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Review

Cellular stress response and innate immune signaling: integrating pathways in host defense and inflammation

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ABSTRACT

Extensive research in the past decade has identified innate immune recognition receptors and intracellular signaling pathways that culminate in inflammatory responses. Besides its role in cytoprotection, the importance of cell stress in inflammation and host defense against pathogens is emerging. Recent studies have shown that proteins in cellular stress responses, including the heat shock response, ER stress response, and DNA damage response, interact with and regulate signaling intermediates involved in the activation of innate and adaptive immune responses. The effect of such regulation by cell stress proteins may dictate the inflammatory profile of the immune response during infection and disease. In this review, we describe the regulation of innate immune cell activation by cell stress pathways, present detailed descriptions of the types of stress response proteins and their crosstalk with immune signaling intermediates that are essential in host defense, and illustrate the relevance of these interactions in diseases characteristic of aberrant immune responses, such as chronic inflammatory diseases, autoimmune disorders, and cancer. Understanding the crosstalk between cellular stress proteins and immune signaling may have translational implications for designing more effective regimens to treat immune disorders. ***J. Leukoc. Biol.*** **94: 000–000; 2013.**

Abbreviations: Aire=autoimmune regulator; ASC=apoptosis-associated speck-like protein containing a caspase recruitment domain; ATF=activating transcription factor; ATM=ataxia telangiectasia-mutated; ATR=ATM and Rad-3-related; ATRIP=ATR-interacting protein; CHOP=C/EBP homologous protein; cIAP=complementary inhibitor of apoptotic protein; CREBH=hepatocyte specific CREB; DAMPs=damage associated molecular patterns; DDR=DNA damage response; DNA-PKcs=catalytic subunit of DNA-PK; DNA-PK=DNA-dependent protein kinase; DSB=double-strand breaks; EAE=experimental autoimmune encephalitis; eIF2α=eukaryotic translation initiation factor; ER=endoplasmic reticulum; ERAD=ER-associated degradation pathway; ERSE=ER stress element; ETC=electron transport chain; FADD=Fas-associated protein with death domain; Gr=granzyme; HMGB1=high-mobility group box 1; HR=homologous recombination; HSF=heat shock factor; Hsp=heat shock protein; IKK=IκB kinase; IPS=IFNβ promoter stimulator; IRAK=IL-1R associated kinase; IRE1=inositol-requiring kinase 1; IRF=IFN regulatory factor; KAP-1=Kruppel-associated box (KRAB)-associated protein 1; LGP2=laboratory of genetics and physiology 2; MAVS=mitochondrial antiviral signaling adaptor; MDA5=melanoma differentiation associated gene 5; MKK=MAP kinase kinase; MRN=Mre11 nuclease, Rad50 coiled-coil protein, and Nbs1 regulator protein; mTOR=mammalian target of rapamycin; NAP=NAK-associated protein 1; Nbs=nucleotide-binding site; NEMO=NF-kappa-B essential modulator; NHEJ=nonhomologous end-joining; NKG2D=natural-killer group 2, member D; NLR=nod-like receptor; NLRP=nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain—containing polymerase; PERK=PKR-like ER kinase; PES=pifithrin-μ; PRRs=pattern recognition receptors; RIP1=receptor-interacting protein 1; RLR=RIG-I-like receptors; ROS/RNS=reactive oxygen and nitrogen species; Ro52=ribonucleoprotein 52 kDa; RPA=replication protein A; SAPK=stress-activated protein kinase; sHsp=small Hsp; SLE=systemic lupus erythematosus; SSB=single-strand breaks; SWI/SNF=switch/sucrose nonfermentable; sXBP=spliced X-box binding protein; TAB=TAK-1 binding proteins; TAK1=TGF-β activated kinase 1; TANK=TRAF-associated NF-κB activator; TBK1=TANK-binding kinase 1; TERS=transmissible ER stress; TIR=Toll/IL-1R; Tpl2=tumor progression locus 2 kinase; TRAF6=TNF receptor-associated factor 6; TRAM=TRIF-related adaptor molecule; Tregs=regulatory T cells; TRIF=Toll/IL-1 receptor domain-containing adaptor inducing IFN-β; UPR=unfolded protein response; XBP1=X-box binding protein 1

The innate and adaptive immune system defends the body against a multitude of pathogens and infections. The first line of the host defense is provided by the innate immune system and comprises cell types such as macrophages, DCs, and NK cells that express PRRs, including TLRs, NLRs, and RLRs, on their cell surface, which can recognize PAMPs on bacterial and viral pathogens [1, 2]. Upon recognition of PAMPs by PRRs, distinct signaling pathways are initiated, culminating in induction of inflammatory mediators including proinflammatory cytokines and chemokines and type I and II IFNs, essential in host defense. Recruitment and activation of adaptive immune cells including T and B cells by these chemokines and cytokines, results in inflammation, elimination of pathogens, and clearance of infection [3, 4]. Increasing evidence suggests a link between the cellular redox state, stress proteins, and immune activation. The fundamental role of PRRs in host defense and their regulation by cellular stress pathways, often activated in infections and chronic diseases, raise interest in

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the crosstalk between these pathways as targets for clinical applications.

Cellular stress responses, originally identified as survival mechanisms activated by cells in response to stressful stimuli, can be classified as the oxidative stress response, heat shock response, UPR, and DDR, depending on the type of stress [5]. Although key proteins in these stress pathways have been extensively characterized in cytoprotection, their crosstalk with innate immune signaling pathways and their role in the regulation of host defense are less clear. Understanding the function of these stress proteins in innate immune defenses, particularly in a setting of disease or infection, may provide a better understanding of disease pathogenesis and present novel targets for manipulation of immune responses in therapeutic treatments. The goal of this review is to illustrate the crosstalk between the major players in innate immune signaling pathways and cellular stress response pathways and to describe the clinical relevance of this crosstalk in translational therapeutic strategies.

We will first describe the TLR, NLR, and RLR signaling pathways and the cytokine and chemokine mediators involved in host innate immune defenses. Then, we will enumerate the major proteins involved in each of the stress responses and their crosstalk with the immune signaling pathways and describe the importance of this crosstalk in the context of infection and immune and inflammatory disorders.

INNATE IMMUNE RESPONSES DURING INFECTION AND INFLAMMATION

The innate immune system provides the first line of host defense against bacterial or viral infection and disease. The recognition of pathogens by PRRs induces activation of specific signaling pathways in innate immune cells. Downstream signaling causes the secretion of microbicidal effectors and inflammatory mediators, resulting in a protective response against the pathogen. This innate immune response, comprising the various cell types, PRR signaling pathways, and inflammatory cytokines, is reviewed below.

Cells involved in innate immune responses

Mast cells, neutrophils, monocytes, macrophages, DCs, and NK cells [6] are all involved in innate immune responses. Each of these cell subsets mounts specific responses and performs distinct functions for the induction of inflammation during the clearance of an infection. One of the mechanisms used by the immune cells for the clearance of pathogens is oxidative stress caused by production of ROS and RNS [7]. Neutrophils are the most abundant innate immune effector cells and are recruited rapidly to the site of infection and inflammation. They eliminate pathogens by phagocytosis or release of granules containing oxidizing agents such as NADPH oxidase, which can generate superoxide and other free oxygen radicals, resulting in oxidative stress. ROS and RNS produced by neutrophils serve dual functions: they act as potent antimicrobial agents that facilitate microbial killing by activating signaling pathways involved in inflammatory and immune responses, and they disrupt homeostasis. Disruption of the equilibrium between microbial pathogens and neutrophils results in a proinflammatory cascade induced by ROS-mediated TLR activation [8]. Thus, the redox state of neutrophils can shift the balance and generate a hyperinflammatory state. Nonphagocytic NK cells kill infected cells by the release of pore-forming proteins called perforins and proteolytic enzymes called granzymes. The NK cells monitor and recognize infected host cells by their low surface expression of the self protein MHC I. Host cells expressing peptide derived from the stress protein Hsp60, which is bound to MHC I, have also been shown to activate NK cells, suggesting a mechanism for recognition and killing of stressed cells by NK cells mediated by Hsps [9].

The most prominent cells of the innate immune system are the monocytes, macrophages, and DCs, which recognize PAMPs through PRRs, such as TLRs, NLRs, and RLRs, and can engulf and phagocytose pathogens directly to degrade them intracellularly. Similar to neutrophils, these phagocytes subject the endocytosed pathogen to lysosomal digestion by enzymes and ROS and RNS production by NADPH oxidase and NO synthase [7]. The combination of ROS superoxide and RNS NO forms peroxynitrite, which is extremely bactericidal and toxic, thus enabling pathogen killing. Macrophages also work though TLR-induced mitochondrial ROS for clearance of bacteria [10]. In addition, macrophages and dendritic cells play an important role as APCs, wherein they present antigens or peptides from the intracellularly degraded pathogenic proteins on their cell surfaces to adaptive immune cells, such as T and B cells. Although ROS mediates pathogen killing, oxidative stress can impair intracellular events, such as antigen processing and generation of peptides [11, 12]. Experimental data on the effect of ER stress on antigen presentation by macrophages has been contradictory. Increased degradation of cytosolic proteins has been shown to increase MHC I-bound antigen presentation, whereas in other cases, ER stress seems to impair antigen presentation by macrophages affecting subsequent T-cell activation, suggesting a mechanism of immune evasion via the ER stress response [13–15]. In the setting of an infection, recognition of pathogenic antigen on APCs in the presence of costimulatory molecules activates T and B cells and thus initiates an adaptive immune response to maintain the host defense. Thus, the APCs bridge the gap between innate and adaptive immunity by initial recognition of the pathogen, which is critical for appropriate immune responses.

PRR signaling pathways in innate immune cells

Innate immune cells recognize broad groups of pathogens, such as bacteria and viruses, through components that are conserved within each group. The different groups of PRRs, including the TLRs, the cytoplasmic NLRs and RLRs, recognize a large variety of PAMPs and thus enable responses to a broad spectrum of pathogens.

Toll-like receptors. Of these PPRs, the TLRs and their downstream signaling pathways have been the most extensively studied [16–21] (**Figs. 1** and **2**). The TLR is a membrane-spanning receptor consisting of an extracellular domain containing leucine-rich repeats and a cytoplasmic signaling Toll/IL-1R (TIR) domain. To date, 11 TLRs have been identified, and TLR1 to

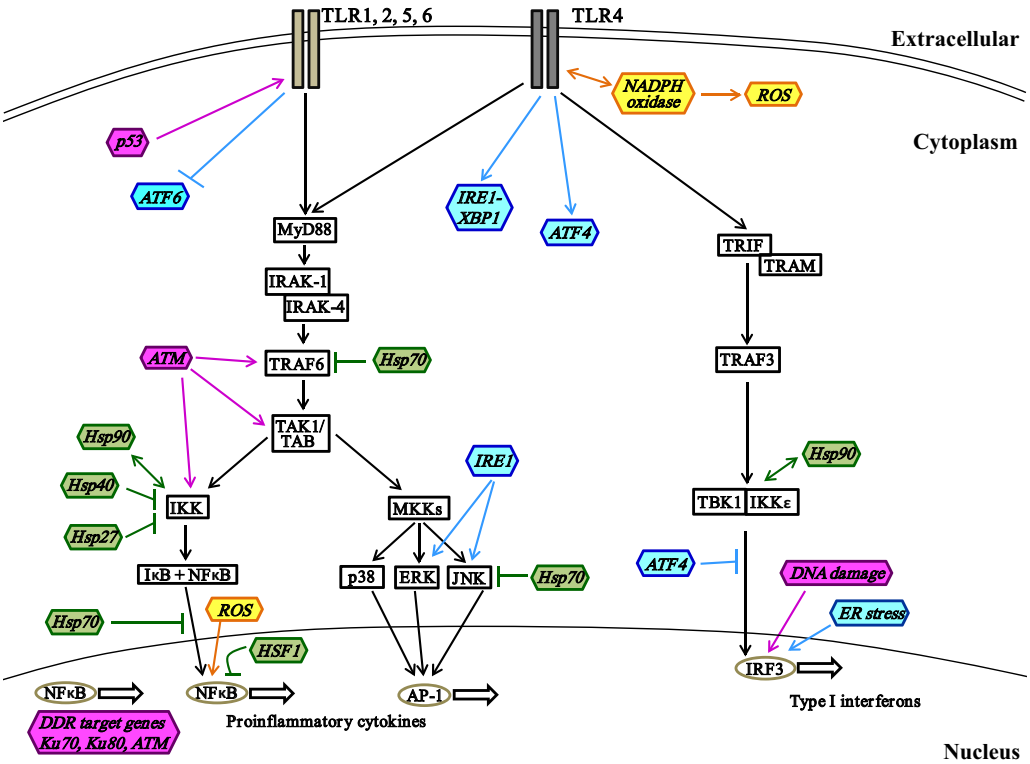

Figure 1. Interactions of stress proteins and cell surface TLR signaling pathways. Engagement of cell surface TLR1, -2, -4, -5, or -6 initiates the MyD88-dependent signaling pathway, which results in activation of the downstream IKK and MKK signaling branches. Each of these branches induces expression of proinflammatory cytokines such as TNFα, IL-6, and IL-1β by the transcription factors NF-κB and AP-1. The TRIF-dependent signaling branch downstream of TLR4 results in expression of type I IFNs mediated by IRF3. The regulatory roles of stress proteins important in oxidative stress (yellow), heat shock response (green), UPR (blue), and DDR (pink) in these TLR signaling pathways are illustrated. $\rightarrow$, stimulation; $\leftrightarrow$, direct interaction; $\dashv$, inhibition.

-10 have been characterized in humans. TLR1, -2, -4, -5, and -6, which recognize bacterial components, such as lipopeptides, LPS, and flagellin, are expressed on the cell surface, and TLR3, -7/8, and -9, which recognize viral double-stranded DNA, single-stranded RNA, and CpG DNA, respectively, are endosomal. In addition to bacterial and viral ligands, TLRs are activated by DAMPs, which are endogenous or exogenous molecules released by cells during stress [22, 23]. For example,

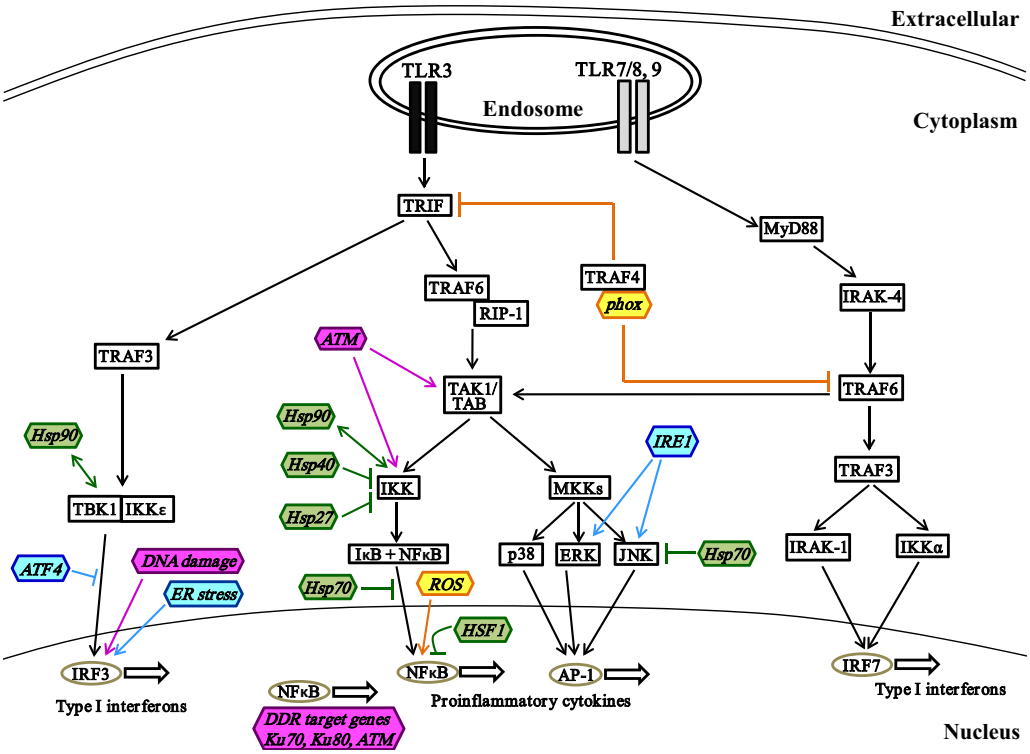

Figure 2. Interactions of stress proteins and endosomal TLR signaling pathways. Endosomal TLR7/8 or -9 activation induces the expression of type I IFNs such as IFNα and -β via MyD88-dependent activation of IRF7, in addition to NF-κB- and AP-1-induced proinflammatory cytokines. The TRIF-dependent signaling branch downstream of TLR3 results in expression of type I IFNs mediated by IRF3. The regulatory roles of stress proteins important in oxidative stress (yellow), heat shock response (green), UPR (blue), and DDR (pink) in these TLR signaling pathways are illustrated. $\rightarrow$, stimulation; $\leftrightarrow$, direct interaction; $\dashv$, inhibition.

Hsps are DAMPs that can bind to TLR2 and -4 to upregulate the expression of costimulatory molecules and induce release of cytokines [24]. TLR engagement by ligands can result in the activation of NADPH oxidase and production of ROS in neutrophils and macrophages [25–27]. ROS, in turn, mediate release of other DAMPs and promote sterile inflammation [28]. For example, ROS-induced oxidation of extracellular matrix proteins also generates DAMPs such as heparan sulfate [29]. TLR4-induced ROS-mediated release of the DAMP HMGB1 protein has been found in liver [30].

TLRs can be classified based on cellular localization, which correlates with the ligands recognized, as cell surface (membrane-bound) (Fig. 1) and endosomal (Fig. 2). TLR signaling is divided into two distinct intracellular pathways: the MyD88 dependent pathway, which is used by all TLRs except TLR3, and the MyD88-independent pathway, which is downstream of TLR3 and -4 [16, 19].

Membrane-bound TLRs. Upon recognition of the appropriate PAMP or DAMP, cell surface TLR dimerization occurs, and downstream signaling pathways are activated (Fig. 1). In the MyD88-dependent pathway, TLR activation results in recruitment of MyD88 to the receptor via the TIR domain. MyD88 in turn recruits and activates IRAK-4 and -1 through its death domain. The IRAKs can then phosphorylate and activate TRAF6, which in turn activates a complex containing TAK1 and TAB-1, -2, and -3 [31–33]. This complex triggers the activation of two signaling branches: the NF-κB pathway and the MAPK pathway [34]. The TAK1 complex phosphorylates and activates the IKK complex, which comprises IKKα, IKKβ, and NEMO [31]. The transcription factor NF-κB, sequestered in the cytoplasm by inhibitory IκB, is released and translocated to the nucleus for subsequent activation of gene transcription as a result of phosphorylation of IκB by IKK [35–38]. The MAPK signaling pathway is triggered by the activation of MKK3/6 and -4/7 (by TAK1) and of MEK1/2 (by Tpl2 kinase downstream of IKK), which phosphorylate downstream molecules such as p38, JNK, and ERK—MAPKs that activate the transcription factor AP-1 [39, 40]. The transcription factors NF-κB and AP-1 promote expression of proinflammatory cytokine genes, such as *TNFα*, *IL-6*, and *IL-1β*, and chemokines, such as *IL-8*, *MCP-1*, and *MIP-1α* [41–43]. TLR4 activation can also induce signaling via the MyD88-independent pathway by recruitment of the adaptor molecule TRIF to the TIR domain (Fig. 1) [44]. TLR4 must have the additional adaptor molecule TRAM for the activation of MyD88-independent signaling, which results in induction of the cytokines and chemokines responsible for viral clearance, such as type I IFNs and RANTES [45]. The MyD88-independent signaling pathway, which is also downstream of endosomal TLR3, is more fully described in the following section. Of note, TLR signaling intermediates have been shown to interact with oxidative-stress–mediated pathways. For instance, in phagocytic cells, TLR4 directly interacts with Nox4, an NADPH oxidase family member, and results in induction of ROS production and oxidative stress, culminating in NF-κB activation [46–49]. NADPH oxidase subunit $p47^{phox}$ can also promote TLR4 expression and trafficking in vascular muscle cells and macrophages [50–52]. ROS also contribute to TLR4-mediated calcium mobilization and calmodulin kinase in monocytic cells [30, 53]. Engagement of TLR2 and -4 activates the ER stress response proteins IRE1α and XBP1 (detailed in the unfolded protein response section), which is necessary for optimal production of inflammatory cytokines by macrophages [54]. Furthermore, MAPKs, including JNK and p38 (also termed SAPKs), are activated downstream of physiological stress including oxidative stress, heat shock, and ER stress in macrophages and fibroblasts [55–58].

Endosomal TLRs. Activation of viral endosomal TLRs such as TLR7/8 and -9 leads to induction of proinflammatory cytokines via MyD88-dependent NF-κB activation and also type I IFNs via IRF-7 activation, (Fig. 2) [59, 60]. Recruitment of the adaptor MyD88 to the TLR results in activation of IRAK-4 and TRAF6 [45, 60, 61], leading to activation of TRAF3 and subsequent phosphorylation and activation of IKKα and IRAK-1. The transcription factor IRF-7 is phosphorylated by IRAK1 and IKKα, leading to its translocation to the nucleus and induction of type I IFNs, such as IFNα and -β which are necessary for elimination of viral infection [45, 60, 61]. Finally, the MyD88-independent pathway downstream of another endosomal receptor, TLR3, involves the adaptor molecule TRIF, which is recruited to the TIR domain (Fig. 2) [44]. TRIF induces activation of TRAF6 and subsequent downstream NF-κB DNA binding activity [62]. TRIF also mediates activation of TRAF3 and leads to the activation of the noncanonical IKKs TBK1 and IKKε, which phosphorylate and activate IRF3, leading to nuclear translocation and transcription of chemokines such as *RANTES* and type I IFNs, such as *IFNβ* [63, 64]. These inflammatory mediators play an important role in the clearance of viral infection. It should be noted that viral infections induce rapid generation of ROS which potentiate activation of downstream TLR signaling in macrophages [65]. ER stress induced by viruses also augments IRF3-mediated production of type I IFN downstream of TLR activation [66, 67]. Cellular oxidative stress can also enhance TLR3 mediated NF-κB in airway epithelial cells, probably by enhancement of TLR3 expression [68]. Modulation of these stress-mediated effects on TLR signaling may be a therapeutic target in viral-induced exacerbations of diseases, including chronic obstructive pulmonary disease.

Cytoplasmic PRRs. In addition to TLRs, cytoplasmic PRRs play a central role in pathogen recognition and activation of immune responses (**Fig. 3**). These include the RLRs RIG-I, MDA5, and LGP2, which are RNA helicases activated by viruses [69]. Upon recognition of double-stranded viral RNA, the RLRs bind to the adaptor protein IPS1 (also known as MAVS and Cardif), which activates IRF3 and -7 through TRAF3, NAP1, and IKKε/TBK1 [70, 71]. NADPH oxidase and ROS are essential for this RLR-mediated induction of type I IFNs [72]. Interaction of IPS-1 with FADD and RIP1 also results in NF-κB activation [70, 71].

The other group of cytoplasmic PRRs are the NLRs, including Nod1 and -2, which recognize bacterial peptidoglycan constituents and activate the MAPK and NF-κB signaling pathways via interacting protein RIP2 [73]. NADPH oxidase-induced ROS are effectors of Nod2-mediated antibacterial responses [74]. NLRPs are another subfamily of NLRs that recognize bacterial DNA, toxins, and double-stranded RNA [75]. Upon

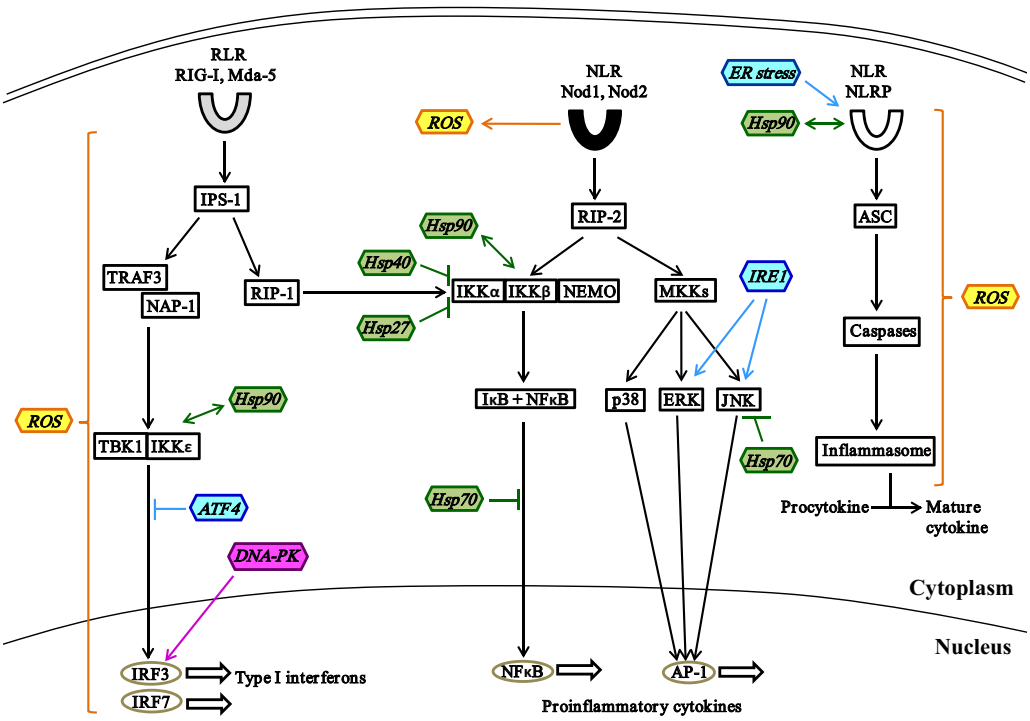

Figure 3. Stress proteins in crosstalk with cytoplasmic PRR signaling. Activation of cytoplasmic RLRs by viral RNA leads to IRF3- and -7-mediated induction of type I IFNs via the IPS-1–TRAF3–TBK1 pathway. DNA-PK, a DDR protein, can also act as a cytoplasmic PRR to induce expression of type I IFNs. IPS-1-activated RIP-1 also induces the expression of proinflammatory cytokines by activating the NF-κB pathway. The recognition of bacterial peptidoglycans by the NLRs Nod1 and -2 upregulates the expression of proinflammatory cytokines via activation of NF-κB and MKK pathways. Cytoplasmic NLRPs induce activation of inflammasomes via ASC and caspases and is essential for processing of procytokines into their active forms. The crosstalk of stress proteins generated by oxidative stress (yellow), heat shock response (green), UPR (blue), DDR (pink) and cytoplasmic PRR signaling is illustrated. →, stimulation; ↔, direct interaction; ⊣, inhibition.

ligand recognition, NLRPs associate with adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (i.e., ASC) resulting in activation of caspases that can cleave procytokines into the active form. Mitochondrial ROS are crucial for activation of the NLRP inflammasome, which in turn plays a major role in the production by monocytes of the proinflammatory cytokine IL-1β [76, 77]. This ROS-mediated activation of the NLRP inflammasome is facilitated by thioredoxin-interacting protein [78]. ER stress also induces NLRP inflammasome activation independent of the UPR pathway in monocytes [79]. Certain NLRPs interact with stress-mediated Hsp90 chaperones, to maintain their correctly folded, signal-receptive state [80]. Thus, it is likely that cellular stress proteins and the PRR signaling molecules interact directly and are necessary for host defense. Activation of PRR signaling pathways ultimately results in the expression of different cytokines that play specific roles in pathogen clearance and host defense.

Cytokines involved in inflammation and clearance of infections

Proinflammatory cytokines, such as TNFα, IL-6, and IL-1β, are induced downstream of PRR activation during bacterial and viral infections. These effector molecules facilitate an inflammatory response to clear infections. Cytokines can induce the production of oxidants, prostaglandins, and mitochondrial ROS by macrophages, thus contributing to inflammatory responses [81]. TNFα stimulates ROS-mediated phagocytosis in macrophages, allowing internalization and destruction of bacteria [82]. TNFα and IL-6 also promote the acute-phase response in the liver, leading to upregulation of proteins such as C-reactive protein, which can promote opsonization of microbes and activate the complement system to clear pathogens. On the other hand, TNFα promotes a proapoptotic profile in macrophages by blocking the heat shock stress response, thus increasing the cell's susceptibility to heat-induced apoptosis [83]. Similarly, IL-1β induces inflammatory and proapoptotic responses mediated by factors such as prostaglandins, ROS, inducible NO synthase, and NO [84–86]. IL-1β also promotes T-cell activation and proliferation, B-cell maturation, and T-cell-dependent antibody production by B cells, thereby initiating an adaptive immune response to the pathogens [87–90]. The heterodimeric proinflammatory cytokine IL-12, produced by stimulation of TLR in innate immune cells, induces production of IFNγ by NK and T cells and also enhances their cytolytic activity [91]. IL-12 plays a role in Th cell differentiation into Th1 cells, which promotes cell-mediated immunity [91]. Production of IL-12 by monocyte-derived DCs upon stimulation of TLR is enhanced by induction of the heat shock stress response [92]. Notably, proinflammatory cytokines can directly cooperate with stress-mediated proteins and contribute to the clearance of bacterial infection by both innate and adaptive immune cells.

Besides proinflammatory cytokines, PRR recognition of viral components induces the type I interferons IFNα and -β. The release of interferons such as IFNβ alerts the neighboring cells to the presence of viral particles in the environment, inducing cell-intrinsic mechanisms to inhibit, or interfere with, viral replication at every stage [93, 94]. For example, induction of 2′–5′ oligoadenylate synthase by IFN activates the nuclease RNase L which can degrade viral RNA [95]. Furthermore Mx GTPase, induced by IFNs, captures viral nucleocapsid proteins

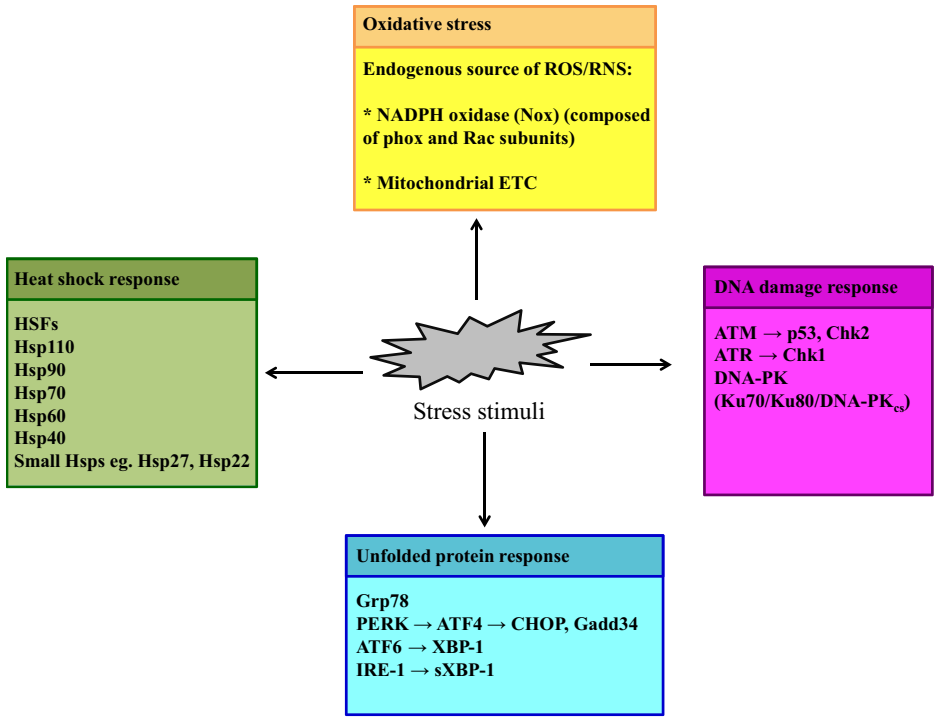

Figure 4. Cellular stress responses. Exposure to stress stimuli (e.g., bacteria, viruses, radiation, and environmental toxins) induces cytoprotective responses that restore cellular homeostasis. Oxidative stress (yellow) is an example of stress that is a result of an oxidant–antioxidant imbalance in cells. The stress responses are categorized into heat shock response (green), UPR (blue), and DDR (pink). The major proteins or molecules responsible for mediating these stresses and stress responses and that play a pivotal role in innate immune signaling are enumerated.

in the cytoplasm, thereby blocking viral assembly [96]. Another effect of IFNs is the upregulation of MHC molecules on cells, making them an easy target for recognition by T cells [97]. Expression of IFNβ downstream of TLR activation is enhanced by induction of ER stress [67]. IFNs also induce production of ROS and sensitize the fibroblasts to apoptosis upon subsequent viral exposure, to prevent spread of infection [98, 99]. Stress-mediated regulation of cytokine responses can play a complementary role in host defense to bacterial or viral infections. Additional studies are needed to further understand the precise interactions between stress proteins and PRRs and their signaling intermediates and their clinical relevance.

CELL STRESS RESPONSES IN IMMUNE SIGNALING

Sudden and substantial changes in the environment of an organism (stress) cause the organism to mount specific cytoprotective responses for survival, including those at the cellular level [5]. For example, via increased ROS/RNS, infectious agents, radiation, and environmental toxins can induce oxidative stress that is countered by antioxidant defense mechanisms. The heat shock response confers thermotolerance during exposure to high heat by preventing denaturation of proteins and facilitating the refolding of already denatured proteins in the heat-exposed cells, thus preventing cellular apoptosis. In this section, we elaborate on the major intracellular stress response pathways, such as the oxidative stress response, the heat shock response, UPR, and DDR, which are critical for crosstalk with the immune PRR signaling pathways (**Fig. 4**). The stress protein interactions with PRR pathways regulate downstream immune responses and play an important role in host defense and inflammation.

ROS and oxidative stress response

Oxidative stress results from an imbalance between the systemic level of oxidants such as ROS/RNS and the body's ability to counter these levels with antioxidants [5, 100]. The ROS, which include superoxide radicals, hydrogen peroxide, and the hydroxyl radical, mediate oxidative stress in addition to RNS such as NO and nitrite. The oxidants are produced endogenously as byproducts or metabolites of various metabolic processes, including aerobic metabolism in mitochondria or reactions mediated by cyclooxygenases, NADPH oxidase, and xanthine oxidase [101]. The endogenous source of cellular ROS is mainly two organelles: the ER and mitochondria. In the ER, the oxidative formation of disulfide bonds during protein folding can result in the accumulation of ROS [102]. The major source of cellular ROS is the mitochondria, as a result of the reduction of molecular oxygen into superoxide ion at the end of the ETC [103, 104]. Chemical agents such as hydrogen peroxide or physical factors such as UV light can also induce production of ROS. When oxidants accumulate, cells mount a stress response for protection against oxidative stress–mediated damage. This includes upregulation of antioxidant proteins, such as glutathione reductase and glutathione peroxidase [103]. In the event of irreparable damage, caspase-mediated apoptotic cell death is induced. The roles of oxidative stress and ROS as mediators of PRR signaling and immune response to bacterial and viral infections and their contribution to inflammation have been described in previous sections (Figs. 1–3).

Heat shock response

The Hsp-mediated cellular defense mechanism in response to heat shock was one of the earliest reported stress responses [105–107]. Hsps, expressed in the cytoplasm, nucleus, ER, and mitochondria of eukaryotic cells, are a class of ATP-dependent molecular chaperone proteins involved in protein folding in response to cellular stress. Hsps are induced by various environmental insults in addition to heat, such as oxidative stress, nutritional deprivation, exposure to toxins, and infectious agents. These cellular insults can cause protein denaturation and unfolding within the cells, leading to formation of unwanted protein aggregates that can eventually kill the cells. Hsps facilitate protein refolding, target misfolded proteins to the proteasome, and stabilize and transport partially folded proteins to different cellular compartments. Thus, Hsps maintain normal cellular homeostasis in response to stress. Heat exposure was originally identified as beneficial to animals by rendering protection from mortality associated with the systemic inflammation induced by sepsis [108, 109]. Subsequent studies have shown that, depending on the extra- or intracellular location and the type of immune cells, Hsps can exert an inflammatory immune activating signal for host defense against infection or an anti-inflammatory immunosuppressive signal to prevent excessive inflammation [110]. The family of Hsps includes the large Hsps (e.g., Hsp110, -90, -70, -60, and -40) and the small Hsps (e.g., Hsp25 and -27) based on their molecular size.

Hsp90. Among the Hsps identified with an immunomodulatory function, Hsp90, -70, and -60 have been extensively studied. The chaperone functions of cell-compartment–specific Hsp90 proteins are predominantly to prevent formation of aggregates of unfolded proteins and to restore stability and function by binding specific client–substrate proteins that are in the late stages of folding. Some client proteins of cytoplasmic Hsp90 that are involved in immune signaling pathways include transcription factors and protein kinases, such as IRF3, IKK, and TBK1 (Figs. 1–3) [111]. Hsp90 plays a regulatory role in the activation or repression of these specific substrate client proteins via direct association or indirect regulation. For instance, activation of the IKK complex requires interaction with Hsp90, whereas noncanonical NF-κB is inhibited by Hsp90-mediated stabilization of the protein Monarch-1, which promotes degradation of NF-κB-inducing kinase in macrophages [112–114]. ER-specific Hsp90, also called gp96, is important for the processing and membrane expression of TLRs, including TLR4, -7, and -9 in macrophages [115]. Hsp90 is also essential for optimal function and activation of NK and T cells [116]. The association of extracellular Hsp90β with peptides leads to receptor-mediated endocytosis of the Hsp–peptide complex and enhances presentation of the peptide by MHC I on DCs [117]. These observations point to a complex pro- or anti-inflammatory role of Hsp90 in immune signaling.

Hsp70. Hsp70 proteins are also implicated in immune responses, and these proteins are also involved in the folding of newly synthesized or stress-denatured proteins, the dissociation of unfolded protein aggregates, and the transport of proteins into different cellular compartments [118, 119]. Of note is the role of extracellular Hsp70 as DAMPs, released after cell death or by active secretion, to activate cell surface receptors on immune cells and induce downstream signaling [120]. Exogenous Hsp70 has been shown to elicit rapid calcium flux, activate NF-κB, and induce the production of inflammatory cytokines and chemokines by monocytes and DCs via the TLR2 and -4 pathways [121]. Extracellular Hsp70 can also associate with peptides and bind to cell surface receptors, such as CD91 and Lox-1, allowing the Hsp–peptide complex to be internalized by endocytosis and thus enhance the cross-presentation of the Hsp-bound peptide by MHC I on DCs [117]. In contrast to these proinflammatory functions, Hsp70 can also dampen the inflammatory response to prevent tissue damage. Heat-shocked macrophages show reduced TNF expression at specific time points that correlate with maximum upregulation of Hsp70 [122]. Overexpression of Hsp70 has been shown to inhibit the LPS-induced production of cytokines such as TNFα and IL-1β by human macrophages [123]. Hsp70 treatment reduces the capacity of DCs to stimulate T cells [124]. The effect of Hsp70 on the NF-κB signaling pathway has been extensively studied over the years: The expression of Hsp70 in macrophages blocks LPS-induced NF-κB activation by binding to TRAF6 and inhibiting its ubiquitination, thus preventing activation of the inflammatory signaling cascade (Figs. 1–3) [125]. Binding of Hsp70 to the NEMO protein impedes formation of the active IKK complex, which in turn inhibits NF-κB activation [126, 127]. Hsp70 expression prevents degradation of IkB and inhibits nuclear translocation of the NF-κB complex, suggesting inactivation of the NF-κB pathway as the mechanism of Hsp70-induced LPS tolerance in macrophages [128, 129]. With regard to the MAPK signaling pathways, Hsp70 can bind to and inhibit JNK activation in fibroblasts [130].

Hsp60. Hsp60, another immunomodulatory stress protein, is expressed in the mitochondria and predominantly plays a role in intracellular protein trafficking, although there is increasing evidence of its expression in the cytoplasm as well. Studies have indicated a possible role for Hsp60 in immune response signaling and have also linked Hsp60 to cancer [131, 132]. On the one hand, Hsp60 can induce a proinflammatory profile by increasing the release of TNFα, IL-12, and other inflammatory cytokines from macrophages mediated by CD14 signaling [133]. On the other hand, treatment of effector T cells with recombinant Hsp60 inhibits activation of NF-κB and production of TNFα in a TLR2-dependent manner, indicating an immunosuppressive role [134]. Stimulation of Tregs with exogenous Hsp60 enhances their immunosuppressive activity on effector T cells in terms of cytokine production and proliferation, and this effect is mediated by TLR2 signaling [135].

Hsp110, Hsp40, and sHsps. Among the other members of the Hsp family, the Hsp110 protein localizes to the nuclear and cytoplasmic compartments in response to hyperthermic exposure [136, 137]. Hsps have adjuvant-like properties, whereby their association with the antigenic peptide elicits a rapid and efficient TLR-mediated immune response to the respective antigen [138]. This phenomenon has been illustrated by the immunization of mice with Hsp110 complexed to melanoma antigen in a model of targeted immunotherapy [139,

140]. Members of the Hsp40 protein family serve as co-chaperones and associate with and activate the ATPase activity of Hsp70 [141, 142]. The DNAJA3 Hsp40 protein family member exerts an anti-inflammatory role via association with IKK and inhibition of its activity, resulting in stabilization of cytoplasmic IκB and inhibition of NF-κB activation, as demonstrated in tumor cells [143]. Among the sHsps, Hsp22 acts as an agonist of TLR4 inducing TNFα and IL-6 by DCs [144]. Hsp27 mediates the interaction between p38 and NF-κB for the induction of proinflammatory mediators during viral infection, and it is also necessary for activation of the TAK1, MKK, and IKK signaling pathways downstream of cytokine stimulation in fibroblasts, illustrating its proinflammatory role [145, 146]. Hsp27 exerts its anti-inflammatory effect by binding to the IKK β subunit and inactivating the IKK complex [147]. Exogenous Hsp27 induces production of the anti-inflammatory cytokine IL-10 from monocytes and promotes differentiation of monocytes into inhibitory DCs [148, 149].

HSFs. The expression of Hsps is regulated by stress-activated transcription factors known as HSFs [150]. There have been reports that illustrate the anti-inflammatory role of HSFs in certain conditions. The expression of the transcription factor HSF1 inhibits transcription of IL-1β in LPS-stimulated monocytes [151]. HSF1 also represses TNFα transcription in macrophages [152]. HSF-1 deficient mice are unable to upregulate expression of Hsp70 and to produce excessive TNF after a single stimulation of LPS, compared with wild-type mice [153]. Heat shock–induced HSF1 has been shown to competitively inhibit binding of NF-κB to target genes in macrophages (Figs. 1 and 2) [154]. These studies illustrate the anti-inflammatory role of HSFs in immune responses. It should also be noted that heat shock stress can directly activate SAPKs such as JNK, which are involved in PRR signaling. Like UV radiation, heat shock response is a potent inducer of JNK activation in fibroblasts, resulting in increased AP-1 activity via different mechanisms [155].

The different inflammatory and anti-inflammatory roles played by the heat shock stress proteins and the crosstalk between Hsps and immune signaling molecules are among the most studied, suggesting that they have a complex immunomodulatory role in host defense (Figs. 1–3). Further studies are needed to highlight the multifaceted role of Hsps in immune signaling pathways. Do Hsps dictate proinflammatory vs. anti-inflammatory responses during bacterial infection, cancer, and autoimmunity? What is the mechanism of action of these Hsps in the immune response? Are their chaperone activity and direct interaction essential? Do they crosstalk with signaling pathways downstream of other immune receptors, such as T-cell receptors? Interaction between Hsp90 and the TCR signaling kinase Zap-70 has been found in T cells, which suggests a role for these stress proteins in adaptive immune signaling pathways, as well [156]. These results could provide information about novel mechanisms of regulation of immune responses and stress-mediated Hsps during infection or disease.

Unfolded protein response

The ER is an important cellular compartment wherein secreted, membrane-bound, or organelle-specific proteins undergo translational modifications and folding. Stress stimuli, such as nutrient deprivation, hypoxia, or viral infection, can perturb this folding process, leading to accumulation of misfolded or unfolded proteins in the ER and activation of the UPR [157, 158]. The UPR is characterized by an increase in the expression of the chaperone proteins Grp78 (also known as BiP) and -94, to aid in protein folding and restore homeostasis. ER stress also mediates leakage of calcium, contributing to ER stress–mediated NF-κB activation [159, 160]. On the other hand, inflammatory cytokines such as TNFα can upregulate ER stress in a ROS-dependent manner [161]. UPR, induced by proinflammatory cytokines such as IL-6 and -1β and also by LPS, can promote further inflammation by cleavage of CREBH in the liver [162]. This cleavage releases an amino terminal fragment that can translocate to the nucleus and activate the transcription of genes such as *C-reactive protein* and *serum amyloid P component*, which play important roles in acute-phase response and in opsonization of microbes for detection by innate immunity. In mammalian cells, UPR is mediated by 3 stress sensors, IRE1, ATF6, and PERK, which sense the protein-folding conditions in the ER and transduce the appropriate signals to initiate transcription of UPR target genes [157, 158]. Upon initiation of UPR, Grp78 is sequestered by unfolded and misfolded proteins, releasing ATF6, PERK, and IRE1 from its effects. The signaling from these 3 proteins converges in the nucleus to activate transcription of target genes, which can be mediated via the ERSE present in the promoter regions of many UPR target genes in mammals.

PERK. Upon ER stress, activated PERK inhibits eIF2α by phosphorylation at serine 51, which blocks the exchange of GDP for GTP that is necessary for eIF2α activation, resulting in overall inhibition of protein translation. Of note, this global inhibition of protein translation initiated by the PERK-eIF2α pathway can result in activation of NF-κB, thus promoting a proinflammatory immune profile, as is seen in fibroblasts [163]. Phosphorylation of eIF2α leads to increased translation of ATF4, which in turn induces expression of genes such as *CHOP* and *Gadd34* [164]. It has been shown that stimulation of TLR2 or -4 inhibits ER stress-mediated activation of PERK and expression of CHOP in macrophages [54]. ER-stress–induced expression of CHOP in peritoneal macrophages is also inhibited by TLR3 or -4 activation in a TRIF-dependent manner [165]. In contrast, a recent study showed that stimulation of human monocytes by TLR4 directly upregulates expression and nuclear translocation of ATF4, which is dependent on MyD88 and JNK, resulting in production of IL-1β, -6 and -8 and RANTES [166]. However, ATF4 inhibits TBK1/IKKε-mediated phosphorylation and activation of IRF7, thereby suppressing expression of type I IFNs (Figs. 1 and 2) [167]. These observations indicate complex crosstalk in the PERK–eIF2α–ATF4 pathway and innate immune signaling, which merits further study.

ATF6. ATF6, another ER stress sensor, activates transcription of target genes including *XBP1*; chaperone proteins, such as *Grp78*; and components of the ERAD. The ERAD targets misfolded proteins from the ER into the cytosol for proteasomal degradation. The induction of acute-phase response proteins by UPR is mediated by interaction of ATF6 with CREBH, to

induce transcription of the target genes [162]. On the one hand, ER-stress–induced ATF6 mediates transient Akt phosphorylation and NF-κB activation in a short timeframe but subsequently blunts NF-κB activation in the later phase in an Akt-mTOR- and C/EBPβ-dependent manner [168, 169]. On the other hand, TLR2 or -4 inhibits ER-stress–induced ATF6 processing in macrophages (Fig. 1) [54]. Viruses such as human cytomegalovirus and hepatitis C induce and regulate the 3 branches of UPR to potentiate viral replication and viral protein folding and prevent early cellular apoptosis [170–172]. Virus-induced ER stress allows the pathogen to evade antiviral type I IFN responses by ATF6/IRE1-mediated inhibition of signaling downstream of interferons in fibroblasts [173].

IRE1. There are two identified isoforms of IRE1 in mammals: IRE1α and -β [174, 175]. Upon activation, IRE1 endoribonuclease excises the intron from XBP1 mRNA, generating the sXBP1 transcription factor. The role of IRE1/XBP1 in immune responses is evident from several observations. XBP1 and IRE1α are necessary for the development of adaptive immune B cells, specifically antibody-producing, terminally differentiated plasma cells [176, 177]. XBP1-deficient mice exhibit a reduced number of conventional and plasmacytoid DCs, and these cells show reduced survival in response to TLR activation, indicating that XBP1 is necessary for the survival and function of DCs [178]. Macrophages undergoing UPR respond to TLR3 and -4 activation with enhanced IFNβ production, which is dependent on XBP1 splicing (Figs. 1 and 2) [179]. LPS also induces increased production of the inflammatory cytokine IL-23 in macrophages undergoing UPR [180]. Of note, TLR4 by itself has been shown to activate this IRE1/XBP1 axis to produce the inflammatory cytokines TNFα and IL-6 in a TRAF6/NADPH oxidase–dependent manner [54]. Cytosolic IRE1 interacts with adaptor proteins, including TRAF2, resulting in activation of SAPKs/MAPKs, JNK, and p38 in fibroblasts [181, 182]. Therefore IRE1 induces activation of TRAF adaptors, MAPKs, and NF-κB, all components of the inflammatory signaling pathway [183].

The mechanism by which TLR mediates inhibition of PERK and ATF6 branches while activating the IRE1 pathway is unclear and warrants further investigation. Based on the current observations, we speculate that an ER-stressed immune cell retains its inflammatory function when encountering PAMPs, permitting activation of inflammatory signaling molecules via XBP1 and blocking protein degradation and inhibition of protein translation mediated by PERK and ATF6. It should also be noted that TLR directly induces IRE1/XBP1 and ATF4 in monocytes in the absence of UPR, indicating that these stress proteins play a UPR-independent role in TLR-induced inflammation [54, 166]. The crosstalk between the UPR pathways and immune responses is further corroborated by observations that abnormalities in the UPR can adversely affect the immune responses, leading to autoimmunity [184].

DNA damage response

The DDR, another stress-mediated pathway, is triggered to repair DNA lesions induced by environmental genotoxins and chemical agents. The DDR, also referred to as the DNA damage checkpoint pathway, consists of sensors that identify DNA lesions, such as SSBs and DSBs; transducers that convey the signal from the sensors downstream; and effectors that induce cell cycle arrest and initiate DNA repair pathways, such as HR or NHEJ [5, 185, 186]. It should be noted that early studies have reported the induction of immunomodulatory cytokines and altered antigen presentation in response to DNA damage, indicating crosstalk between DDR and immune signaling [187, 188]. This stress pathway plays a role in immune cell detection and killing of damaged cells that may be virally infected as illustrated by the following observations. Activation of the DDR by the arrest of DNA replication or ionizing radiation induces upregulation of cell surface expression of the ligand for activating the NK cell receptor NKG2D, thereby making the stressed cell a target for NK cell–mediated lysis [189]. Induction of DNA damage is also one of the means of ROS-mediated cytotoxicity used by immune cells for the elimination of infected cells [190]. Furthermore, the DDR proteins are necessary for the genetic recombination of antigen receptors and antibodies in adaptive immune T and B cells (called V(D)J recombination). This V(D)J recombination allows wide diversity in these receptors in recognizing antigens of a broad spectrum of pathogens and is mediated by the NHEJ DNA repair pathway [191]. In the event of irreparable and extensive DNA damage, cellular apoptotic pathways are activated by the DDR pathway. The major regulators of the DDR are the primary transducer proteins, ATM, ATR, and DNA-PK, which belong to a family of PI3K-related serine-threonine kinases [185]. Each of these proteins is activated by different kinds of DNA damage and stimulates specific signaling pathways in the DDR.

ATM. Upon detection of DSBs by the sensor MRN complex, ATM is recruited to the site of DNA damage, resulting in its autophosphorylation and activation [192, 193]. ATM-mediated phosphorylation of different substrate proteins such as Chk2 and p53 potentiates DNA repair. Components of the ATM pathway play an important role in adaptive immune cell development and function. ATM-deficient animals display defects in T-cell development, indicating the requirement of this kinase in V(D)J recombination [194]. Nbs-1, the histone protein γ-H2AX, and ATM have been observed to form foci that colocalize to the DSBs introduced during V(D)J recombination [195, 196]. ATM-phosphorylated γ-H2AX serves as a platform for the recruitment of chromatin remodeling complexes, such as SWI/SNF and KAP-1 [192]. Upregulation of SWI/SNF increases expression of transcription factor AP-1, which enhances cytokine production and proliferation of adaptive immune T cells [197]. Treatment of cells with DNA damaging agents also results in the upregulation of expression of TLRs which is directly mediated by p53 [198, 199]. Stress-activated JNK has in turn been shown to play a role in regulating p53 expression in fibroblasts [200, 201]. Induction of DNA damage by genotoxic stress also induces expression of the IFN transcription factor IRF1, but this reaction is inhibited in cells deficient in ATM signaling [202]. IRF1 regulates DNA damage–induced apoptosis, indicating that it plays a functional role in DNA-damaged T cells [203]. Similar observations have been made with IRF3. Treatment of cells with DNA-damaging agents stimulates activation of IRF3 in terms of phosphorylation, nuclear translocation, and transcriptional activity (Figs. 1 and 2)

[204]. Thus, DNA damage–induced ATM regulates expression and promotes activation of key transcription factors in immune signaling, such as IRFs and NF-κB. ATM has been shown to bind and phosphorylate NEMO, the regulatory subunit of IKK, to activate NF-κB downstream of DNA damage [205]. More recently, studies have shown that, in fibroblasts, ATM activates TAK1, which is upstream of IKK in the PRR signaling pathways [206]. ATM has been shown to bind to TRAF6 to induce polyubiquitin synthesis, leading to activation of TAK1 and NEMO by ubiquitination in a cIAP-1–dependent manner [207]. This process requires the activity of another DNA repair protein, PARP-1, and ultimately results in NF-κB activation. Conversely, activation of NF-κB enhances the repair of DNA damage–induced DSBs by homologous recombination, which is mediated by ATM and BRCA1 [208]. DDR genes such as *Ku-70* and *80* (DNA-PK subunits), *ATM*, and *BRCA2* have also been identified as targets for transcription by NF-κB in T cells and tumor cells [209–211]. These observations indicate crosstalk between the ATM DNA damage stress pathway and the inflammatory signaling pathways in innate immune responses.

ATR. In contrast to ATM, ATR is primarily activated and recruited to ssDNA coated with sensor RPA via ATRIP [185, 212]. Stress caused by blocked DNA replication also results in activation of SAPKs, p38, and JNK in fibroblasts that collaborate with Chk1, which is essential in cell cycle progression [213]. Recent data suggest a certain degree of redundancy between the ATM and ATR pathways. Components of the ATR pathway, ATR and Chk1, are necessary for DNA damage–induced upregulation of the NKG2D ligand [189]. A global phosphoproteome analysis of the kinases regulated downstream of the TLR4 ligand also revealed activation of proteins involved in the DDR pathway, including ATM/ATR kinases and Chk1 in LPS-stimulated macrophages [214]. Inhibition of ATM in these TLR-stimulated macrophages enhanced expression of genes, including *CXCL-10* and *IL-10*, suggesting that TLR-induced ATM is a negative regulator of these genes. These findings suggest that ATM/ATR and Chk kinases play a functional role downstream of TLR activation during immune responses.

DNA-PK. DNA-PK, activated by the sensors Ku70 and -80, which bind DSBs, is also linked to immune responses and host defense [215, 216]. Mutations in TLR4 cause a decrease in expression of Ku70 and -80, indicating that PRRs can regulate the expression of these DNA damage stress proteins [217]. Conversely, DNA-PKcs has been found to interact with the transcription factor Aire, to upregulate the expression of TLR-1, -3, and -8 in macrophages [218]. Of particular importance, DNA-PK itself has recently been characterized as a cytoplasmic PRR that activates IRF3 in response to bacterial and viral infections in fibroblasts (Fig. 3) [219, 220]. Recognition of DNA viruses by DNA-PK results in induction of cytokines, including IL-6 and IFNβ, and chemokines, such as CXCL10, in an IRF3- and TBK1-dependent manner [220]. Stimulation of macrophages with CpG DNA (a TLR9 ligand) results in nuclear translocation of Akt in a DNA-PKcs-dependent manner [221]. DNA damage stress-induced DNA-PKcs is implicated in the activation of NF-κB via MEK–ERK–IKK signaling in fibroblasts [222]. In contrast, in an earlier report, DNA-PK phosphorylation of IκB was observed, which increased its association with NF-κB and resulted in the inhibition of NF-κB DNA binding activity in fibroblasts [223].

Overall, components of the DNA damage response and repair clearly play a role in immune signaling, whether it is nuclear proteins, such as ATM and ATR, or DNA-PK, which can colocalize to both nucleus and cytoplasm. The regulation of expression and activation of the DDR proteins by immune activation and vice versa indicates crosstalk between these two pathways. In addition to improving our understanding of the crosstalk between DDR and immunity, these observations identify DDR proteins as likely translational targets that are useful in regulating host immune activation in viral and bacterial infections and in inflammatory diseases.

CLINICAL SIGNIFICANCE OF STRESS RESPONSE IN INFECTION AND IN IMMUNE AND INFLAMMATORY DISORDERS

The functional significance of stress proteins in immune responses and host defense is evident at various levels, ranging from interactions of stress-induced Hsps, which serve as molecular chaperones, with the PRR signaling pathways, to the role of ER stress proteins and DNA damage response mediators in inflammation and signaling. The crosstalk between these stress and immune signaling pathways becomes clinically relevant in host defense against bacterial and viral infections and diseases associated with an abnormal or hyperactive immune response in autoreactive or autoimmune diseases, chronic inflammatory diseases, and cancer (**Fig. 5**). Research pertaining to the analysis of precise interactions between cellular stress pathways and innate immune signaling in the setting of infections, inflammatory diseases, and cancer has been sparse. Findings in recent studies suggest that oxidative stress generated by mitochondrial and cellular ROS regulates bactericidal activity and inflammatory responses in autoinflammatory diseases [10, 77]. Systematic analysis of stress and immune signaling interactions will not only provide a better understanding of the pathophysiology of immune disorders but will aid in identifying targets for drug discovery.

Infections

The diverse effects of pathogen-induced oxidative stress on upstream immune signaling intermediates and downstream transcription factors determine host resistance and susceptibility to infections. The highly regulated NADPH oxidase is a potent contributor to host resistance against infections, and an oxidative burst of ROS production is used by immune cells such as neutrophils for clearance of microbes [224]. Although intracellular ROS induces bactericidal activity and pathogen elimination, mitochondrial ROS can serve as signaling molecules to induce inflammatory responses. NLRX1-induced ROS enhance NF-κB and JNK signaling, and PRR-induced ROS can activate the NLRP3 inflammasome [76, 225]. NADPH oxidase could be an attractive target for therapeutic intervention dur-

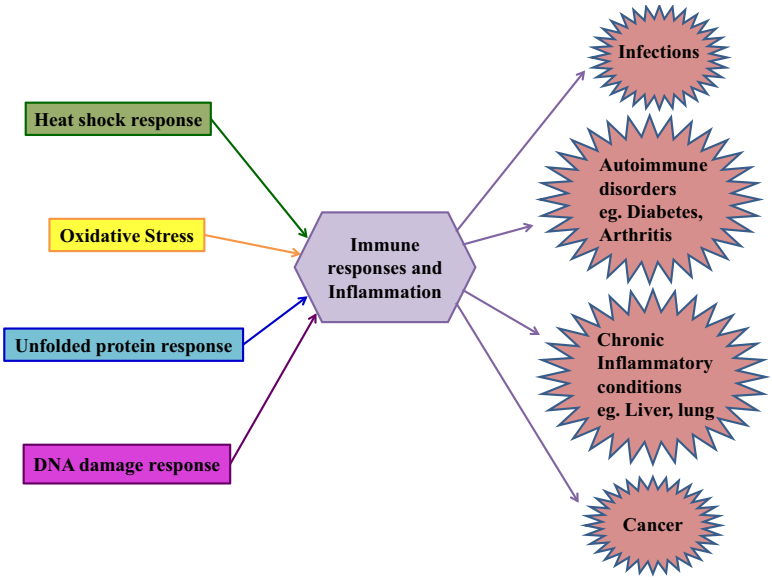

Figure 5. Clinical consequences of crosstalk between stress proteins and immune signaling molecules. The clinical consequences of crosstalk between immune signaling and the individual stress responses in the context of infection, autoimmunity, chronic inflammation, and cancer are illustrated. The cellular stresses are categorized into oxidative stress (yellow), heat shock response (green), UPR(blue), and DDR (pink).

ing infections, in that microbes can subvert ROS-mediated effects via inhibition of the recruitment of NADPH oxidase subunits (phox and Rac) to the phagosome, resulting in increased host susceptibility to infections [226–228]. Recent studies have also shown increased production of Hsps in pathologic conditions, indicating that cellular stress caused by infection or immune assault upregulates the production of both host and pathogenic Hsps [229–232]. These Hsps serve as molecular chaperones for signaling kinases that are essential in host defense or survival and contribute to either elimination of infections or progression of disease.

Autoimmune Disorders

In addition to their roles in host defense against infection, stress proteins have been implicated in autoimmune disorders. Host Hsps appear to modulate immune responses directly and to serve as circulating DAMPs to induce uncontrolled immune activation. For example, immune reactivity to Hsp70 and -90 has been shown in autoimmune and chronic inflammatory diseases, such as rheumatoid arthritis, SLE, and multiple sclerosis [233, 234]. Pharmacologic inhibition of these Hsps in animal models of SLE and rheumatoid arthritis has resulted in ameliorated disease, indicating that these Hsps play a significant role in the pathogenesis of autoimmune disease [235, 236]. Since Hsps are phylogenetically highly conserved between mammals and pathogens, the leading hypothesis is that immune activation against pathogenic Hsps leads to cross-reactivity with sequence-homologous host Hsps, resulting in various autoreactive disorders [237]. Hsp22, which is known to induce DC maturation and cytokine production in a TLR4-dependent manner, is another example of Hsps in autoimmune disease, as illustrated by its abundant expression in the synovial tissue of patients with rheumatoid arthritis [144]. ER and oxidative stresses are also involved in autoimmunity and a broad range of inflammatory diseases. These pathways have been implicated in development of diabetes, wherein proinflammatory cytokines induce stress-mediated death of insulin-producing β cells [86, 238]. Activation of stress-mediated SAPK-JNK is also associated with insulin resistance and type 2 diabetes [239]. Activation of JNK downstream of ER stress or ATM-mediated DDR responses in obesity can result in insulin resistance. In the case of arthritis, deficiency of the NADPH oxidase complex, which lowers ROS production, increases susceptibility to disease in rodents [240]. The ER stress protein Grp78 associates with the autoantigen Ro52, which leads to Grp78's becoming a bystander target for subsequent immune reactivity in an animal model of arthritis [241]. Expression of the ER stress genes *Grp78*, *CHOP*, and *Gadd45* is upregulated in the muscle tissue of patients with autoimmune myositis, indicating a role for these UPR proteins in the muscle damage that is characteristic of this disease [242]. In contrast, a study involving EAE, the inducible animal model of multiple sclerosis, showed that induction of ER stress by IFNγ in oligodendrocytes protects mice from subsequent disease in a PERK-dependent manner [243].

Chronic inflammatory diseases

The role of the stress pathways in disease can be extended to chronic inflammatory conditions. Oxidative stress, specifically that induced by ROS, plays a central role in lung and liver inflammatory disorders. Neutrophil-produced ROS, which diffuse into the liver cells, cause oxidative stress, leading to the efficient killing of these cells and causing inflammatory liver injury [244]. TLR4 interaction with Nox4 is necessary for LPS-induced ROS generation and NF-κB activation [46]. This TLR-stimulated production of oxidants by liver resident macrophages (Kupffer cells) has been shown to contribute to alcohol-induced inflammation and injury in the liver [245]. Persistent inhalation of pathogens or toxic agents can cause an oxidant–antioxidant imbalance in the lungs, resulting in excessive production of ROS. ROS-mediated activation of signaling pathways such as NF-κB and AP-1 produces proinflammatory mediators, such as TNFα, IL-8, and IL-1β, and promotes tissue injury and inflammation in the airways, as observed in cystic

fibrosis, asthma, and chronic obstructive pulmonary disease [246]. The inflammatory responses in the lung that are observed in influenza infection and cigarette smoking are reduced in ROS-deficient mice [247, 248]. The UPR stress pathway has been implicated in intestinal inflammation. Induction of ER stress in the intestinal cells results in multicytokine-mediated colitis, similar to human ulcerative colitis [249]. Polymorphisms in the UPR gene *XBP-1* has been associated with inflammatory bowel disease [250]. The significant role of these stress pathways in autoimmune and inflammatory disorders suggests possible targets for manipulation in the treatment of these diseases.

Cancer

In the context of cancer, the role of stress pathways in immune responses to tumors has been elucidated. The frequency of mutations and loss of p53 correlating with cancer suggests a critical role for this DDR protein in cancer [251]. The induction of NKG2D ligand expression by the DDR also facilitates tumor surveillance by the immune system. Inhibition of ATM or Chk1 blocks expression of Rae, an NKG2D ligand, in tumor cell lines [189]. In contrast, the anti-inflammatory role of Hsps can be exploited by tumor cells for immune evasion. Tumors cells express and secret Hsp70, which in turn promotes immunosuppression in a TLR2/MyD88-dependent manner [252–254]. Tumor-produced Hsp10 exerts a similar suppressive effect on T-cell activation [255]. Elevated expression of Hsps such as Hsp10 and -60 can also serve as biomarkers for diagnosis and prognosis of cancer [256, 257]. Targeting Hsp70 and -90 has shown promising results in the treatment of different cancers. Several chemical Hsp90 inhibitors such as 17-DMAG and BIIB021 are undergoing clinical trials for treatment of multiple myeloma, breast cancer, and leukemia. The first Hsp90 inhibitor tested in vivo was 17-AAG (tanespimycin), which was trialed in 1999 for treatment of solid and hematologic malignancies [258–260]. Targeting the transcription factor HSF1, a pivotal regulator of Hsp induction, by a triazole nucleoside analogue elicited anticancer activity in pancreatic cancer [261]. Neutralization of Hsp70 with an AIF-derived peptide and treatment with Hsp70 inhibitors such as PES and VER-155008 have also shown potent antitumor activity [262]. The complex role of stress-mediated JNK in cancer is established. Detection of high levels of JNK activity in cancer cell lines supports the observation that JNK promotes tumorigenesis, but tumor suppression may also be mediated by its proapoptotic properties [239]. Furthermore, in cancer, upregulation of UPR pathways, such as Grp78, ATF6, and XBP1 splicing in tumor cells in response to ER stressors, such as hypoxia, glucose deprivation, and low pH in the tumor microenvironment, is essential for tumorigenesis [263–266]. The induction of proinflammatory mediators such as TNFα and IL-6 by UPR proteins such as IRE1α and PERK in cancer cells facilitates tumor growth and regulates immune function [267]. Inflammation induced by oxidative stress potentiates tumorigenesis in a similar manner [268]. In addition to this cell-intrinsic regulation, recent studies have indicated a cell-extrinsic role for UPR in tumor cells via immunomodulation. Macrophages treated with conditioned medium of such ER-stressed tumor cells upregulated UPR signaling and production of inflammatory cytokines in a phenomenon termed transmissible ER stress (TERS), mediated by TLR4 [269]. Thus, the tumor microenvironment uses ER stress to initiate a tumorigenic inflammatory phenotype in APCs. Overall, several interactions between stress and immune signaling proteins in infections, autoimmunity, inflammatory diseases, and cancer suggest a significant role for stress proteins in disease pathogenesis, making them attractive therapeutic targets.

CONCLUDING REMARKS

Cellular stress and inflammation can activate or inhibit each other, depending on the immune cell type and the stress-inducing signals, such as pathogens and chemical or physical agents. Although understanding the pathophysiological role of cellular stress proteins in host defense and inflammatory diseases has progressed in recent years, future research should address critical questions. What are the key interacting mechanisms between stress-regulated cellular proteins and immune mediators crucial to host defense and disease pathogenesis? Can we target stress proteins to regulate inflammatory responses? An improved understanding of the underlying molecular mechanisms of stress proteins and their crosstalk with inflammatory pathways will provide new targets for therapeutic intervention.

AUTHORSHIP

S.M. composed, revised, and edited the manuscript. P.M. generated the overall concepts and critically reviewed the manuscript.

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DISCLOSURES

The authors declare no conflicts of interest.

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