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Type I interferons and endoplasmic reticulum stress in health and disease

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Abstract

Type I interferons (IFNs) comprise of pro-inflammatory cytokines created, as well as sensed, by all nucleated cells with the main objective of blocking pathogens-driven infections. Owing to this broad range of influence, type I IFNs also exhibit critical functions in many sterile inflammatory diseases and immunopathologies, especially those associated with endoplasmic reticulum (ER) stress-driven signaling pathways. Indeed, over the years accumulating evidence has indicated that the presence of ER stress can influence the production, or sensing of, type I IFNs induced by perturbations like pattern recognition receptor (PRR) agonists, infections (bacterial, viral or parasitic) or autoimmunity. In this article we discuss the link between type I IFNs and ER stress in various diseased contexts. We describe how ER stress regulates type I IFNs production or sensing, or how type I IFNs may induce ER stress, in various circumstances like microbial infections, autoimmunity, diabetes, cancer and other ER stress-related contexts.
1. Introduction

Type I interferons (IFNs) are a family of pro-inflammatory cytokines (especially IFNα or IFNβ) created by nucleated cells with the main objective of blocking (pathogenic) infections (Makris et al., 2017; McNab et al., 2015; Negishi et al., 2018; Tailor et al., 2006). A number of non-sterile or sterile factors associated with stress, injury, or trauma, are all sensed by our cells through a combination of pattern recognition receptors (PRRs) that, in reaction, enhance the production of immunological factors like type I IFNs (Bianchi, 2007; Garg and Agostinis, 2017; Tang et al., 2012; Tatematsu et al., 2018; van de Veerdonk et al., 2008). Due to the very extensive presence of type I IFN-binding receptor complex composed of IFN-α/β receptor-1/2 (IFNAR1/2), on almost all cells in an organism’s body, type I IFNs exert widespread cellular or immunological functions (Bald et al., 2014; de Weerd et al., 2013; Taft and Bogunovic, 2018). Additionally, type I IFNs are decisive for the maturation and differentiation of assorted innate immune cells (Longhi et al., 2009; Nardelli et al., 2002). Owing to this broad range of influence, type I IFNs exhibit critical functions in many inflammatory diseases thereby positioning them at the core of almost all functional immunological paradigms (Bracci et al., 2017; Parker et al., 2016; Sprooten et al., 2019; Wu et al., 2016; Zitvogel et al., 2015).

Like a number of cytokines and their cognate receptors, IFNα/β and IFNAR1/2 are considerably glycosylated (especially N-glycosylated but also O-glycosylated) (Ling et al., 1995; Sommereyns and Michiels, 2006) and hence the endoplasmic reticulum (ER)/Golgi apparatus system, where such protein glycosylations are executed (Smirle et al., 2013), is critical for the proper functioning of the type I IFNs signaling. Indeed, the ER is an important organelle that is accountable for the production, maturation and post-translational modifications of a number of proteins (Garg et al., 2015d; Kang and Hegde, 2008; Sovolyova et al., 2014). Moreover, a number of pathological perturbations that can elicit type I IFNs also tend to affect ER homeostasis, e.g., chemotherapeutic or radiotherapeutic stress, oxidative injury, and microbial infections (especially of viral origin) (Garg et al., 2012a, 2014; Kang and Hegde, 2008; Tardif et al., 2005). Such interference with ER homeostasis compromises ER-associated proteostasis thereby causing ER stress (Cabral-Miranda and Hetz, 2018). The ER typically responds to such insults by stimulating a complex signaling cascade, called the
unfolded protein response (UPR) (Ron and Walter, 2007; Rutkowski and Kaufman, 2007; Schröder and Kaufman, 2005). Herein, the primary aim of the UPR is to overcome “proteotoxicity” and rescue ER homeostasis thereby prolonging cellular survival (Gorman et al., 2012; Hendershot, 2004). However this primary aim is only met in conditions of low-to-medium ER stress such that severe ER stress almost always steers the UPR to engage pro–death signaling that tends to culminate into intrinsic (mitochondria–driven) apoptosis (mostly but not always) (Estornes et al., 2014; Urra et al., 2013; Verfaillie et al., 2012). Due to the overlaps between type I IFNs production or sensing and the ER, not surprisingly, ER stress has critical consequences for type I IFNs–associated functions. Moreover, even type I IFNs themselves are capable of eliciting ER stress in target cells, given the right conditions (Mollereau et al., 2014; Rahmati et al., 2018; Yoshida, 2007).

In this article we discuss the link between type I IFNs and ER stress in various pathological contexts. Initially, we introduce the basic concepts underlying type I IFNs production and sensing, ER stress and ER stress–associated inflammatory signaling pathways. Thereafter we describe how ER stress regulates type I IFNs production or sensing, or how type I IFNs may induce ER stress, in various pathological contexts like microbial infections (viral, bacterial or parasitic), diabetes, cancer and general ER stress–related contexts.

2. Type I interferons: An introduction

2.1 Mechanisms underlying type I IFNs production

Type I IFNs, as mentioned above, evolved to hinder pathogenic diseases (Hron and Peng, 2004; Ivashkiv and Donlin, 2014), which they accomplish by stimulating innate as well as adaptive immune cells, and balancing this with the blunting of any unfavorable immune reactions, thereby ensuring rapid purging of microbial infections coupled with eventual resolution of inflammation (Ivashkiv and Donlin, 2014; Iwasaki and Medzhitov, 2015). A large majority of cells are highly competent at producing IFNβ, however only particular immune cells have evolved to proficiently secrete IFNα, e.g., particular dendritic cell (DC) subsets like plasmacytoid DCs (Björck et al., 2011; Diebold et al., 2003; Garg et al., 2017a,e; Ivashkiv and Donlin, 2014). Despite this, production of type I IFNs is not specific for non-sterile pathologies. In various sterile pathologies, type I IFNs play either a disease
ameliorating (e.g., cancer) or even a disease exacerbating role (e.g., autoimmune diseases especially interferonopathies) (Arimoto et al., 2018; Burdick et al., 2009; Durbin et al., 2000; Palucka et al., 2005; Rizzo et al., 2014). This is made possible by a major overlap (in terms of shared cognate PRRs) between danger signals derived from pathogens (together classified under the term, pathogen-associated molecular patterns or PAMPs) and those of “self” or endogenous origin (together classified under the term, damage-associated molecular patterns or DAMPs); as well as the ubiquitous expression of IFNAR1/2 (de Weerd et al., 2013; Garg and Agostinis, 2017; Garg et al., 2017c; Ragimbeau et al., 2003; Rubartelli and Lotze, 2007).

Binding of PAMPs (during microbial invasion) or DAMPs (during tissue injury, trauma, or due to toxic insults) to cellular PRRs drives the production of type I IFNs (Fig. 1) (Janeway’s, 2016; Janeway and Medzhitov, 2002; Zhang et al., 2010). PRRs tend to have diverse subcellular localizations (e.g., surface, cytosol and endosomes/phagosomes) in order to effectively sense microbial threats capable of entering the cells from disparate routes (Hoffmann et al., 2015; Liu et al., 2011; Thompson et al., 2011; Wu and Chen, 2014). As far as induction of type I IFNs is concerned, nucleic acids of either microbial or endogenous origin are the most potent inducers engaging either cytosolic or endosomal PRRs (Fig. 1) (Roers et al., 2016; Tan et al., 2018; Thompson et al., 2011; Wu and Chen, 2014; Yang et al., 2010). On the cell surface, type I IFNs are majorly elicited through agonists of TLR4, e.g., bacterial lipopolysaccharide (LPS) (Leu et al., 2011; Ohto et al., 2012; Walker and Tough, 2006). Similarly, major endosomal PRRs crucial for type I IFN induction include TLR9, TLR3 or TLR7/8, that are frequently engaged by danger signals like unmethylated CpG DNA, double-stranded RNA (dsRNA) or single-stranded RNA (ssRNA), respectively (Moynagh, 2005; Stetson and Medzhitov, 2006; Sykes et al., 2013; Thompson and Locarnini, 2007). Lastly, major cytosolic PRRs crucial for type I IFN induction include, cytosolic cGAMP-AMP synthase (cGAS)/absent in melanoma 2 (AIM2)-like receptors (ALRs) or, melanoma differentiation-associated gene 5 (MDA5)/RNA helicases retinoic acid-inducible gene I (RIG-I), that are frequently engaged by danger signals like cytosolic DNA species or microbial RNA species (e.g., dsRNA or 5’ppp-RNA), respectively (Fig. 1) (Elion and Cook, 2018; Iurescia et al., 2018; Lee et al., 2019; Saito and Gale, 2008; Tan et al., 2018; Vanpouille-Box et al., 2018).

A diversity of adaptor proteins or downstream signaling modules function beyond the above mentioned PRRs to tightly regulate the production of type I IFNs (Battesti and Gottesman, 2013; Koretzky and Myung, 2001) (Fig. 1).
Fig. 1  See legend on next page.
For instance, TLRs, cGAS or RIG-I/MDA5 mostly function through cytosolic proteins like TIR-domain containing adaptor-inducing interferon-β (TRIF)/myeloid differentiation primary response 88 (MyD88), stimulator of interferon genes (STING) or mitochondrial antiviral-signaling protein (MAVS), respectively (Liu et al., 2015; Yamamoto et al., 2003). Mostly “standard” biochemical events like protein-protein binding based activation, phosphorylation or modification of protein structure/conformations underlie the mobilization of the above signaling pathways; however in some cases, this downstream signaling might be conveyed through intermediate metabolites, e.g., stimulation of cGAS tends to generate 2′3′-cGAMP, a potent agonist of STING (Ahn et al., 2018; Khoo and Chen, 2018; Kranzusch et al., 2015). Beyond the standard PRR agonists, specific inflammatory factors like cytokines can also elicit type I IFNs production, e.g., receptor activator of NF-κB ligand (RANKL), tumor-necrosis factor (TNF) or, macrophage colony-stimulating factor (M-CSF) (Ivashkiv and Donlin, 2014; McMahon and Ueki, 2009; Venkatesh et al., 2013; Yarilina et al., 2008; Zauli et al., 2004). These signaling pathways ultimately pave way for the activation of specific kinases like the kinases IKKε (IKKe) and TANK-binding kinase 1 (TBK1), which thereafter recruit the nuclear activity of particular transcription factors belonging to the

Fig. 1 A schematic depiction of production and sensing mechanisms for type I interferons (IFNs). Danger signals like lipopolysaccharide (LPS) or different nucleic acid species (single-stranded RNA or ssRNA, double-stranded RNA or dsRNA, CpG DNA) bind their cognate receptors like, Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), or cyclic GMP-AMP (cGAMP) synthase (cGAS). These receptors execute a complex intracellular pathway that ultimately leads to the activation of transcription factors like IFN regulatory factor (IRF)-3/7 that eventually transcribe IFNα/β, which are thereafter translated and secreted. Upon extracellular emergence, IFNα/β bind to the IFNα receptor (IFNAR) complex, which causes activation of tyrosine kinase 2 (TYK2) and receptor-associated Janus kinase 1 (JAK1). This eventually activates various downstream pathways that primarily aim to induce production of various interferon-stimulated genes (ISGs) derived protein products but also modulate cellular homeostasis. Of note, the inflammatory potential of IFNα/β is often limited by ubiquitination (Ub)-driven, lysosomal degradation of the IFNAR complex. AKT, protein kinase B alpha; ER, endoplasmic reticulum; IKKβ, I-kappa-B kinase beta; IKKe, I-kappa-B kinase epsilon; IRS1/2, insulin receptor substrate 1; ISRE, interferon-stimulated response element; MAVS, mitochondrial antiviral signaling protein; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappα-light-chain-enhancer of activated B cells; PI-3K, phosphoinositide-3-kinase; STAT1/2/4/5/6, signal transducer and activator of transcription 1/2/4/5/6; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1.
IFN-regulatory factor (IRF) family, such as IRF1/3/7, for the transcription of type I IFNs (Ikeda et al., 2007; Lei et al., 2010; Li et al., 2017; Taft and Bogunovic, 2018; Tanaka and Chen, 2012; Vanpouille-Box et al., 2018). Type I IFNs transcription is often induced in a wave-like format such that TLRs tend to be relatively faster than other PRRs in inducing type I IFN production (Katakura et al., 2005; Ma et al., 2015; Perkins and Vogel, 2015; Sato et al., 1998).

Like many other cytokines, IFNα/β transcripts are translated and folded at the ER and thereafter transported from the ER to the cis-Golgi (Kurokawa et al., 2014; Oku et al., 2011; Stow and Murray, 2013). While in the ER/Golgi, IFNα/β are also glycosylated (mostly N-glycosylation which happens in the Golgi but also some degree of O-glycosylation that happens in the ER) (Ling et al., 1995; Smirle et al., 2013; Sommeregns and Michiels, 2006). Thereafter within the Golgi complex, these cytokines are directed toward the trans-Golgi network (TGN) and sorted into the post-Golgi secretory vesicles that transport them toward the cell surface for eventual extracellular secretion (Gu et al., 2001; Stow and Murray, 2013). It is still debatable to what extent the type I IFNs trafficking pathway deviates from this conventional secretory pathway (Stow and Murray, 2013). There are some unconventional secretory routes observed for various cytokines including IFNγ but it remains unclear whether type I IFNs are also sorted into these pathways, e.g., recycling endosomes-plasma membrane pathway or the Golgi-early endosome pathway (Short, 2015; Zemskov et al., 2011). The role of these pathways in type I IFNs is also unclear because it is not known whether it matters how type I IFNs are secreted, i.e., is it enough that they are secreted via multiple points on the cell surface or do they also need to be secreted in a directionally-defined manner (Reefman et al., 2010; Stow and Murray, 2013).

2.2 Sensing of type I IFNs

Upon release, extracellular IFNα/β engage their cognate IFNα receptor (IFNAR1/2), which activates receptor-associated tyrosine kinases like tyrosine kinase 2 (TYK2) and Janus kinase 1/2 (JAK1/2) (Fig. 1) (Ragimbeau et al., 2003; Uzé et al., 2007; Wallweber et al., 2014). In basal conditions the IFNAR1/2 cytoplasmic tails remain bound, in an inactive conformation, by the JAK proteins (Gui et al., 2017; Ma et al., 2019; Ragimbeau et al., 2003; Teijaro et al., 2016). Engagement by IFNα/β causes dimerization of IFNAR1/2 receptor chains thereby triggering the JAK/TYK2 kinase

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domains to undertake activation directed through their trans-phosphorylation (Pfeffer et al., 1997; Schneider et al., 2014). Consequently, JAK/TYK2 kinases phosphorylate Signal transducer and activator of transcription 1/2 (STAT1/STAT2) proteins causing their dimerization, nuclear translocation, and binding to the IRF9 protein thereby creating the IFN-stimulated gene factor 3 (ISGF3) complex (Ivashkiv and Donlin, 2014; Liu et al., 2018; Schneider et al., 2014; Tenoever et al., 2007). Thereafter, ISGF3 engages the IFN–stimulated response elements (ISREs) thus guiding the transcription of throngs of interferon-stimulated genes or ISGs (Fig. 1) (Ivashkiv and Donlin, 2014; Liu et al., 2018; Schneider et al., 2014; Tenoever et al., 2007). In principle the above described pathway is considered to be “canonical”; however some variants of this pathway can also be activated and these are mediated by different STAT1/2 homodimers, some of which are generally linked with IFNγ–associated signaling (Ivashkiv and Donlin, 2014; Ramana et al., 2002). Interestingly, even diverse STAT isomers such as STAT3/4/5A and 5B can direct the production of ISGs (Blaszczyk et al., 2015; Rauch et al., 2013). Such diversity, in terms of downstream mediators activated following engagement of IFNAR1/2 by IFNα/β, account for the broad immunological effects of type I IFNs in both health and disease (de Weerd et al., 2013; Mizutani et al., 2012).

Protein products resulting from translation of ISGs (i.e., ISG-products) chiefly strive to minimize the injury instigated by contagions through, disturbing the processes enabling their growth, and proliferation (Fig. 1) (Borden, 2019; Cheon et al., 2014; Lai et al., 2019; Schneider et al., 2014). The best known ISG-products comprise of (Parker et al., 2016): proteins functioning in antigen processing and presentation cascades, T cells or inflammatory myeloid cells-attracting chemokines (e.g., CXCL10 or CXCL9), proteins or micro–RNAs that impede or inhibit angiogenesis, factors capable of inducing or modulating cell death (e.g., ligands that engage death receptors–driven apoptosis or necroptosis) or immunological ligands crucial for myeloid or lymphocytic inflammatory sensitization (e.g., co-stimulatory proteins like CD40 or CD80) (Borden, 2019; Schoggins, 2014, 2018; Schoggins and Rice, 2011; Schneider et al., 2014; van der Vorst et al., 2019; Wang et al., 2017). Type I IFNs and its ISG-products function together to enhance the cell-to-cell communication (in both tissue and immune cells context) so as to eliminate the pathogenic or sterile threat challenging the organismal homeostasis and to resolve inflammation (Borden, 2019; Cheon et al., 2014; Divangahi et al., 2015; Kono et al., 2014; Schneider et al., 2014).
It is clear from the above discussion that type I IFNs are extremely crucial for maintaining tissue homeostasis and impeding progression of diseases (Chovatiya and Medzhitov, 2014; Divangahi et al., 2015; Goldmann et al., 2016). Thus not surprisingly, cellular processes crucial for type I IFNs production are also considered to be important (Ludigs et al., 2012; Mancuso et al., 2007; Schmeisser et al., 2014). Although type I IFN-aiding cellular processes directly associated with immunological signaling have received considerable attention yet some others haven’t received as much attention despite being foundational for type I IFNs production (Bogdan et al., 2004; Haque et al., 2014; Steinman, 2009). One such process is ER stress or UPR signaling. In the following sections, we introduce the basic concepts underlying ER stress/UPR signaling before discussing the broad trends within the current literature connecting it with the regulation of type I IFN responses.

3. ER stress and inflammation: An introduction

3.1 ER stress-associated UPR signaling

A stressed ER, as mentioned earlier, aims to overcome the disturbance in its homeostasis by activating a complex set of signaling pathways together representing the UPR signaling (Imanikia et al., 2018; Menu et al., 2012; Oliveira et al., 2011; Szegezdi et al., 2009). The UPR involves a multifaceted interaction amongst three main signaling pathways, each of which is activated by three different ER-sessile sensors of ER stress, i.e., pancreatic ER kinase (PKR)-like ER kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) (Fig. 2) (Chen and Brandizzi, 2013; Glembotski et al., 2019; Hetz, 2012; Mori, 2010; Pytel et al., 2016; Verfaillie et al., 2012). PERK, IRE1 and ATF6 are ER-transmembrane proteins that, in basal or homeostatic conditions, exist in an inactive conformation enforced by the direct binding of the chaperone, 78 kDa glucose-regulated protein (GRP78), to their luminal domains (Carrara et al., 2015; Pincus et al., 2010; Sepulveda et al., 2018; Sundaram et al., 2018). Upon increased accumulation of unfolded or misfolded proteins that create ER-localized proteotoxicity, GRP78 seizes to bind these ER stress sensors in order to prioritize its main function of protein chaperone so it can amplify ER’s protein re-folding capacity (Christis et al., 2010; Das et al., 2013; Ma and Hendershot, 2004; Määttänen et al., 2010; Pincus et al., 2010; Schröder and Kaufman, 2005). This stoppage in GRP78 binding paves way for the activation of PERK, IRE1 and
ATF6 (Gardner et al., 2013; Sundaram et al., 2018). In the following sub-sections, we give an overview of mechanisms underlying ER stress sensors’ activation (Fig. 2) however it is worth noting that for the sake of focus and clarity we present a relatively simplified overview of these mechanisms although these are much more complex and multi-factorial. For those who want to gain a deeper understanding of this subject, we refer to other more comprehensive reviews focussing on ER stress-associated mechanisms.

Molecularly speaking, PERK is a Ser/Thr kinase that conveys signaling through at least two known downstream substrates, i.e., eukaryotic initiation factor 2-alpha (eIF2α) or nuclear factor-E2-related factor 2 (NRF2) (Fig. 2) (Atkins et al., 2013; Harding et al., 2000; Marciniak et al., 2006). Upon ER stress, PERK orchestrates the phosphorylation of eIF2α on its Ser51 amino acid residue thereby restraining Cap-dependent protein
translation (Balsa et al., 2019; Gonen et al., 2019; Gupta et al., 2012). Of note, Cap-dependent translation is distinguished by the obligatory requirement for the ribosomes to first engage the mRNA transcript at its 5’ end (i.e., 5’ cap sequence) before moving toward the start codon whereas the process when a ribosome is “directly” transported to the start codon site thereby bypassing this obligation is simply termed as cap-independent protein translation. The PERK-eIF2α phosphorylation driven impediment of protein translation helps in dropping the amount of new proteins arriving at the ER for maturation (Araki and Nagata, 2011; Ellgaard et al., 2016; Naidoo, 2009; Nehls et al., 2000; Pedrazzini and Vitale, 2018). Of note, this inhibition of Cap-dependent translation is sometimes termed as global translational shut-down which may not be entirely correct since under eIF2α inhibitory conditions, Cap-independent protein translation can still continue and may in fact be crucial for UPR functioning itself (Kim et al., 2011; Knutsen et al., 2015; Thakor and Holcik, 2012; Van Der Kelen et al., 2009; Walters and Thompson, 2016). More specifically the transcription factor, activating transcription factor 4 (ATF4), that is crucial for the downstream deliverables of the PERK signaling pathway, is one of the products of Cap-independent translation (Ameri and Harris, 2008; Saito et al., 2011; Wang et al., 2012). This PERK-eIF2α-ATF4 signaling module controls the expression of numerous genes necessary for restoration of the ER homeostasis including, those relevant for regulating ordered synthesis of amino acids, protein or peptide transportation, and antioxidant responses (amongst others) (Grootjans et al., 2016; Todd et al., 2008; Wang and Kaufman, 2014) (Fig. 2). Similarly, PERK also phosphorylates NRF2 which encourages NRF2’s detachment from its cytosolic repressor protein, Kelch-like Ech associated protein 1 (KEAP1) (Chien et al., 2015; Cullinan et al., 2003; Del Vecchio et al., 2014; Holland and Fishbein, 2010; Uruno et al., 2015). This allows NRF2 to transit into the nucleus where it directs transcription of several genes involved in the antioxidant responses (Faraonio et al., 2006; Levings et al., 2018; Sun et al., 2009; Xue et al., 2015). Thus, through coordination of these two (parallel) signaling modules, the PERK arm of the UPR strives to help increase the survival of ER stressed cells by facilitating ER’s adaptation to stress, especially oxidative stress (Dadey et al., 2018; Karali et al., 2014; Verfaillie et al., 2012; Walter et al., 2015; Zhang et al., 2013).

In comparison to PERK, that operates primarily through phosphorylation of its substrates, IRE1 arm of the UPR orchestrates a relatively more complex set of biological processes (Fig. 2) (Jwa and Chang, 2012;
Reverendo et al., 2019; Rubio-Patiño et al., 2018; Sundaram et al., 2018). On one hand, activated IRE1 functions as an endoribonuclease or RNase to splice X-Box binding protein 1 (XBP1) mRNA (or XBP1u), and cause the emergence of a fully functional form of it, i.e., spliced XBP1 (XBP1s) (Hassler et al., 2015; Lee et al., 2002; Mimura et al., 2012; Yanagitani et al., 2011; Yoshida et al., 2006). This XBP1s functions as a transcription factor and directs the transcription of several crucial genes involved in quality control within the ER, redox homeostasis, biogenesis of ER/Golgi structures, antioxidant response, as well as proteins involved in the ER-associated protein degradation (ERAD; a process that helps in degradation of misfolded proteins accumulating in the ER via cytosolic proteasomes) (Almanza et al., 2019; Hiller et al., 1996; Lhomond et al., 2018; Logue et al., 2018; Ruggiano et al., 2014; Wu and Rapoport, 2018). Of note, beyond XBP1 splicing, IRE1 also undertakes another RNase activity involving degradation of ER membrane-associated mRNAs, a process termed as the IRE1-dependent decay of mRNA (RIDD) activity (Blazanin et al., 2017; Guydosh et al., 2017; Hollien et al., 2009; Maurel et al., 2014; So et al., 2015). IRE1’s RIDD activity has a highly context-dependent role in facilitating stress adaptive responses, or cell death (Bouchecareilh et al., 2011; Coelho and Domingos, 2014; Hassler et al., 2012; Lerner et al., 2012; Maurel et al., 2014; Rubio et al., 2011). On the other hand, activated IRE1 also displays some degree of kinase activity, which it exploits for trans-autophosphorylation; although the exact identity of other downstream substrates targeted for phosphorylation by IRE1 remains enigmatic (Ali et al., 2011; Feldman and Maly, 2017; Korenykh et al., 2009; Lee et al., 2008; Prisch et al., 2014). In comparison to PERK and IRE1, ATF6 activation mechanism is highly distinct in the UPR setting (Jerry Chiang and Lin, 2014; Sundaram et al., 2018; Tam et al., 2018; Teske et al., 2011; Yoshida et al., 2001). The titration of GRP78 away from ATF6 encourages its transportation toward the Golgi complex wherein it is sliced by particular Golgi-resident proteases (Fig. 2) (Papaioannou et al., 2018; Schindler and Schekman, 2009; Shen and Prywes, 2005; Shen et al., 2002; Sommer and Jarosch, 2002). This processing of ATF6 liberates it as an active transcription factor that not only transcribes specific ER chaperones, or proteins involved in the ERAD, but also contributes toward adaptive lipid metabolism, and expansion of the ER to better cope with the proteotoxic stress (Oka et al., 2019; Shen et al., 2002; Tam et al., 2018; Ye et al., 2000; Zeng et al., 2004).
The above pathway mainly represents the attempt of the UPR to re-establish ER homeostasis and facilitate the survival of the stressed cell. However this cascade is best executed only in condition of low or mild ER stress where the ER-associated signaling still has enough time and resources to tackle the proteotoxic insult (Binet and Sapieha, 2015; Gorman et al., 2012; Hendershot, 2004; Lindholm et al., 2006; Yoshida, 2007). However in some situations, prolonged stress or very intense stress in a short amount of time, can both overwhelm the UPR’s ability to restore ER homeostasis (Chevet et al., 2015; McGrath et al., 2018; Senft and Ronai, 2015; Urra and Hetz, 2014). In such a situation, the UPR is inclined to engage the pro-death signaling pathways. The molecular switching between these two crucial cell fates (i.e., cell survival versus cell death) in the context of ER stress is complex and still poorly understood (Chevet et al., 2015; Maurel et al., 2015; Szegezdi et al., 2006). However this is facilitated by the ability of the main ER stress sensors to control a dualistic signaling cascade that balances stress adaptation with pro-death signaling (Rutkowski et al., 2006; Sano and Reed, 2013; Sovolyova et al., 2014). A possible contrivance that may account for this dichotomy is the differential stability of mRNAs coding for proteins regulating pro-survival or pro-death signaling wherein this stability might depend upon the overall intensity of ER stress (Haynes et al., 2004; Kaneko and Nomura, 2003; Kondo et al., 2012; Rutkowski et al., 2006; Urra et al., 2013). So for instance, a transiently activated PERK will likely direct the ATF4-driven transcription program to undertake pro-survival signaling (Dadey et al., 2018; Rozpedek et al., 2016). This program will not readily engage pro-death signaling via downstream mediators, like C/EBP homologous protein (CHOP), largely because of the intrinsic instability of mRNAs coding for pro-apoptotic proteins (Cubillos-Ruiz et al., 2017; Tavernier et al., 2017). These mRNA species probably require a stronger and sustained PERK activation (as in the case of severe or prolonged ER stress) to allow commencement of an apoptotic program driven through ATF4-directed activation of CHOP (Balsa et al., 2019; Wang et al., 2019). In case of the IRE1 arm of the UPR, published research indicates that the IRE1→XBP1 signaling elicited by mild ER stress plays a predominantly pro-survival role whereas in case of severe ER stress, IRE1 tends to orchestrate a XBP1-independent scaffold signaling characteristics to commence apoptotic signaling (Back et al., 2005, 2006; Cubillos-Ruiz et al., 2016; Gupta et al., 2010; Heindryckx et al., 2016; Tang et al., 2014; Yoshida et al., 2001). More specifically, upon exposure to severe ER stress, IRE1 can recruit pro-death signaling proteins like
TNF-receptor-associated receptor 2 (TRAF2) (Hu et al., 2006; Pincus et al., 2010; Qiu et al., 2013; Salzberg et al., 2017; Takeda et al., 2019; Urano et al., 2000), which is an E3 ubiquitin ligase that can facilitate IRE1’s ability to engage activation of other signaling cascades like those involving, apoptosis signal-regulating kinase 1 (ASK1), c-Jun N-terminal kinase (JNK), and/or p38 mitogen-activated protein kinases (MAPK) cascades, to modulate cellular fate (Covino et al., 2018; Fey et al., 2012; Gallo and Johnson, 2002; Madden et al., 2019; Mitra and Ryoo, 2019; Preissler and Ron, 2019; Urano et al., 2000; Yang et al., 2009) (Fig. 2).

Beyond the above disparate routes connecting ER stress with pro-death signaling, it is clear from a series of studies that the transcription factor CHOP plays a dominant role in driving ER stress–induced apoptosis (Chiribau et al., 2010; Mihailidou et al., 2010; Teske et al., 2013). In fact, activation of CHOP is not exclusive for the PERK arm of the UPR, since its formation or activation is shared between transcription factors downstream of all UPR arms, i.e., ATF4, XBP1 and ATF6 (Hirsch et al., 2014; Masuda et al., 2013; Shoulders et al., 2013; Takayanagi et al., 2013; Teske et al., 2011; Tsuru et al., 2016). CHOP facilitates apoptosis via transcription of various pro-apoptotic genes like, growth arrest and DNA-damage inducible protein (GADD34), and ER oxidoreductase 1 alpha (ERO1α) (amongst others) (Brush et al., 2003; Fransson et al., 2014; Hollander et al., 2003; Iwasaki et al., 2015; Kojima et al., 2003; Novoa et al., 2001). For instance, GADD34 directs protein phosphatase 1 (PP1) to de-phosphorylate the eIF2α protein thereby causing recommencement of (Cap-dependent) protein synthesis (Choy et al., 2015; Perego et al., 2018; Rojas et al., 2015). This resumption of protein synthesis overwhelms the protein-folding capacity of the ER, which is already dealing with proteotoxicity, thereby amplifying ER stress and pushing the cell toward cell death (Han et al., 2013; Haynes et al., 2004; Malhotra and Kaufman, 2011; Sano and Reed, 2013; Sovolyova et al., 2014; Thomas et al., 2013). Similarly, ERO1α activation can severely disturb the redox homeostasis of the ER, thereby also facilitating proteotoxicity-driven lethality (Appenzeller–Herzog et al., 2008; Araki and Nagata, 2011; Gomez et al., 2014; Kim et al., 2012; Sevier and Kaiser, 2008; Sevier et al., 2007). Thus, the UPR signaling, that strives to maintain the redox homeostasis of the ER during stressful conditions, can instead facilitate oxidation within the ER via CHOP activity, thereby paving way for apoptosis (Menu et al., 2012; Song et al., 2008; Urra et al., 2013; Verfaillie et al., 2012; Xu et al., 2017). Besides these proteostasis and redox homeostasis regulating proteins, CHOP can also control the expression of
specific proteins belonging to the B-cell lymphoma 2 (BCL2) family, which can not only directly regulate mitochondrial or intrinsic apoptosis but can also modify UPR signaling cascades (Hollville et al., 2014; Szegezdi et al., 2009; Zagorodna et al., 2012; Zheng et al., 2016). For example, the pro-apoptotic BCL2 proteins, BCL2-associated X (BAX) and BCL2 homologous antagonist/killer (BAK), can directly regulate the release of Ca\(^{2+}\) from the ER by forming membrane pores there (a potent initiator event for intrinsic apoptosis) (Andreu-Fernández et al., 2017; Jones et al., 2007; Wang et al., 2011; Willis et al., 2007); but, BAX/BAK can also modulate IRE1 activity through a direct interaction to facilitate intrinsic apoptosis (Castillo et al., 2011; Hetz et al., 2006; Hollville and Martin, 2012; Lisbona et al., 2009; Peña-Blanco and García-Sáez, 2018). Moreover, CHOP can also encourage the transcription of pro-apoptotic proteins like BCL2-like protein 11 (BIM), while simultaneously subduing the stimulation of anti-apoptotic BCL2 proteins (Chipuk et al., 2008; John et al., 2011; Zhu et al., 2004). Of note, ER-associated BAK can also activate an atypical pathway involving IRE1 → TRAF2 cascade, which mobilizes ER Ca\(^{2+}\) and promotes persistent activation of the multi-functional protein, JNK, all of which further facilitates mitochondrial apoptosis (Chen and Brandizzi, 2013; Chen et al., 2014; Hu et al., 2006; Kato et al., 2012; Pincus et al., 2010; Urano et al., 2000; Xu et al., 2018; Zhu et al., 2014). Thus, a dynamic but complex cross-talk between BCL2 proteins and the UPR signaling axes underlies the cellular response to ER stress, and this interplay also regulates the fate of an ER-stressed cell (Chevet et al., 2015; Pihán et al., 2017; Rodriguez et al., 2011; Senft and Ronai, 2015; Szegezdi et al., 2009).

### 3.2 ER stress-induced inflammation

Stress adaptive processes co-ordinated by ER stress are not limited to taking only life or death decisions in a cellular context (Imanikia et al., 2018; Malhotra and Kaufman, 2011; Sano and Reed, 2013). Along with these cell fate-related resolutions, ER stress in a particular cell can also establish cross-talk of these stressed cells with the rest of the tissue, in which they are located, by modulating inflammation (Dandekar et al., 2015; Reverendo et al., 2019; Yoshida, 2007). ER stress or UPR-associated modulation of inflammation generally strives to limit tissue damage, thereby allowing tissue-level adaptation to extrinsic or intrinsic stress (aided by the immune system) (Garg et al., 2012a; Reverendo et al., 2019; Rodvold et al., 2016). But, in line with the multifaceted characteristics of ER stress, in specific
settings ER stress-induced inflammation aggravates circumstances (Garg et al., 2012a; Lindholm et al., 2006; McGuckin et al., 2011; Scull and Tabas, 2011; Yoshida, 2007; Zhang et al., 2016). Such ER stress-associated worsening of pathologies is especially applicable to diseases like, atherosclerosis, cancer, diabetes, and obesity (Binet and Sapieha, 2015; Garg et al., 2012a; McAlpine et al., 2010; Mollereau et al., 2014; Morita et al., 2017; Yoshida, 2007). In such inflammatory situations, ER stress/UPR can strongly modulate the durability, strength, and the nature of immune reactions (Fung and Liu, 2014; Imanikia et al., 2018; Reverendo et al., 2019; Rodvold et al., 2016). However, the final immunological outcome of ER stress-induced inflammation tends to be harmful or protective depending on various factors consisting of (but not limited to): the cellular or tissue context, types of inflammatory signals generated by ER stress/UPR (i.e., pro-inflammatory or anti-inflammatory factors), type of immune cells interacting with ER stressed cells, the intensity of ER stress, and the overall immunological or health status of the organism (Cubillos-Ruiz et al., 2015; Dandekar et al., 2015; Garg et al., 2015d; Lindholm et al., 2006; Minamino and Kitakaze, 2010; Morito and Nagata, 2012; Verfaillie et al., 2013; Zhang, 2010).

Indeed, UPR signaling is frequently connected to the creation of numerous pro-inflammatory cytokines or chemokines (Dandekar et al., 2015; Fung and Liu, 2014; Garg et al., 2012a; Morito and Nagata, 2012; Rodvold et al., 2016; Turner et al., 2014). In fact, all three UPR axes discussed above can facilitate inflammatory transcriptional programs (Guo and Li, 2014; Medzhitov and Horng, 2009; Mogilenko et al., 2019). Such ER stress/UPR-directed inflammatory program is usually executed by notorious inflammatory transcription factors like, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) or activator protein 1 (AP1) (Erbay et al., 2009; Garg et al., 2012a; Jorgensen et al., 2008; Lenna et al., 2014; Meyerovich et al., 2016; Mozzini et al., 2017; Zhang et al., 2008). It is indeed common knowledge that NF-κB is one of the most dominant regulators of pro-inflammatory signaling since, it transcribes for a plethora of cytokines, immunological enzymes, or chemokines crucial for deciding both the amplitude and the duration of inflammation (Bottero et al., 2006; Hanada and Yoshimura, 2002; Hayden and Ghosh, 2011; Hayden et al., 2006; Lawrence, 2009; Novack, 2011; Pasparakis, 2009; Sun, 2012). NF-κB driven inflammation is amongst the most fastest immunological processes and can be elicited by a large array of microbial products, as well as endogenous factors released or secreted during tissue injury, or damage (Baldwin, 1996;
NF-κB is also downstream of almost all immune receptors (Chalmers et al., 2019; Dev et al., 2011; Ju Hwang et al., 2019). Interestingly, NF-κB can influence type I IFN responses. For instance, NF-κB can suppress expression of specific ISGs like guanylate-binding protein 1 (GBP1), interferon gamma inducible protein 47 (IFI47), myxovirus resistance 1/2 (MX1 or MX2), transporter associated with antigen processing (TAP1), while enhancing expression of other ISGs like, GBP2 or, TAP2 (Pfeffer, 2011).

PERK, IRE1 and ATF6 axes are all capable of activating or modulating the NF-κB signaling cascade, although each of these UPR arms may differ in terms of qualitative and quantitative NF-κB activity (Sundaram et al., 2018; Tam et al., 2012; Teske et al., 2011; Wang et al., 2014; Wolfson et al., 2008). Usually NF-κB is preserved as an inactive cytosolic form by the IκB proteins, thereby avoiding its instigation and nuclear transportation (Capece et al., 2018; May and Ghosh, 1997; Mussbacher et al., 2019; Sun, 2017). However, inflammatory factors engage IκB kinase (IKK) complex to enforce proteasomes-mediated IκB protein degradation, thereby unleashing NF-κB’s (nucleus-associated) inflammatory transcriptional activity (Capece et al., 2018; May and Ghosh, 1997; Mussbacher et al., 2019; Sun, 2017).

Similarly, the IRE1 axis also stimulates NF-κB activity by enforcing proteasomal degradation of IκB (Duran-Aniotz et al., 2017; Rubio et al., 2011; Tam et al., 2012). PERK commands a slightly different pathway for this purpose, it enforces translational inhibition of IκB thereby freeing NF-κB for engaging its transcriptional program (Blais et al., 2006; Halliday et al., 2017; Pytel et al., 2016; Qiao et al., 2017; Tam et al., 2012). Lastly, although ATF6 axis has been shown to influence NF-κB activation yet, the exact mechanism underlying this cascade has not been established (Tam et al., 2018; Yamazaki et al., 2009). Similar to NF-κB, AP1 is an important inflammatory transcription factor composed of monomers of a variety of proteins, like Jun proto-oncogene or JUN, Fos proto-oncogene or FOS, ATF and/or, musculoaponeurotic fibrosarcoma (MAF) (Uluçkan et al., 2015; van Dam and Castellazzi, 2001; Wagner, 2010). Different combinations of these proteins give rise to functional AP1 homo/hetero-dimers, which in turn influence the nature of the transcriptional program (Macián et al., 2001; Shaulian and Karin, 2001; Vesely et al., 2009). TNF, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 8 (IL8), and various cytokine receptors, are some of the most notorious genes within the transcriptional control of AP1 (Adcock, 1997; Hamilton, 2002; Hansen et al., 2008; Kyriakis, 1999; Thomas et al., 1997; Wu et al., 2001).
Herein, mainly the IRE1 axis has been documented to activate the AP1-driven transcriptional program whereas the direct role of other UPR signaling arms is still controversial (Rubio et al., 2011; Shah et al., 2016).

Apart from the specific inflammatory transcriptional programs, ER stress/UPR can also initiate the more multifarious inflammatory process of acute-phase response (APR) (Morito and Nagata, 2012; Reverendo et al., 2019; Zhang, 2010; Zhang et al., 2006). APR is typically elicited during the very early phases of an innate immune reaction, driven primarily by a set of pro-inflammatory acute-phase proteins (APPs) consisting of cytokines, like IL1, IL6 and/or TNF (Banks et al., 1995; Bode et al., 2012; Slaats et al., 2016). However APR is not a solitary (coherent) reaction but, rather, a cluster of cell, tissue, and organ-level stress adaptive processes, aimed at activating the immune system so it can prepare to tackle an impending pathological, or sterile injury (Joung et al., 2019; Kubes and Mehal, 2012; McDonald and Kubes, 2016; Natoli and Ostuni, 2019; Zelenay and Reis e Sousa, 2013). APR is largely responsible for various early physiological signs of injury or trauma, like fever, increased “permeability” of the vascular network, shift in the metabolites profile (often detectable via serum diagnostic methods), modified neurological reactions, and other similar (macroscopic) pathological symptoms (Joung et al., 2019; Kubes and Mehal, 2012; McDonald and Kubes, 2016; Natoli and Ostuni, 2019; Zelenay and Reis e Sousa, 2013). This is typically accompanied by a sharp increase in serum levels of nearly 200 different APPs including pro-inflammatory cytokines, factors modulating the pituitary-adrenal hormonal axis or cardiovascular system (e.g., C-reactive protein or CRP), and factors eliciting localized or systemic neutrophilia (mainly contributed by hepatocytes, and supported by few other cell-types) (Dinarello, 2006; Hribal et al., 2014; Kim and Moudgil, 2017; Li and Li, 2019; Paik et al., 2007; Tilg et al., 1997; Walsh et al., 2007). Even though APR aims to control damage to the tissue yet, very prolonged persistence of APPs can be the reason behind APR-associated adverse immunological events (Joung et al., 2019; Kubes and Mehal, 2012; McDonald and Kubes, 2016; Natoli and Ostuni, 2019; Zelenay and Reis e Sousa, 2013). In contrast to activation of NF-κB or AP1, where PERK/IRE1 axes of UPR dominate, in case of APR the ATF6 axis of the UPR seems to play a more important role (Duvigneau et al., 2018; Lehotský et al., 2009). In some cases, the cyclic-AMP-responsive-element-binding protein H (CREBH) may support the pro-APR activity of the ATF6 (Zhang et al., 2006, 2012).
Last but not least, ER stress/UPR can also modulate danger signaling mediated by damage-associated molecular patterns (DAMPs) acting as danger signals (Brenner et al., 2013; Fucikova et al., 2015; Hou et al., 2013; Krysко et al., 2012; Land et al., 2016a,b; Ravichandran, 2011; Reverendo et al., 2019; Rufo et al., 2017; Vénéreau et al., 2015). Danger signaling is a context-dependent inflammatory process, that can aid or impede canonical inflammatory reactions, depending upon the type of DAMPs emitted and cognate receptors engaged, thereby either ameliorating or exacerbating a particular disease (de Haan et al., 2013; Brenner et al., 2013; Foell et al., 2007; Garg and Agostinis, 2017; Garg et al., 2016a; O’Shea and Murray, 2008; Rock and Kono, 2008). For instance, in case of diseases with dysregulated inflammatory milieu (e.g., cancer), ordered exposure of prophagocytic, chemotactic and immune cell activating DAMPs can be crucial for induction of anticancer immunity (Bracci et al., 2017; Cronin and Penninger, 2007; Fang et al., 2019; Galluzzi et al., 2017; He et al., 2013; Iurescia et al., 2018; Lee et al., 2016; Ma et al., 2011; Ravichandran, 2011; Seong and Matzinger, 2004). In contrast, DAMPs can not only support autoimmune diseases (e.g., GRP78 in case of autoimmune diabetes) but, they can also sometime be the primary pathological factors underlying their progression (e.g., nucleic acids during lupus) (Anaya et al., 2007; Anders, 2005; Cheng and Anderson, 2012; Cunha-Neto et al., 2011; Pedersen et al., 2011; Rizzo et al., 2014; Rondas et al., 2015). Nevertheless, in case of cancer it has been shown that the PERK axis can facilitate the active secretion or, surface exposure of danger signals, like calreticulin (a well-established “eat me” signal) or, ATP (a short-range “find me” signal) during the process of apoptotic immunogenic cell death (ICD) (Garg et al., 2012b, 2015c, 2017b; Kepp et al., 2014; Tesniere et al., 2008). However it is apparent that this function is sometimes contingent on PERK’s UPR-related role (in case chemotherapy-induced surface-calreticulin) but, on other occasions it involves an as-yet-uncharacterized direct role of PERK in regulating the expansion of the secretory apparatus (in case of surface-calreticulin or secreted ATP elicited by ER-directed therapeutic oxidative stress achieved by hypericin-based photodynamic therapy) (Galluzzi et al., 2018; Garg et al., 2012b, 2015a,b,c, 2016b; Kroemer et al., 2013; Liu et al., 2019; Martins et al., 2014; Moserova et al., 2017; Panaretakis et al., 2009).

From the above sections it is clear that ER stress/UPR can influence both qualitative and quantitative aspects of inflammation. Indeed, type I
IFN response is also a crucial inflammatory process (Mancuso et al., 2007; Uccellini and García-Sastre, 2018); however, the connection of ER stress/UPR with type I IFN responses has received comparatively much less attention than its connection with canonical transcriptional processes, like those mediated by NF-κB/AP1 or, underlying APR and danger signaling. In the next sections, we elaborate and attempt to summarize the broad interplay between type I IFNs and ER stress.

4. ER stress and type I IFNs: There and back again

4.1 Impact of ER stress on production or sensing of type I IFNs

A direct link between ER stress/UPR and type I IFNs has always been obscure because most chemical or pharmacological ER stress inducers do not (autonomously) cause considerable production of type I IFNs (Smith, 2014). However over the years accumulating evidence has indicated that the presence of ER stress can influence the production or sensing of type I IFNs induced by other perturbations like PRR agonists, infections (bacterial, viral or parasitic), autoimmune reactions or sterile injury-related factors (Smith, 2014). To understand the exact impact of ER stress/UPR on production or sensing of type I IFNs, we carried out a systematic literature analyses of publications indexed in PubMed database (Table 1). Remarkably it is clear that ER stress never directly engages type I IFNs production (Table 1). However, in presence of other inducers of type I IFNs (like infectious agents, PRR agonists, pharmacological ER stressors), ER stress plays an important role in modulating type I IFNs production, although whether it augments or suppresses it depends strongly on the context (Table 1).

Mechanistically speaking, the IRE1/XBP1 arm of the UPR mostly augments type I IFN production (Table 1), a function that seems to be aided by other stress-responsive proteins (protein kinase R or PKR, CREB-binding protein or CBP, p300), interferon-pathway related proteins (STING, IRF3) or even UPR-related proteins (ATF6). Interestingly this pro-type I IFNs activity of the IRE1 arm often operates through XBP1s’ ability to bind the IFNβ enhancer and promoter sequences (Table 1). Type I IFNs induced by agonists of PRRs, especially TLR2/3/4/9, cGAS/STING, melanoma differentiation-associated protein 5 (MDA5), seem to gain most advantage from the enhancing effects of the IRE1/XBP1 arm of the UPR (Table 1). In couple of instances, phosphorylation of eIF2α (either by PERK or PKR)
| Context                  | UPR or ISR entity involved   | Effect of ER stress on production of type I IFNs or their sensing by IFNα-receptor (IFNAR) | ER stressor or UPR activator | Cell type | Refs.          |
|-------------------------|-----------------------------|------------------------------------------------------------------------------------------|-----------------------------|-----------|----------------|
| Bacterial infection     | IRE1α → XBP1 → ATG9A        | Suppression of production; bacteria-induced UPR limits STING-dependent IFNβ production via ATG9A | *Streptococcus pneumoniae* | Murine BMDMs | Mitzel et al. (2014) |
|                         | IRE1α → PKR                | Augmentation of production; TLR4-mediated IRE1α activation causes PKR-driven stimulation of IFNβ production | *Chlamydia trachomatis*     | Human mDCs and murine BMDMs | Webster et al. (2016) |
|                         | STING → XBP1               | Augmentation of production; bacteria-elicited, STING-dependent, XBP1 activation enhances IFNβ production | *Brucella abortus*          | Murine BMDMs | Guimarães et al. (2019) |
| DCs responding to poly(I:C) or VSV | IRE1α → XBP1 | Augmentation of production; XBP1s enhances poly(I:C)-induced IFNβ                      | Tunicamycin, thapsigargin and VSV | Murine BMDCs | Hu et al. (2011) |
| Diabetes                | PERK                        | Suppression of sensing; whole-body or pancreas-specific ablation of PERK increases IFNAR1 levels thereby causing pancreatic toxicity-driven diabetes in mice | PERK knock-out phenotype?   | Mouse derived pancreatic islets | Yu et al. (2015) |
| General ER stress       | ATF6 or STING              | Augmentation of production; Ca²⁺ mobilizing ER stressors caused STING-dependent & IRF3-induced IFNβ; other ER stressors exploited ATF6 for IRF3-induced IFNβ | Thapsigargin, oxygen-glucose deprivation, tunicamycin and 2-DE | RAW264.7 cells and murine BMDMs | Liu et al. (2012) |
| Context                                      | UPR or ISR entity involved | Effect of ER stress on production of type I IFNs or their sensing by IFNα-receptor (IFNAR) | ER stressor or UPR activator | Cell type                                      | Refs.                        |
|----------------------------------------------|----------------------------|-----------------------------------------------|------------------------------|-----------------------------------------------|------------------------------|
| Hepatocellular steatosis during HCV infection | Not tested                 | Suppression of sensing; FFAs-based UPR causes phosphorylation-dependent and ubiquitination-driven IFNAR1 degradation | Saturated and unsaturated FFAs | S3-GFP replicon cell line (HCV2a)             | Gunduz et al. (2012)         |
| Macrophages responding to LPS                | XBP1                        | Augmentation of production; XBP1 together with IRF3, CBP and p300, enhances LPS-induced IFNβ | Thapsigargin                 | RAW264.7 cells and murine BMDMs               | Zeng et al. (2010)           |
| Parasitic infection                          | IRE1α→XBP1                 | Augmentation of production; XBP1s enhances IFNβ production (and shows increased binding to IFNβ enhancer and promoter sequences) | Leishmania amazonensis and thapsigargin | RAW264.7 cells and murine BMDMs               | Dias–Teixeira et al. (2016) |
| PBMCs and pDCs responding to PRR agonists (TLR2/4/9) | XBP1                        | Augmentation of production; XBP1s enhances PRR agonists-induced IFNα | PRR agonists                 | PBMCs and pDCs                               | Beisel et al. (2017)         |
| PRR agonist and chemical ER stress           | IRE1α                       | Augmentation of production; In cells depleted of SKIV2L or XRN1, UPR-associated IRE1α generates endogenous RLR ligands that stimulate type I IFNs | Thapsigargin and tunicamycin | BMDMs                                         | Eckard et al. (2014)         |
| PRR agonist (TLR3) and viral infection | PKR → phospho-eIF2α → ATF4 → GADD34 | Augmentation of production; GADD34 activity enhanced IFNβ production | Chikungunya virus and poly(I:C) | Mouse embryonic fibroblasts | Clavarino et al. (2012) |
|--------------------------------------|--------------------------------------|---------------------------------------------------------------|-------------------------------|-----------------------------|-------------------------|
| PRR agonists (TLR4/3, MDA5) | XBP1 | Augmentation of production; XBP1 (but not PERK or ATF6) enhances TLR4/3 or MDA5 agonists-induced IFNβ | Tunicamycin and thapsigargin | RAW264.7 cells and murine BMDMs | Smith et al. (2008) |
| Viral infection | PERK → phospho-eIF2α → ATF4 → CHOP | Suppression of sensing; 3a protein & UPR causes phosphorylation-dependent and ubiquitination-driven IFNAR1 degradation | 3a protein of SARS-CoV | Huh7 | Minakshi et al. (2009) |
| | CHOP | Suppression of production; knocking-down CHOP activates IFNβ production | HCV and Dengue virus | Huh7 | Ke and Chen (2011) |
| | IRE1α → XBP1; ATF6 | Suppression of sensing; IRE1α-XBP1 and ATF6 together inhibit JAK–STAT signaling thereby obstructing responses to IFNα | WNV | Mouse embryonic fibroblasts | Ambrose and Mackenzie (2011, 2013) |
| | PERK | Suppression of sensing; PERK and UPR-induced autophagy caused IFNAR1 degradation | HCV and thapsigargin | Huh7 | Chandra et al. (2014) |
| | PERK → phospho-eIF2α | Augmentation of production; TGEV-induced UPR enhances type I IFN production via the PERK arm | TGEV | ST cells | Xue et al. (2018) |

*Continued*
| Context                          | UPR or ISR entity involved | Effect of ER stress on production/sensing of type I IFNs or their sensing by IFNα-receptor (IFNAR) | ER stressor or UPR activator | Cell type                  | Refs.                  |
|---------------------------------|----------------------------|------------------------------------------------------------------------------------------------|-----------------------------|----------------------------|-------------------------|
| Viral infection and chemical ER stress | Not tested                 | Suppression of sensing; During UPR, CK1α kinase causes S535 phosphorylation-dependent and ubiquitination-driven IFNAR1 degradation | VSV and thapsigargin        | Mouse embryonic fibroblasts, HeLa and 2fTGH | Bhattacharya et al. (2010) and Liu et al. (2009a) |
| PERK                            |                            | Suppression of sensing; PERK promotes phosphorylation-dependent and ubiquitination-driven IFNAR1 degradation | VSV, HCV and thapsigargin   | Mouse embryonic fibroblasts | Liu et al. (2009b)      |
| PERK → p38                      |                            | Suppression of sensing; p38 protein kinase causes phosphorylation-dependent and ubiquitination-driven IFNAR1 degradation | VSV and thapsigargin        | Mouse embryonic fibroblasts, HeLa and 2fTGH | Bhattacharya et al. (2011) |

Abbreviations: 2-DE, 2-deoxyglucose; ATF4/6, activating transcription factor 4 or 6; ATG9, autophagy related 9; BMDC, bone marrow derived dendritic cells; BMDM, bone marrow derived macrophages; CBP, cAMP response element binding protein (CREB)-binding protein; CHOP, CCAAT-enhancer-binding protein homologous protein; CK1α, casein kinase 1-alpha; DCs, dendritic cells; ER, endoplasmic reticulum; FFAs, free fatty acids; GADD34, growth-arrest and DNA damage-inducible protein 34; HCV, hepatitis C virus; IFN, interferon; IFNAR, interferon alpha/beta receptor; IRE1α, inositol-requiring enzyme 1 alpha; IRF3, interferon regulatory factor 3; ISR, integrated stress response; JAK, janus kinase; LPS, lipopolysaccharide; MDA5, melanoma differentiation-associated protein 5; mDCs, monocyte-derived dendritic cells; PBMCs, peripheral blood mononuclear cells; pDCs, plasmacytoid dendritic cells; PERK, PKR-like endoplasmic reticulum kinase; Phospho-eIF2α, phosphorylated eukaryotic translation initiation factor 2A; PKR, protein kinase R; Poly(I:C), polyinosinic:polycytidylic acid; PRR, pattern recognition receptor; RLR, retinoic acid-inducible gene I (RIG-I)-like receptors; SARS-CoV, severe acute respiratory syndrome-related coronavirus; SKIV2L, superkiller viralicidic activity 2-like RNA helicase; STAT, signal transducer and activator of transcription; STING, stimulator of interferon genes; TGEV, transmissible gastroenteritis virus; TLR, toll-like receptor; UPR, unfolded protein response; VSV, vesicular stomatitis virus; WNV, West Nile virus; XBP1, X-box binding protein 1; XBP1s, spliced XBP1 isoform; XRN1, 5′–3′ exoribonuclease 1.
also seems to support type I IFNs production, however this occurs much less often when compared to the Ire1/Xbp1 arm (Table 1).

Nonetheless in line with the complex nature of UPR’s functional effects (Hazari et al., 2016; Milev and Gatfield, 2018), UPR signaling also plays a detrimental role by suppressing type I IFN responses. Based on our survey (Table 1), two main type I IFN impeding pathways emerged: (1) in most cases, UPR was found to disrupt the sensing of type I IFNs by reducing the overall expression of its cognate receptor IFNAR1; (2) in other cases, ER stress-autophagy interplay (Klionsky et al., 2016) was found to target particular components of the type I IFNs signaling pathway, thereby disrupting either the type I IFNs production itself or its IFNAR1-dependent sensing. Interestingly, the PERK arm of the UPR was mostly reported to play a role in suppressing type I IFNs production or sensing (Table 1). In most cases the major pathway PERK was enforcing for suppressing type I IFN responses involved, IFNAR1 phosphorylation that drove the ubiquitination-based degradation of IFNAR1, which compromised the sensitization of target cells toward type I IFNs (Table 1; Fig. 1). Of note, degradation of IFNAR1 is one of the most prevalent phenomena for compromising responsiveness to type I IFNs in various diseased contexts (Araya and Goldszmid, 2017; Bhattacharya et al., 2010, 2014). It involves TYK2-dependent phosphorylation of serine residues in IFNAR1 (S526 in mice or S535 in humans) that attracts βTrcp E3 ubiquitin ligase-dependent IFNAR1 ubiquitination. Thereafter the ubiquitinated IFNAR1 is internalized and degraded via the lysosomes (Liu et al., 2009b) (Fig. 1). Signaling modules mostly reported to cause IFNAR1 degradation include those operated by the p38 protein kinase pathway (Araya and Goldszmid, 2017; Bhattacharya et al., 2011), casein kinase 1α (CK1alpha) (Liu et al., 2009a), and sphingosine 1-phosphate receptor (S1PR1)-associated pathway (Teijaro et al., 2016).

In terms of types of physicochemical ER stressors (Couve and Hetz, 2014), a wide-range of ER stress inducers including oxygen–glucose deprivation and pharmacological agents (tunicamycin, thapsigargin) can modulate type I IFNs induced by PRR agonists (Liu et al., 2012) (Table 1). However the mechanisms behind this modulation, as well as, its ultimate outcome (i.e., augmentation or deprivation of type I IFNs production or response) varies significantly from one ER stress–inducing agent to another (Liu et al., 2012). Such variation is even applicable to the context of viral infections despite the fact that, unlike the above physicochemical ER stressors, viruses
are capable of eliciting both ER stress and type I IFNs (Jheng et al., 2014; Tardif et al., 2005; Yoshida, 2007). As evident from Table 1, whereas viral induction of ER stress-driven UPR signaling is indeed a ubiquitous phenomenon yet, the qualitative characteristics of virus-induced UPR do differ depending on the type of virus (Liu et al., 2009b; Shinjo et al., 2013). More specifically, depending on the virus, the UPR signaling might be driven by either the IRE1 arm or, PERK arm (Lin et al., 2009; Song et al., 2019); and this differential dominance of UPR arms may eventually govern the effects of UPR on production or sensing of type I IFNs (Table 1). Of note, ATF6 activation is not always analyzed with as much consistency as IRE1 or PERK (Sundaram et al., 2018; Tay et al., 2014); however in few studies where this arm was investigated, it seemed that ATF6 tended to synergize more with IRE1’s contribution in regulating type I IFN production or sensing (Table 1).

Finally, although none of the studies mentioned in Table 1 were directly dealing with cancer, yet several utilized cancer cells lines (e.g., HeLa cells). Thus, these results may also have direct implications for cancer immunology, at least in the context of oncolytic virotherapy.

4.2 Induction of ER stress by type I IFNs

Type I IFNs, as mentioned previously, do not always have a disease-impeding effect (Burdick et al., 2009). In the context of specific autoimmune pathologies like type 1 diabetes or interferonopathies, type I IFNs can play a disease-supportive, or even a disease-initiating role (Burdick et al., 2009; Lee-Kirsch et al., 2015). Research has shown that persistent presence of type I IFNs that fails to resolve in time supports chronic inflammation that may cause worsening of some pathologies (Akbar et al., 2000; Lee-Kirsch et al., 2015). This scenario is particularly applicable to type 1 diabetes wherein inflammation and/or autoimmunity causes apoptosis of pancreatic beta cells thereby impairing secretion of insulin (Eizirik et al., 2009). For instance, children with genetic predisposition toward type 1 diabetes often exhibit an augmented type I IFN-associated genetic signature, preceding the emerge of auto-antibodies (Marroqui et al., 2017). Moreover, antibody-based blockade of IFNAR1 has been often shown to ameliorate type 1 diabetes, at least pre-clinically (Marroqui et al., 2017). It is known for a long time that ER stress has an important role in regulating beta cell apoptosis during type 1 diabetes, thereby leading to prioritization of preclinical research on ER stress modulators for treating type 1 diabetes.
Interestingly, recently a link between type I IFNs and ER stress is starting to emerge in this context. Apparently IFNα, along with IFNβ, can augment apoptosis of beta cells in-part via ER stress thereby facilitating type 1 diabetes (Marroqui et al., 2017). In fact, even without beta cell apoptosis, IFNα-induced ER stress can create ER–associated proteotoxicity that can impede the maturation and secretion of insulin (Lombardi and Tomer, 2017). Thus not surprisingly, pre-treatment of beta cells with ER stress-impeding chemical chaperones can almost completely prevent the negative effects of IFNα on beta cells (Lombardi and Tomer, 2017). Nevertheless, apoptosis induced by type I IFNs, while detrimental in contexts like type 1 diabetes, can also be beneficial in case of other pathologies. For example, during infections (to eliminate an infected cell, and along with it, the endogenous microbes) and cancer (to eliminate cancer cells via apoptosis), type I IFN-induced elimination of diseased cells is highly desirable. Interestingly, type I IFNs can indeed cause apoptosis in cancer cells or virally infected cells at least partially via ER stress induction (Mihailidou et al., 2017; Shi et al., 2016; Smith, 2014). In case of cancer however, from the available data it is not conclusive whether this ER stress induction by type I IFNs is as potent as pharmacological ER stressors in inducing high levels of apoptosis. Moreover, most studies reporting this phenomenon achieved this effect in vitro, and hence it remains unclear whether type I IFNs can reach high enough concentrations in vivo to elicit ER stress-driven apoptosis consistently.

### 4.3 ER stress and STING-based type I IFN signaling

Besides serving as a biosynthetic “factory” for type I IFNs production, ER can also provide a certain degree of structural support to type I IFN response. More specifically STING, which is part of an important PRR complex (i.e., cGAS/STING, as discussed above), localizes to the ER membrane in basal conditions (Ishikawa and Barber, 2008). When cGAS encounters its cognate PAMPs or DAMPs, it elicits (via cGAMP moieties-driven activation) translocation of STING toward the ER–Golgi intermediate compartment (ERGIC) wherein STING engages TBK1 and IRF3 to eventually orchestrate type I IFNs production (Barber, 2015). Of note in basal conditions, STING might also be present in mitochondria-associated ER membrane (MAMs), a site of physical association between mitochondria and ER (Ishikawa et al., 2009). However, this partial MAMs localization is of no palpable functional significance since upon activation, STING is only found in the ERGIC
(Ishikawa et al., 2009). Interestingly, several lines of evidence have linked STING with ER stress-linked pathologies (Garg et al., 2012a; Wu et al., 2019). For instance, Gram-positive bacteria based elicitation of STING causes ER stress, which can engage an autophagic pathway to carryout ER-phagy (in order to ameliorate bacteria-induced ER stress) (Moretti et al., 2017). Interestingly, this ER-phagy stimulates an interferon response by transferring STING to the autophagosomes (Moretti et al., 2017). Overall, this pathway seems to play an important role in ensuring the post-infection viability of cells (Moretti et al., 2017). On the flip side, STING-mediated disruption of Ca^{2+} homeostasis can end up activating ER stress that can cause apoptosis of various normal cells thereby leading to STING-linked immunopathologies (Wu et al., 2019). Similarly STING and IRF3 can together drive alcoholic liver disease by linking ER stress with apoptosis (Petrasek et al., 2013). More specifically, alcoholic insult can elicit ER stress accompanied by IRF3-STING interaction that paves way for the activation of pro-apoptotic machinery (Petrasek et al., 2013). Interestingly, deletion of STING overcomes these disparities and also reduces ER stress thereby substantiating a direct connection in this context (Petrasek et al., 2013). Mechanistically it seems that ER might be restraining over-activation of STING in basal conditions via the Ca^{2+}-binding protein, Stromal Interaction Molecule 1 (STIM1); since, absence of STIM1 causes spontaneous activation of the STING-TBK1-IRF3 pathway thereby leading to type I IFN-mediated autoimmune reactions (Srikanth et al., 2019).

Although these cross-talks between ER stress and STING is largely independent of the cGAS/STING-based type I IFNs production pathway yet it is of critical importance considering the attention STING agonists (for cancer immunotherapy) or antagonists (for autoimmune diseases) have recently received in preclinical and clinical studies (Berger et al., 2019; Corrales and Gajewski, 2015; Garg et al., 2017d; Lemos et al., 2015; McCaffrey, 2017; Ramanjulu et al., 2018). In case these STING-targeting therapeutics cause adverse side-effects like autoimmune reactions in the clinic, then this may create a precedent to explore the application of ER stress ameliorating therapeutics, in combinatorial manner.

5. Conclusion

Type I IFNs exhibit critical functions in many sterile as well as non-sterile inflammatory diseases or immunopathologies, thereby positioning them at the core of almost all therapeutic paradigms. Like several other
cytokine families, there also exist extensive overlaps between type I IFNs production or sensing, and the ER, which positions ER stress at a critical cross-road with the type I IFNs-associated functions. Indeed, stress adaptive processes co-ordinated by ER stress are not limited to taking only life or death decisions in a cellular context. Along with these, ER stress also modulates inflammation in order to recruit the services of immune cells to maintain tissue homeostasis. Thus, it is not surprising that ER stress is frequently connected to the creation of numerous pro-inflammatory cytokines. However, a direct link between ER stress and type I IFNs has always been obscure because, unlike many other cytokines, most ER stress inducers do not (autonomously) cause considerable production of type I IFNs. However, the presence of ER stress can in fact influence the production or sensing of type I IFNs induced by other perturbations like PRR agonists, infections (bacterial, viral or parasitic), interferonopathies, autoimmune reactions, or trauma/injury-related factors. Despite this crucial interplay between ER stress and type I IFNs that can have overarching implications for several human diseases, this connection has received comparatively much less attention than the connection of ER stress with, canonical transcriptional processes (like those mediated by NF-κB/AP1), APR or danger signaling. Thus, in future it is crucial to carryout both systematic as well as large-scale explorative studies to comprehensively understand how ER stress influences type I IFNs. This is especially important for disease contexts where these two play an important role however their cross-talk is not completely understood, e.g., cancer, respiratory pathologies, Crohn’s disease or ulcerative colitis (amongst others).

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