome: a potential therapeutic target for inflammatory disorders

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Abstract

Inflammation is the result of a complex network of cellular and molecular interactions and mechanisms that facilitate immune protection against intrinsic and extrinsic stimuli, particularly pathogens, to maintain homeostasis and promote tissue healing. However, dysregulation in the immune system elicits excess/abnormal inflammation resulting in unintended tissue damage and causes major inflammatory diseases including asthma, chronic obstructive pulmonary disease, atherosclerosis, inflammatory bowel diseases, sarcoidosis and rheumatoid arthritis. It is now widely accepted that both endoplasmic reticulum (ER) stress and inflammasomes play critical roles in activating inflammatory signalling cascades. Notably, evidence is mounting for the involvement of ER stress in exacerbating inflammasome-induced inflammatory cascades, which may provide a new axis for therapeutic targeting in a range of inflammatory disorders. Here, we comprehensively review the roles, mechanisms and interactions of both ER stress and inflammasomes, as well as their interconnected relationships in inflammatory signalling cascades. We also discuss novel therapeutic strategies that are being developed to treat ER stress- and inflammasome-related inflammatory disorders.

Keywords: endoplasmic reticulum stress, inflammasome, inflammatory disorder, NLRP3

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INTRODUCTION

Humans are constantly exposed to a myriad of potentially harmful exogenous stimuli, particularly opportunistic and pathogenic microorganisms, environmental allergens and noxious particles and irritants. To defend against these challenges, humans have evolved a fine-tuned and highly effective immune system comprised of innate and adaptive immunity.[1] The innate immune system consists of anatomical barriers, the complement system, inflammatory cascade and immune cells (e.g. neutrophils, macrophages, eosinophils, mast cells). It plays an essential role as the frontline of immune defence in preventing pathogen invasion. The innate system detects danger signals by recognising pathogen (PAMPs)- and danger (DAMPs)-associated molecular patterns.[1] PAMPs, such as bacterial endotoxins and flagellin, are distinguishable from host factors. DAMPs include heat shock (HSP) and high-mobility group box proteins, adenosine triphosphate (ATP), cytosolic ribonucleic acids (RNAs), and cytosolic and mitochondrial deoxyribonucleic acids (DNAs) that are released by damaged or stressed cells. PAMPs and DAMPs are recognised by membrane-bound or cytosolic pattern recognition receptors (PRRs), enabling innate immune cells to discriminate pathogen and foreign materials from host cells.[1] The adaptive immune system is mainly regulated by T- and B-lymphocytes and provides long-lasting protection against previously encountered microbes through the recognition of foreign antigens.

Inflammation is initiated and regulated by complex interactions of immune cells that encounter exogenous stimuli, as well as endogenous pro-inflammatory cytokines.[1,2] These factors impact the resultant severity, type and duration of inflammation. Infection with microbes, either opportunistic or pathogenic, can exaggerate inflammatory responses, damaging host cells and leading to acute, chronic, local and systematic inflammatory disorders. Among immune system mediators, inflammasomes have recently attracted global attention as potential therapeutic targets for treating chronic inflammatory diseases. Inflammasomes are innate immune system mediators that induce and regulate inflammation upon challenge by pathogens and environmental allergens. They are linked to a myriad of autoimmune and inflammatory diseases, including multiple sclerosis, Alzheimer's disease, atherosclerosis, diabetes, inflammatory bowel disease, severe asthma and chronic obstructive pulmonary disease (COPD).[3–10]

ENDOPLASMIC RETICULUM (ER) STRESS

Endoplasmic reticulum stress is a cellular stress that occurs when the protein folding function of the ER has reached its maximum capacity leading to impairment of the folding process.[11] In eukaryotic cells, cytoplasmic ribosomes continuously synthesise proteins that are required for daily metabolic activity. Before secretion, these proteins are transferred to the membrane-bound ER for further post-translational modification and quality control.[12] The ER is exquisitely sensitive to intracellular and extracellular stimuli.[11] Any perturbations in the cell, such as pathogen infection, allergen exposure, redox homeostasis imbalance and the effects of cytotoxins, can affect protein biosynthesis and may result in misfolded proteins with altered functions.[11,13] Misfolded proteins are continuously produced in cells, in direct proportion to the complexity and amount of proteins generated.[12] For instance, intestinal goblet cells, which produce significant amounts of complex mucin (MUC)-2 protein under physiological conditions, are particularly susceptible to ER stress.[12,14] Due to perturbations in protein folding processes, irregular functional proteins are produced, along with misfolded proteins.[13] In order to meet homeostasis demands, cells upregulate protein biosynthesis processes to increase the production of required proteins, and this response simultaneously increases the formation of misfolded protein, which further exacerbate misfolded protein aggregation and reinforce ER stress.

Most misfolded proteins do not exert any cellular function and pose a burden for cells. Hence, these proteins need to be re-folded or removed. Several mechanisms have evolved to reduce and remove misfolded proteins. The ER is responsible for protein proofing and ensuring that all initiated proteins are correctly folded before secretion out of the cell. Misfolded proteins are subject to re-folding until they are successfully folded, whereas terminally misfolded proteins are retro-translocated into the cytosol for ER-associated degradation (ERAD) either *via* the

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ubiquitin-proteasome system or are degraded in a ubiquitin independent manner.[15–17] The ER contains numerous chaperones that assist the protein folding process, including HSP60, calnexin, calreticulin and glucose-regulated protein (GRP) 78.[15] These chaperones facilitate the quality control and post-translational modifications of the nascent proteins, promote the protein re-folding process, transfer nascent protein into and out of the ER, identify and bind to misfolded proteins, and retro-translocate terminal misfolded protein into the cytosol for ERAD.[15,18] Moreover, chaperones play vital roles in various molecular processes, such as peptide cleavage, glycosylation and disulphide bonding. Overall, chaperones assist ER activities while maintaining ER homeostasis.

Even with advanced quality control and turnover of protein production in the ER, altered physiological and pathological conditions can compromise ER homeostasis, reduce the efficiency of protein folding mechanisms and cause aggregation of misfolded proteins.[19] The triggers for ER dysfunction include inflammation, hypoxia, nutrient depletion, oxidative stress, redox imbalance, upregulated protein biosynthesis, and calcium deficiency.[19] This can drive diseases, and indeed, patients with pathological conditions, such as infection, neurodegenerative disorders, metabolic syndrome, and inflammatory diseases, have perturbations in ER homeostasis.[19] Notably, if the production of misfolded proteins overwhelms protein re-folding mechanisms in the ER, misfolded proteins will accumulate in cells.[20] Consequently, cells undergo the cellular stress condition of ER stress. Cells with ER stress exhibit distinct morphological changes compared to healthy cells, including ribosome dissociation, ER luminal swelling and expansion, and atypical ER structure. Moreover, ER stress has a substantial impact on overall cellular activities by altering protein biosynthesis, reducing functional protein production, and interfering with intracellular and extracellular signalling cascades,[21] and when chronic can induce apoptosis.[21,22] All of these mechanisms contribute to pathogenesis in various inflammatory conditions, including inflammatory bowel disease, atherosclerosis, diabetes, asthma and COPD.[20,23–26]

To limit ER stress-induced cellular abnormalities, cells are equipped with a network of multifactorial, parallel, and independent transcriptional and signalling pathways, collectively known as the unfolded protein response (UPR).[27] The major role of the UPR is to increase ER folding capacity, re-fold marginally misfolded proteins, and remove terminally misfolded proteins. The UPR consists of numerous cellular pathways that promote the ER protein folding process, reduce overall protein biosynthesis, and activate ERAD to eliminate aggregated misfolded proteins in the ER.[27] The UPR can also trigger apoptotic cascades if the stress condition overwhelms its' capacity.[27] In the UPR process, the chaperone GRP78 has a pivotal role in controlling protein synthesis, folding and assembly. This chaperone is a sensor of misfolded proteins, and initiates the UPR signalling cascade.[27] Under normal conditions, GRP78 is attached to and inhibits three ER-localised transmembrane UPR signal transducers, including inositol-requiring kinase (IRE)1, activating transcription factor (ATF)6, and protein kinase RNA-like ER Kinase (PERK).[28] However, in ER stress, misfolded proteins are produced and aggregate in the ER, where they are sensed by GRP78.[28] As a result, UPR signal transducers are released by GRP78, and bind to misfolded proteins within the ER. This activates the UPR signal transducers and downstream signalling cascades.[11] These transducers collaborate to promote protein folding mechanisms and eliminate misfolded proteins. This is the traditional view of how the ER recognises misfolded proteins. However, several reports show that misfolded proteins can directly bind to IRE1 or PERK to initiate the UPR.[29,30] Although the UPR is a cytoprotective process, it can be cytotoxic during severe and persistent ER stress.[31] It is notable that ER stress is not exclusively a pathological condition as healthy cells undergo this while secreting large amounts of proteins. The IRE1–X-box binding protein (XBP1) signalling pathway is induced during the differentiation of B cells to plasma cells, and in the development and survival of conventional and plasmacytoid dendritic cells.[32–35] Thus, the UPR is involved in proteostasis and in fine-tuning the protein synthesis process during normal cellular functions, but can become dysfunctional and contribute to the pathogenesis of disease.

IRE1

The IRE1 signalling cascade is the most conserved UPR signalling mechanism, and is present in all eukaryotes.[36] IRE1 is a type 1 transmembrane

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sensor protein, which has an amino-terminal ER luminal domain, a single-pass transmembrane segment, and a carboxyl-terminal cytoplasmic kinase and RNase domain.[37] In mammalian cells, there are two IRE1 isoforms, IRE1α and IRE1β.[38] IRE1α is ubiquitously expressed in all mammalian cells that have an ER, whereas IRE1β is only found in lung and gut-derived cells.[38] Under physiological conditions, IRE1 is constitutively bound to GRP78. During ER stress, GRP78 releases IRE1, allowing it to undergo activation and oligomerisation.[38] IRE1 has a kinase domain that can be autophosphorylated as part of its activation process.[39] This triggers its RNA endonuclease activity, which is crucial for the downstream signalling cascade.[39] Oligomerisation of IRE1 has been visualised microscopically as foci *in vivo* and is required for downstream signalling.[18,40] Importantly, autophosphorylation of IRE1 does not trigger downstream signalling by initiating a phosphorylation cascade, but instead signalling occurs as a result of oligomerisation and activation of the nucleotide-binding site of the IRE1 RNase domain.[41] Once activated, IRE1 selectively excises a messenger (m)RNA that encodes the transcription factor XBP1. This process occurs through precise cleavage either side of a 22 nucleotide intron, and the remaining mRNA is re-joined by RtcB ligase.[39] The excision causes a frameshift in the XBP1 translational sequence and produces the functional protein, spliced XBP1 (XBP1s). Activated XBP1 contains a basic leucine zipper domain (bZIP) that promotes the expression of target genes, which encode ER chaperones and ERAD components to increase protein folding and ERAD capacity.

PERK

Similar to IRE1, PERK is also a type 1 transmembrane protein. It has an ER luminal domain and a cytosolic kinase domain that is structurally and functionally identical to IRE1, and undergoes autophosphorylation during ER stress.[42] Although it has a similar activation pattern, activated PERK recruits and phosphorylates a different transcription factor, eukaryotic initiator factor (EIF)2α.[42] EIF2α is critical in protein biosynthesis, as it promotes the binding of initiator transport RNA (tRNA) to 40S ribosomal subunits, as well as forming a ternary complex with guanosine triphosphate and methionyl tRNA, which are vital in the early stages of protein synthesis.[43]

EIF2α phosphorylation can inhibit general protein synthesis and thereby reduce the demand for protein folding processes and relieve the burden on the ER. EIF2α phosphorylation also simultaneously initiates another protein translation process that is exclusive for ER-resident proteins. It allows the translation of mRNA that contain inhibitory upstream open reading frames in their untranslated regions, which do not translate under normal conditions.[44] As a result, the ATF4 is produced. In the PERK signalling pathway, ATF4 initiates the translation of two critical downstream UPR target proteins, DNA damage-inducible transcript (DDIT)3 and the growth arrest and DNA damage-inducible protein (GADD)34. GADD34 is vital in dephosphorylating EIF2α and restores protein biosynthesis. Activated GADD34 recruits the serine/threonine-protein phosphatase 1 complex (PP1), which dephosphorylates EIF2α and recovers protein synthesis mediated by the PERK signalling cascade. DDIT3 triggers apoptosis if the cell undergoes persistent and unsolved ER stress.[45] Thus, the PERK signalling pathway controls cell fate under conditions of ER stress, although it remains unclear how PERK regulates the balance of both GADD34 and DDIT3 expression.

ATF6

ATF6 is the ER stress transducer that regulates the third branch of the UPR signalling cascade. It is a 90 kDA protein with a transmembrane domain.[46] Similar to PERK and IRE1, it is localised to the ER membrane and constitutively bound and inhibited by GRP78. In mammalian cells, there are two ATF6 isoforms, ATF6α and ATF6β.[47] ATF6α, but not ATF6β, is essential in the regulation of protein folding and ERAD processes.[47,48] *In vivo*, *Atf6*α-deficient mice are more susceptible to ER stress than wild-type mice, whereas *Atf6*β deficiency did not affect *in vivo* responses to challenge with tunicamycin that induces ERS stress,[48,49] an inhibitor of N-linked protein glycosylation that robustly induces ER stress. ATF6 has distinct UPR activation mechanisms that differ from those in IRE1 and PERK. ATF6 is an ER-resident oligomer under normal conditions. During ER stress, GRP78 detects and binds to misfolded proteins, and simultaneously releases ATF6. ATF6 then translocates to the Golgi apparatus, where its N-terminal domain is cleaved by sphingosine-1-phosphate and sphingosine-2-phosphate *via*

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intramembrane proteolysis.[50] Cleaved ATF6 then translocates to the nucleus where it binds to the ER stress response element 1 and CAAT binding protein. ATF6 thereby promotes target gene expression and upregulates ER-resident protein synthesis. It plays essential roles in maintaining ER homeostasis, such as upregulating ER-resident chaperones and initiating ER stress-dependent ER expansion, as well as promoting protein folding, trafficking and modification.[50]

INFLAMMASOMES: KEY MEDIATORS OF INFLAMMATORY DISEASES

Inflammasomes are signalling complexes[51,52] that can assemble in most innate immune cells, including mast cells, basophils, neutrophils, and macrophages.[1] These are supramolecular, cytosolic complexes containing the protease caspase-1, an adaptor known as Apoptosis-associated Speck-like protein containing Caspase Activation and Recruitment Domain (CARD, ASC, CARD5, PYCARD), and a sensor protein.[53] Sensor protein activation induces the recruitment and fibrillation of ASC to form a large signalling platform called the ASC speck or pyroptosome,[4] and this complex acts as a platform for proximity-induced activation of caspase-1 protease function.[54] Active caspase-1 then cleaves the inactive pro-interleukin (IL)-1β and pro-IL-18 into active pro-inflammatory cytokines IL-1β and IL-18. Inflammasome-driven IL-1β and IL-18 production requires two signals. The first signal can be either PAMPs, such as bacterial lipopolysaccharides (LPS), or cytokines, such as IL-1 or tumour necrosis factor (TNF).[55,56] During pathogen challenge, PAMPs and cytokines trigger downstream signalling cascades, for example *via* nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB).[55,57] Primary functions of this signal are to upregulate NLRP3 and pro-IL-1β gene and protein expression .[55] The second signal activates the inflammasome, and can be provided by DAMPs or microbial virulence factors, such as *Shigella* sp. toxin and *Staphylococcus aureus* α-haemolysin.[55,57] This second signal activates inflammasome sensor proteins, which then recruit ASC and caspase-1 monomers to assemble the inflammasome.[1] Caspase-1 monomers dimerise on the inflammasome to partially activate this protease.[54] Caspase-1 then self-cleaves in one linker region to fully activate the protease and induce substrate cleavage, after which it cleaves in a second linker region to inactivate the protease.[54] Activated caspase-1 is a cysteine-dependent protease that cleaves pro-IL-1β and pro-IL-18 into functional IL-1β and IL-18 to initiate the inflammatory responses.[1] Active caspase-1 can also trigger a form of cell death called pyroptosis, by cleaving gasdermin D to generate an N-terminal fragment that binds to the inner leaflet of the plasma membrane to form 10–3-nm diameter pores. Gasdermin D pores facilitate the export of mature functional IL-1β and IL-18.[58–60] As a consequence, cytosolic contents, including IL-1β and IL-18, are released. Interestingly, microbial NLRP3-activating signals, such as the bacterial toxin nigericin, elicit a more potent and greater inflammasome response compared to sterile signals, such as ATP, reflecting the important functions of the inflammasome in eliminating pathogens and infection.[56]

Inflammasomes are categorised into three groups: tripartite motif, AIM2-like receptors and nucleotide-binding domain-like receptors (NLR) based on their unique sensor protein that forms the core for the assembly of inflammasome complexes.[61,62] The NLR family is distinguished by its unique central nucleotide binding and oligomerisation NACHT domain, which is usually bookended by C-terminal leucine-rich repeats (LRR) and an N-terminal CARD or Pyrin domain.[63] Four distinct inflammasome sensors are characterised within the NLR family: Nucleotide-binding oligomerisation domain, LRR and Pyrin domain containing (NLRP)3, NLRP1, NLRP6, and Nucleotide-binding oligomerisation domain, LRR and CARD containing (NLRC)4.[55,57,61,63–65] We will focus on the NLRP3 inflammasome that is most widely implicated in ER stress and inflammatory diseases.

NLRP3 inflammasome

The NLRP3 inflammasome has attracted much attention as a therapeutic target, due to its disease-inducing roles in many inflammatory diseases, including arthropathy, COPD, inflammatory bowel disease, multiple sclerosis, Parkinson's disease, diabetes, and severe asthma.[5,6,8–10,66,67] For instance, the essential role of NLRP3 inflammasome is well presented in multiple chronic inflammatory lung diseases, such as asthma and COPD. Elevated NLRP3 inflammasome expression is reported in patients with neutrophilic asthma,[68] and drives the pathogenesis of severe steroid-resistant

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experimental asthma.[5] Similar events are also observed in COPD models, and knockout of NLRP3 reduces the expression of inflammation markers (IL-1 and IL-18).[69]

Like most other inflammasomes, NLRP3 contains three major domains: a C-terminal LRR domain, a central NACHT and an N-terminal Pyrin domain.[53] NLRP3 activity requires ATP produced *via* the ATPase function within the NACHT domain.[70] Gain-of-function mutations in NLRP3 cause cryopyrin-associated periodic syndromes (CAPS), such as Muckle–Wells syndrome, familial cold autoinflammatory syndrome and chronic infantile neurologic cutaneous and articular syndrome.[71] Conversely, loss-of-function NLRP3 variants are yet to be discovered in humans, and are potentially lethal. Bats, however, have suppressed inflammasome responses enabling them to tolerate many viruses such as coronaviruses including SARS-CoV-2 that causes COVID-19[72,73].

The NLRP3 inflammasome orchestrates cell stress-induced inflammatory responses. NLRP3 is activated by a myriad of stimuli, including extracellular ATP that is released by damaged host cells,[74,75] and microbial molecules such as RNA and bacterial toxins, that enable responses to invading pathogens such as bacteria, viruses, fungi, and parasites. Sha *et al*. showed that human NLRP3 detects mRNA, tRNA, and ribosomal RNA from both Gram-negative (e.g. *Escherichia coli, Pseudomonas aeruginosa, Chromobacterium violaceum, Salmonella enterica* and *Moraxella catarrhalis*) and Gram-positive (e.g. *S. aureus, Listeria monocytogenes* and *Enterococcus faecalis*) bacteria.[76] Intriguingly and unlike human NLRP3, the murine NLRP3 inflammasome only responds to bacterial mRNA but not to bacterial tRNA or rRNA.[76] Animal studies highlight the protective functions of the NLRP3 inflammasome in host defence against opportunistic fungi including *Aspergillus furmigatus*, *Saccharomyces cerevisiae*, and *Candida albicans*.[77–81] Indeed, NLRP3 inflammasome signalling restricts fungal spread in mice.[82,83] Several studies also show that NLRP3 is also a sensor for viral infection. NLRP3 inflammasome signalling drives IL-1β production in Ebola infection.[84] However, some viruses, such as Sendai virus and NS1 mutant influenza A virus, inhibit IL-1β production by preventing NLRP3 assembly and detection of these viruses, highlighting the limitations of NLRP3 in combating such viral infections.[85,86] However, NLRP3 inflammasome activation does not always play a protective role in infection. NLRP3 inflammasomes are deleterious late in influenza A virus infections and NLRP3 knockout promotes animal survival in some microbial infections.[87–89]

The mechanisms of activation of the NLRP3 inflammasome cascade remain to be fully elucidated. Under physiological conditions, NLRP3 sensor molecules are thought to be in an auto-inhibition state that renders them unable to initiate signalling.[90] Inflammasome licensing or priming processes are required to induce NLRP3 into a signal-competent state ready for activation by a second signal.[91] During the priming process, priming signals, including PAMPs, are recognised by PRRs and acts as ligands that bind to toll-like receptors (TLRs). These PAMPs include bacterial lipopolysaccharide, lipoproteins, lipoteichoic acid, peptidoglycans, 23S RNA, zymosan, mannan, flagellin, viral double stranded RNA, small interfering RNA, profilin, and viral DNA that are enriched with unmethylated CpG-DNA motifs.[92] Once attached to TLR, this interaction subsequently activates the transcription factor NF-kB, which then upregulates NLRP3 and pro-IL-1β expression.[93,94] This process is tightly regulated *via* other cellular mechanisms including G-protein-coupled receptor (GPCR) signalling and microRNAs.[95,96] In addition to regulating NLRP3 and pro-IL-1β expression, priming also induces several post-translational modifications in inflammasome components that facilitate pathway activation by a second stimulus[97,98] (Figure 1).

After priming, an activation signal such as reactive oxygen species (ROS), lysosomal damage, or damage to other membranes leading to potassium efflux is required to initiate calcium mobilisation and trigger NLRP3 activation.[99–101] NLRP3 then undergoes oligomerisation and attaches to the ASC adaptor protein *via* Pyrin-Pyrin domain interactions.[102,103] As a result, long ASC filaments are generated through self-association.[102,103] Thereafter, inactive monomers of caspase-1 bind to ASC through CARD-CARD interactions.[102,103] One study found that NLRP3 oligomerises before stimulation but this is contrary to all others addressing this issue.[104] Caspase-1 recruitment is essential for inflammasome activation and allows for caspase-1 proximity-induced dimerisation and self-cleavage reactions that convert inactive caspase-1 monomers into active protease dimers.[54]

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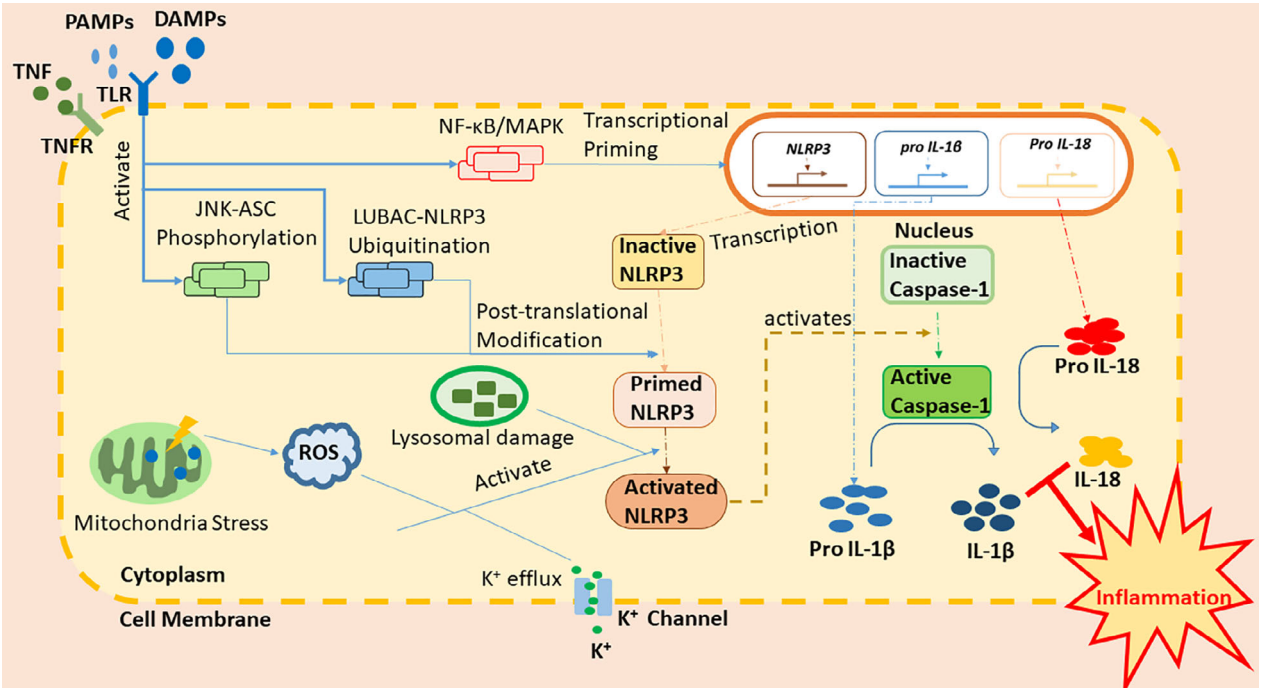

Figure 1. NLRP3 inflammasome signalling cascade. This cascade is separated into three stages, which are transcriptional priming, post-translational modification, and activation. During the transcriptional priming stage, PAMPs or DAMPs bind to TLR or TNF induce the first signal, which subsequently initiates the NF-κB/MAPK signalling pathway that upregulates NLRP3, pro-IL-1β and pro-IL-18. In parallel, the first signal also triggers JNK-mediated ASC phosphorylation and LUBAC-mediated NLRP3 ubiquitination, which are essential for post-translational modification of the NLRP3 receptor. The third activation stage is initiated when there is K^+ efflux, mitochondrial stress or lysosomal damage occurs in the cytoplasm. These events generate another signal that activates the primed NLRP3 receptor, which then initiates NLRP3 inflammasome complex assembly. The inflammasome complex then promotes the conversion of inactive caspase-1 to active caspase-1, which then cleaves pro-IL-1β and pro-IL-18 into active IL-1β and IL-18. Both IL-1β and IL-18 then initiate inflammation. ASC, Apoptosis-associated Speck-like protein containing a CARD; DAMP, Danger-Associated Molecular Pattern; IL-1β, Interleukin 1β; IL-18, Interleukin 18; JNK, c-Jun N-terminal kinase; K^+, Potassium Ion; LUBAC, Linear Ubiquitin Assembly Complex; MAPK, Mitogen-Activated Protein Kinase; NF-kB, Nuclear Factor Kappa-light-chain-enhancer of activated B cell; NLRP3, NLR family pyrin domain containing 3; PAMP, Pathogen-Associated Molecular Pattern; ROS, Reactive Oxygen Species; TLR, Toll-Like Receptor; TNF, Tumor Necrosis Factor; TNFR, TNF Receptor.

Several non-exclusive models are proposed for NLRP3 inflammasome activation. The most common posits that NLRP3 is a sensor for perturbations in cytosolic ion balance. According to this model, NLRP3-activating ionophores and microbial pore-forming toxins (e.g. nigericin, valinomycin, gramicidin, perfringolysin-*O* and streptolysin-*O*) induce potassium efflux and calcium mobilisation in the cell, which serves as an activation signal for NLRP3.[105,106] Chloride channel-mediated chloride efflux is proposed as an alternative pathway to activate NLRP3.[107,108] Inhibition of chloride efflux through volume-regulated anion channels using fenamate suppresses NLRP3 activation.[7]

Emerging literature suggests that mitochondria also play important roles in activating NLRP3. Studies indicate that mitochondria facilitate the assembly of the NLRP3 inflammasome,[109–111] such as *via* the resident mitochondrial anti-viral signalling adaptor protein (MAVS). Subramanian *et al.*[109] reported that MAVS deficiency selectively suppressed macrophage NLRP3 responses to ATP and nigericin but did not affect NLRP3 responses to crystalline compounds such as silica and alum. NLRP3 can also be activated by mitochondrial-derived molecules, such as ROS and mitochondrial DNA.[110,111]

Since NLRP3 signalling is critical in many inflammasome-related disorders, inhibitors offer high therapeutic potential for suppressing NLRP3-induced inflammation. A specific and potent NLRP3 inhibitor (MCC950) was recently developed for the treatment of inflammasome-mediated diseases including CAPS and other complex disorders like type 2 diabetes and atherosclerosis.[112,113] A strong body of evidence also suggests that MCC950 effectively suppresses

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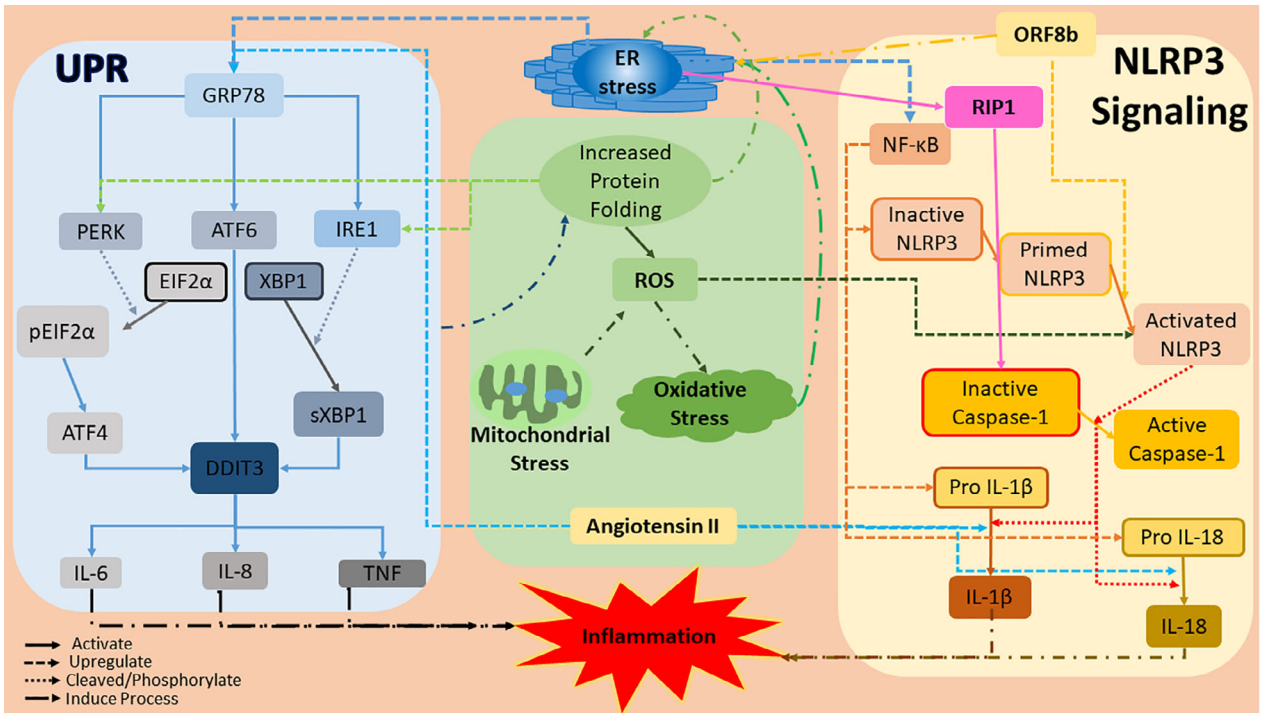

Figure 2. Complex interplay of ER stress and NLRP3 inflammasomes in inflammation. ER stress- and NLRP3 inflammasome-induced inflammation demonstrate strong inter-relationships. They are linked *via* cell stressors such as mitochondrial stress, cytokines, RIP1 and Angiotensin II. Infectious agents, such as SARS-CoV, also induce ER stress/NLRP3 inflammasome-induced inflammation *via* its RNA's open reading frame, ORF8b. ATF4, Activating transcription factor 4; ATF6, Activating Transcription Factor 6; DDIT3, DNA Damage-Inducible Transcript 3; EIF2α, Eukaryotic Initiation Factor 2α; GRP78, Glucose-Regulated Protein 78; IL-1β, Interleukin 1β; IL-6, Interleukin 6; IL-8, Interleukin 8; IL-18, Interleukin 18; IRE1, Inositol-Requiring Enzyme 1; NF-kB, Nuclear Factor Kappa-light-chain-enhancer of activated B cell; NLRP3, NLR family pyrin domain containing 3; PERK, PKR-like ER kinase; pEIF2α, Phosphorylated EIF2α; ORF8b, Open Reading Frame 8b; RIP1, Receptor-Interacting serine/threonine-Protein kinase 1; ROS, Reactive Oxygen Species; sXBP1, spliced XBP1; TNF, Tumor Necrosis Factor; UPR, Unfolded Protein Response; XBP1, X-box Binding Protein 1.

cardiovascular disease,[114] Alzheimer's,[115] non-alcoholic fatty liver disease,[116] Chikungunya,[117] multiple sclerosis[118] and severe steroid-resistant asthma.[5] Interestingly, interferon (IFN) and the nitric oxide synthase-2-mediated NO pathways were shown to inhibit NLRP3 activation and thereby prevent tuberculosis-associated pathology.[119] Mao *et al.*[120] showed that a similar NO-dependent mechanism suppresses NLRP3 activation during LPS challenge to protect against septic shock. Several NLRP3 inhibitors, such as IZD334 and IZD174 are currently in human clinical trials, including clinical trials NCT04086602, NCT04338997 and NCT04015076.[121–123]

ER STRESS, INFLAMMASOMES AND INFLAMMATION

Like inflammasomes, but to a lesser extent, ER stress has been linked to the induction of inflammation, and also now to inflammasome-induced inflammation (Figure 2).

ER stress and inflammation

Several links between ER stress/UPR and inflammation have been proposed.[13,124] Such links are well demonstrated in genetic- and pharmacologically induced hepatic steatosis *in vivo* models.[125] In these models, ER stress induced by tunicamycin challenge in mice caused significant caspase-1-dependent upregulation of UPR (DDIT3, GRP78, and IRE1α) and inflammation (IL-1β) marker expression .[125,126] Tunicamycin-induced hepatic inflammation was suppressed, and steatosis and ER stress-induced hepatocyte cell death and pyroptosis was ameliorated by deletion of caspase-1.[125] Guthrie *et al.*[127] used an ER stress-challenge astrocyte model to show that inhibiting PERK could reduce the expression of

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inflammatory cytokines (e.g. IL-6) and chemokines (e.g. C-C motif chemokine ligand [CCL]2, and CCL20) to suppress inflammation. While complete inhibition of PERK can induce apoptosis and haplo-insufficiency, its partial inhibition relieved ER stress-induced inflammation without impinging on UPR-dependent pro-survival responses showing that these processes are not completely dependent.[127] Collectively, these studies show essential roles for ER stress/UPR during inflammation.

ER stress, inflammasomes and inflammation

Notably, while NLRP3 inflammasome is known to have essential roles, the pathogenic functions of UPR in chronic inflammatory diseases such as those in the lung are also becoming increasingly clear.[13,128–130] Caspase-1 and IL-1β and involved. Thus, it is likely that ongoing chronic ER stress/UPR induces inflammasome activation to drive inflammation in chronic lung and other diseases; however, the mechanisms that underpin these links remain to be elucidated. Many studies have identified roles for ER stress or NLRP3 inflammasome in inflammation pathway, some studies now link ER stress with NLRP3 inflammasome activity and inflammation. Several non-alcoholic fatty liver diseases, ranging from simple steatosis to non-alcoholic steatohepatitis that can lead to hepatocellular carcinoma.[131] Here, there are associations between increased circulating LPS in patients with steatohepatitis that is thought to lead to the induction of ER stress/UPR and consequently NLRP3 inflammasome activation and hepatocyte death.[132] Showing cause and effect, challenge of obese mice with LPS or tunicamycin triggers IRE1α and PERK signalling cascades, leading to DDIT3 overexpression, NLRP3 inflammasome activation and hepatocyte death.[131,132] Furthermore, hepatocytes could be rescued from LPS-induced cell death by treatment with TUDCA, an ambiphilic bile acid capable of relieving ER stress, indicating the therapeutic potential of ER stress inhibitors.[132] Similar links between ER stress, inflammation and NLRP3 inflammasome pathways are also observed in driving chronic pancreatitis. Cerulein-induced acute and chronic pancreatitis in mice is underpinned by increased UPR and NLRP3 inflammasome activation and pro-inflammatory responses.[133] Moreover, treatment with withaferin A, a small molecule inhibitor of NF-κB activity, significantly attenuated all of these cerulein-induced processes, suggesting a close relationship between ER stress-induced inflammasome activation and inflammation in acute and chronic pancreatitis.[133] Collectively, these findings provide strong evidence for the involvement of both ER stress and NLRP3 inflammasome in different disorders.

Although studies have demonstrated the presence of both ER stress and NLRP3 inflammasome in different inflammatory disorders, the mechanism by which ER stress triggers NLRP3 inflammasome function and inflammation is unclear. So far, there are no studies that have directly interrogated the effects of ER stress markers (GRP78, IRE1α, PERK or ATF6α) in the NLRP3 inflammasome signalling cascade. Some studies report that ER stress can alone initiate NF-kB-dependent inflammation *in vitro* and *in vivo,* to promote NLRP3 and IL-1β expression and contribute to inflammasome priming.[134] Bronner *et al*.[135] showed that ER stress activates NLRP3, through a mechanism requiring caspase-2-related mitochondrial dysfunction and ROS. Menu *et al*. showed that ER stress activates NLRP3 inflammasomes independently of a classical UPR, through a mechanism involving ER–mitochondrial interactions.[136] Specifically, they showed that knock down of UPR effectors, PERK, IRE1α and ATF6α did not affect ER stress-induced inflammasome activation, which instead required ROS generation and potassium efflux.[136]

Other studies have suggested that some factors act as essential regulators of both ER stress and NLRP3 inflammasomes during inflammatory responses. One of them is receptor-interacting serine/threonine-protein kinase 1 (RIP1), which was reported to critically regulate ER stress-induced NLRP3 inflammasome activation.[137] Here, ER stress-induced RIP1 phosphorylation, and pharmacological inhibitors of RIP1 activity reduced ER stress-induced caspase-1 cleavage and IL-1β secretion in macrophages.[137] Also, downstream effectors of RIP1, ROS and mitochondria fission factor dynamin-related protein (DRP)1 activate NLRP3 inflammasomes.[137] Angiotensin II administration to human kidney proximal epithelial cells elevated the expression of both UPR (GRP78, phosphorylated EIF2α) and NLRP3 inflammasome signalling (NLRP3, ASC, caspase-1, IL-1β, IL-18) markers that could be suppressed by the angiotensin II antagonist, telmisartan.[138] Collectively these findings suggest

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that some factors may potentially link ER stress with NLRP3 inflammasome activity.

Interestingly, microbial infection may also induce ER stress and NLRP3 inflammasome activation. During *Mycobacterium bovis, Mycobacterium tuberculosis,* and *Treponema pallidum* infection ER stress triggered macrophages to produce mature IL-1β *via* the NLRP3 inflammasome cascade.[139–141] Similar events were also observed in severe acute respiratory syndrome (SARS) – coronavirus (SARS-CoV) infection.[142] In that study, a SARS-CoV accessory protein, open reading frame 8b (ORF8b), was shown to interact with NLRP3 and induce inflammasome signalling.[142] Accumulation of ORF8b can also induce ER stress, and subsequently cause autophagy and lysosomal damage *via* transcription factor EB.[142] SARS-CoV viroporin 3a also activates the NLRP3 inflammasome to trigger the production of IL-1β production in LPS-primed macrophages.[143] It is currently unclear whether SARS-CoV-2, the causative agent of COVID-19, is similarly able to directly activate the NLRP3 inflammasome, but this seems likely, given their genetic similarity and conserved ORF8b and viroporin 3a proteins.[73,144,145] Indeed, patients with severe COVID-19 show evidence of an excessive inflammatory response, including increased circulating inflammatory cytokines such as IL-1β, IL-2, IL-6, IL-7, IFN-γ, IP-10 and TNF.[73,146,147] These patients also experience significant lung inflammation and acute lung injury, often resulting in acute respiratory distress syndrome (ARDS) and the need for mechanical ventilation.[73,148,149] Importantly, NLRP3 inflammasome signalling drives acute lung injury and ARDS, suggesting that NLRP3 may be responsible for lung damage in severe COVID-19.[150] Nevertheless, further studies are required to understand whether and how such ER stress-induced inflammasome activation pathways are initiated by specific types of microbial infections.

THERAPEUTIC STRATEGIES TO AMELIORATE ER STRESS AND INFLAMMASOME-INDUCED INFLAMMATION

Various phytochemicals extracted from traditional medicinal plants as are increasingly being pursued as potential therapies for treating inflammation induced by ER stress and the inflammasome. For example, Momordica charantia, which also known as bitter melon, is traditionally used as medicine in relieve colitis, which strongly linked with ER stress and inflammation.[14,151] Puerarin, an active compound of Kudzu root, which is a widely used functional food in treating ARMD in China, was reported to relieve ER stress and the exacerbation of NLRP3-activated inflammation.[49] It suppressed amyloid β-induced ER stress, lipid peroxidation, and NLRP3 inflammasome activation in LPS-primed ARPE cells in a dose-dependent manner. The anti-inflammatory effects were exerted by activating the nuclear factor (erythroid-derived 2) like (NRF)2 antioxidant pathway, as well as attenuating IRE1 and PERK phosphorylation and ATF6 nuclear expression. Mangiferin, a natural polyphenol with a C-glycoxylxanthone structure from mangos (*Mangifera indica*), also possesses potential therapeutic benefit for treating ER stress and inflammasome-induced disease. Mangiferin inhibited ER stress in saturated fatty acid palmitate-challenged mice, and suppressed the expression of NLRP3, caspase-1 and IL-1β.[152] A phytochemical gastrodin was isolated from a native herb (*Gastrodia elata*) that is widely used for treating pain-relief and may have therapeutic potential for suppressing ER stress and NLRP3 inflammasome activity.[153] Gastrodin administration in mice with streptozodin-induced diabetes mellitus significantly reduced the expression of ER stress markers (e.g. PERK, GRP78, DDIT3) and NLRP3 inflammasome pathway components (e.g. NLRP3, ASC, IL-1β).[153] Collectively, the data suggest that phytochemicals may hold therapeutic potential for ameliorating inflammation induced by ER stress and the NLRP3 inflammasome.

Interestingly, several endogenous factors in humans may offer therapeutic potential for ameliorating ER stress and inflammasome-induced inflammation. β-hydroxybutyrate is a ketone body produced by the liver, that is utilised by the brain, muscle, and heart as an energy source under hypoglycaemic conditions.[154] β-hydroxybutyrate suppressed both and ER stress (IRE1, PERK, ATF6) and inflammasome activity *in vitro* (HEPG2 human hepatoma cell line) and *in vivo* (Sprague Dawley rats).[154] Ghrelin is another endogenous factor proposed to be a potential inhibitor of ER stress-dependent NLRP3 inflammasome-induced inflammation.[155] It is a brain protein that binds to the growth hormone secretagogue receptor and upregulates growth hormone production; hence, it plays essential roles in cell growth and

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development.[155] Ghrelin induction reduced the expression of ER stress components, including DDIT3, ATF4, IRE1α, GRP78, PERK and phosphorylated EIF2α, and of NLRP3 inflammasome-induced inflammatory responses, such as caspase-1, NLRP3, IL-1β and IL-18 in unilateral ureteral obstruction-induced renal fibrosis mouse models.[155] Collectively, these results provide evidence that ghrelin is a potential therapy in treating ER stress- and NLRP3-inflammasome-related inflammation.

The artificial chemical chaperone 4PBA was also shown to suppress ER stress and NLRP3 inflammasome-induced inflammation. It interacts with the hydrophobic domain of misfolded proteins to prevent their aggregation and thereby suppress ER stress.[156] Wang *et al*.[138] revealed that cells pre-treated with 4PBA exhibited significantly reduced expression of inflammasome markers, including NLRP3, ASC, caspase-1, IL-1β and IL-18, during angiotensin II-induced inflammation. Thus, 4PBA could also be a viable therapeutic option for ER stress and inflammasome-induced inflammation.

CONCLUSIONS

ER stress has a strong causative relationship with inflammasome-mediated inflammation. There is growing evidence for the significant roles of ER stress and inflammasomes in the pathogenesis of inflammatory diseases. Targeting ER stress or the NLRP3 inflammasome may pave the way for the development of novel and effective therapies for inflammatory diseases, as well as enhancing the efficacy of current agents for improved disease management.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Wai Chin Chong: Conceptualization; Writing-original draft; Writing-review & editing. **Madhur D Shastri:** Conceptualization; Writing-original draft; Writing-review & editing. **Gregory M Peterson:** Writing-review & editing. **Rahul P Patel:** Writing-review & editing. **Prabuddha S Pathinayake:** Writing-review & editing. **Kamal Dua:** Writing-review & editing. **Nicole G Hansbro:** Writing-review & editing. **Alan C Hsu:** Writing-review & editing. **Peter A Wark:** Writing-review & editing. **Shakti Dhar Shukla:** Writing-review & editing. **Matt D Johansen:** Writing-review & editing. **Kate Schroder:** Writing-review & editing. **Philip Hansbro:** Writing-review & editing, Funded the APC charges.

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