Cytokine 124 (2019) 154577

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Crosstalk between inflammatory mediators and endoplasmic reticulum stress in liver diseases

J. Catharina Duvigneau[a], Andreia Luís[b], Adrienne M. Gorman[c], Afshin Samali[c], Doris Kaltenecker[d,e], Richard Moriggl[d,e,f], Andrey V. Kozlov[b,g,*]

[a] Institute for Medical Biochemistry, University of Veterinary Medicine Vienna, Vienna, Austria
[b] Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria
[c] Apoptosis Research Centre, National University of Ireland, Galway, Ireland
[d] Ludwig Boltzmann Institute for Cancer Research, Vienna, Austria
[e] Institute of Animal Breeding and Genetics, University of Veterinary Medicine, Vienna, Austria
[f] Medical University Vienna, Vienna, Austria
[g] Laboratory of Navigational Redox Lipidomics and Department of Human Pathology, IM Sechenov Moscow State Medical University, Russian Federation

ARTICLE INFO

Keywords:
IL-1β
Interleukin-6
Endoplasmic reticulum stress
Unfolded protein response
Liver diseases
TNF-α
Inflammatory response

ABSTRACT

An excessive inflammatory response is frequently associated with cellular dysfunction and cell death. The latter may cause single and multiple organ failure. The most susceptible organs are liver, lung, kidney, heart and intestine. This review will focus on the liver as a target organ for an excessive inflammatory response. It is commonly accepted that organ failure is caused by the action of inflammatory cytokines released in excess during the inflammatory response. It has been suggested that inflammation mediated liver failure is not due to an increased death rate of parenchymal cells, but due to an intracellular metabolic disorder. This metabolic disorder is associated with mitochondrial and endoplasmic reticulum (ER) dysfunction during the acute phase response elicited by systemic inflammation. An overproduction of acute phase proteins in the liver as well as elevated reactive oxygen species (ROS) generation induce ER stress, triggering the unfolded protein response (UPR), which may initiate or aggravate inflammation. It is known that certain inflammatory mediators, such as the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α induce ER stress. These findings suggest that ER stress and the subsequent UPR on the one hand, and the inflammatory response on the other create a kind of feed forward loop, which can be either beneficial (e.g., elimination of the pathogen and restoration of tissue homeostasis) or deleterious (e.g., excessive cell dysfunction and cell death). This review aims to unfurl the different pathways contributing to this loop and to highlight the relevance of UPR signaling (IRE1α, ATF6, and PERK) and mediators of the inflammatory response (NF-κB, STAT3, IL-1β, IL-6, TLR) which have a particular role as pathophysiological triggers in the liver.

1. Manifestation of ER stress and inflammation in liver diseases

The liver is a metabolic organ that continuously provides the organism with nutrients, eliminates waste and toxic or harmful compounds. The liver is also a site of complex immunological activity. Dietary and microbial products challenge liver-resident immune cells (Kupffer cells/macrophages) and activate immune response mechanisms, producing cytokines which regulate the function of hepatocytes and other non-hematopoietic cells in the liver. An appropriate inflammatory reaction induced by invading pathogens or by damaged

Abbreviations: ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; BiP, binding immunoglobulin protein (gene GRP78); CHOP, CAAT/enhancer binding protein (C/EBP) homologous protein; eIF2α, eukaryotic translation initiation factor 2α; ER, endoplasmic reticulum; ERAD, ER-associated protein degradation; GADD34, growth arrest and DNA-damage-inducible 34; GRP78, glucose regulated protein 78; iNOS, inducible nitric oxide synthase; IRE1α, inositol-requiring enzyme 1 α; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 OR Nod-like receptor protein 3; NO, nitric oxide; p-eIF2α, phospho-eIF2α; PERK, protein kinase RNA-like (PKR-like) endoplasmic reticulum kinase; RIDD, regulated IRE1-dependent decay; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TLR, toll-like receptor; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor alpha; TRAF2, TNF receptor-associated factor 2; TUDCA, tauroursodeoxycholic acid; UPR, unfolded protein response; XBP1, X box-binding protein 1; XBP1s, spliced isoform of XBP1

* Corresponding author at: Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Donaueschingen Str. 13, 1200 Vienna, Austria.
E-mail address: andrey.kozlov@trauma.lbg.ac.at (A.V. Kozlov).

https://doi.org/10.1016/j.cyto.2018.10.018
Received 25 September 2018; Accepted 18 October 2018
Available online 14 November 2018

tissue is essential for the clearance of the invader and for the restoration of homeostasis [1–4]. However, failure to eliminate the invader or to resolve inflammation leads to the development of liver pathologies associated with chronic infection, autoimmunity and malignancy (for review see:[3,5–7]). Chronic inflammation is associated with deranged tissue remodelling, resulting in liver fibrosis, hepatocyte dysfunction and steatosis [6,7].

Although the endoplasmic reticulum (ER) was discovered by *K. R. Porter* in 1945 [8], it is just in the last decade that many vital functions of the ER are being explored in the liver, including protein production, lipid synthesis, drug detoxification, and Ca^{2+} homeostasis. Evidence for a role for the ER in a range of liver diseases has also emerged. Perturbation in ER homeostasis, including Ca^{2+} levels, redox homeostasis, reduced availability of monosaccharides required for protein glycosylation, can all compromise proper folding of proteins within the ER. This results in a condition that is termed ER stress, which is characterised by an accumulation of unfolded proteins within the ER lumen [9,10]. ER stress is notably associated with viral and autoimmune hepatitis, alcoholic liver disease [11–15]; for review see: [16–19]. Furthermore, chronic accumulation of misfolded proteins and subsequent sustained ER stress plays a particular role in nutrient-mediated liver diseases (non-alcoholic fatty liver diseases) and steatosis [12,13,20,21] via dysregulated lipid metabolism [15,21,22] (for review see: [16,19,20,23–26]).

Accumulating evidence indicates that the liver's role in regulating the immune response is linked to ER stress and inflammation. Agents that induce inflammation, i.e., pathogen-associated molecular pattern molecules (PAMPs) and damage-associated molecular pattern molecules (DAMPs), activate the so-called 'acute phase response', an early systemic response which is mediated primarily by interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signaling (for review see:[27–29]) and the pro-inflammatory cytokines IL-1-beta (IL-1β) and tumor necrosis factor alpha (TNF-α) [30]. The acute phase response targets hepatocytes, the main cells of liver parenchyma, which adapt metabolism and the repertoire of secreted proteins to the changed demands by producing acute phase proteins [31]. The acute phase proteins alert the system and constitute a first-line and non-specific defence of the organism against invading pathogens [32]. Elimination of the invader activates mechanisms to resolve inflammation and restore liver homeostasis. Failure to eliminate the invader or to resolve inflammation can lead to the development of liver pathologies associated with chronic infection, autoimmunity and malignancy (for review see: [3,6,7]). Chronic inflammation is associated with deranged tissue remodelling, resulting in liver fibrosis, hepatocyte dysfunction and steatosis [6,7].

Evidence shows that ER stress is directly linked to the induction of an inflammatory response [33]. However, there is also evidence for the converse, i.e., that inflammatory mediators directly or indirectly impact on the ER. This suggests the existence of a feedback loop between ER stress and inflammatory responses in the liver with the potential to generate a vicious cycle, which amplifies the inflammatory response and thereby aggravates liver injury. In this review we address the pathophysiological impact of ER stress and selected inflammatory mediators in the liver, focussing on their points of intersection, and how

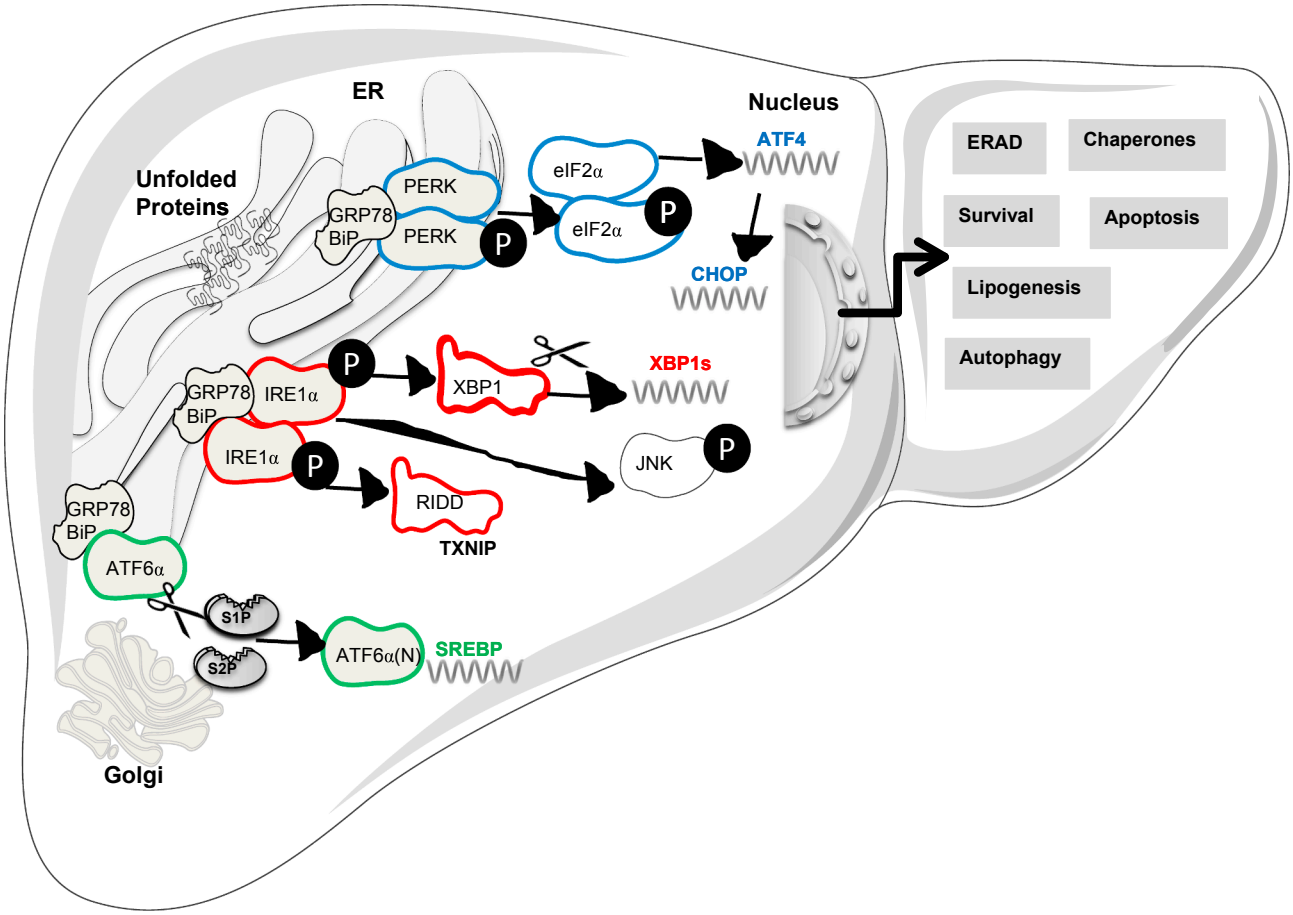

Fig. 1. Physiological functions of the UPR in the liver. The canonical branches of the UPR are three-fold: (i) RNA-dependent protein kinase (PKR)-like ER kinase (PERK), (ii) inositol-requiring enzyme-1-alpha (IRE1α) and (iii) activating transcription factor 6 (ATF6). The liver is one of the major secretory organs in the body and because of this it is more prone to errors in synthesis, folding and transport of proteins than other organs. A well-functioning UPR is essential for hepatocyte function, controlling decisions between survival and death, as well as regulating autophagy and lipogenesis.

these contribute to resolution or the deterioration of hepatic pathophysiology and a detrimental progression of liver disease.

2. ER stress and UPR in liver physiology (Fig. 1)

The liver produces the majority of plasma proteins, at a synthesis rate that can be particularly high, reaching up to 30 g/day [34,35]. The great majority of proteins produced and secreted by the liver comprise albumin, peptide hormones, carrier proteins, apolipoproteins, coagulation factors, transferrin, ceruloplasmin, thyroid-binding globulin, haptoglobin, globulins and α-1-antitrypsin. Hepatocytes synthesise most of these serum proteins. Since the ER controls the synthesis, folding and trafficking of secreted proteins its optimal functioning is particularly important for liver function. Another important role of the ER in the liver is its impact on lipid homeostasis [13]. Several transcription factors and coactivators, comprising cAMP response element-binding protein (CREB) [36,37], peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) [36,38], forkhead box protein O1 (FOXO1) [39], sterol regulatory element binding protein 1c (SREBP-1c) [40], and CREB regulated transcription coactivator 2 (CRTC2) [37], all regulate key steps in lipid metabolism through ER surveillance [41]. In addition, the liver is rich in smooth ER equipped with enzymes that metabolize lipid-soluble compounds. These detoxifying enzymes inactivate a number of potentially harmful drugs by converting them to water-soluble compounds that can be eliminated from the body in the urine [42]. The ER is also an important organelle for the storage and release of Ca^{2+} [43].

Disturbances of the ER homeostasis can be caused by depletion of Ca^{2+} [44–46], alterations in the redox status [47], deprivation of glucose [48], gene mutations [49–51], hypoxia [52,53], mitochondrial dysfunction [54,55] and inflammation [56–58]. In the face of ER stress the cell triggers an adaptive response, the Unfolded Protein Response (UPR), which aims to restore homeostasis by increasing folding capacity of the ER (through upregulation of chaperones) and by decreasing the input burden of the ER (by inhibiting general protein synthesis and promoting degradation of ER-targeted mRNAs). The accumulation of unfolded proteins within the ER is sensed by three ER *trans*-membrane signal transducers: inositol-requiring kinase 1 alpha (IRE1α), double-stranded RNA-activated protein kinase-like ER kinase (PERK) and activating transcription factor 6 (ATF6) [18]. Under homeostatic conditions the chaperone protein GRP78 (also known as BiP) is bound to the ER luminal domains of IRE1α, PERK and ATF6 preventing their activation. Under stress conditions, GRP78/BiP is redirected towards unfolded proteins in the ER, allowing activation of the three transducers.

During ER stress, IRE1α undergoes dimerization and activation when it is released from GRP78/BiP [59]. IRE1α has both protein kinase and endonuclease activity, catalyzing one of the most studied UPR events - the splicing of XBP1 mRNA, producing a frame-shift that allows synthesis of an active transcription factor, XBP1s [60]. XBP1 preferentially transcribes genes that display the unique ER stress response element (ERSE). These genes include proteases, which degrade excess amounts of unfolded proteins by the ER-associated degradation mechanism (ERAD), proteins for an increased capacity for ER-chaperoning and for an increased synthesis of membrane lipids (lipogenesis) for enlarging ER volume. Similarly, the release of GRP78/BiP from PERK allows its dimerization and activation which promotes the phosphorylation of eIF2α, and leads to a reduction of general translation [61]. Paradoxically, eIF2α phosphorylation induces the translation of ATF4 mRNA, a transcription factor that regulates the expression of anti-oxidative stress-response genes and genes encoding proteins with pro-apoptotic functions, such as transcription factor C/EPB homologous protein (CHOP) [62]. In contrast to the other two transducers, when ATF6 is liberated from GRP78/BiP it is transported to the Golgi compartment, where it is cleaved by site-1-protease (S1P) and site-2-protease (S2P) [62]. The resultant cytoplasmic fragment is then translocated to the nucleus where it acts as a potent transcription factor targeting UPR genes, in redundancy with XBP1s. Overall, the main purpose of UPR induction is to relieve the ER stress and restore normal cellular homeostasis [18,63].

If ER stress is severe or prolonged, this adaptive response is frequently unsuccessful and ER function is continuously compromised, then the ER stress may induce pathological changes in the liver such as hepatic fat accumulation and liver inflammation. In addition, the UPR can also trigger apoptosis and/or autophagy [29,64–67]. Among other proteins, CHOP [68], growth arrest-and DNA damage-inducible gene 34 (GADD34) [69], apoptosis signal-regulating kinase 1 (ASK1) [70], and c-Jun N-terminal kinase (JNK) [71,72] have been reported to regulate a complex interplay between the adaptive and apoptotic branches of the UPR response [5]. For example, it was recently reported that CHOP may favor ER stress-induced apoptosis in hepatocellular carcinoma cells via inhibition of autophagy. Importantly, in the context of the liver, unresolved ER stress has been linked to the development of liver pathology and will be described in the following section.

3. Unresolved ER stress as a mechanism of liver dysfunction

Due to vital role of ER for the hepatic tissue, ER stress has been explored in liver dysfunction in hepatic viral infections [65,73–75], metabolic disorders [76,77], mutations of genes encoding ER-resident proteins, cancers, abuse of alcohol or drugs [78], and non-alcoholic fatty liver disease (NAFLD) [79]. The increasing interest in the role of ER stress in liver diseases is contributing to a greater understanding of liver disease pathophysiology. Still, the direct relationship between ER dysfunction and liver failure is not completely clear. Unresolved ER stress, resulting in sustained or chronic ER dysfunction, activates the CHOP branch of UPR, a pro-death signaling pathway, which causes apoptotic cell death [80]. Interestingly, the apoptotic cell death could be prevented at multiple levels by interrupting the pro-death signaling pathway of UPR, e.g., CHOP deficiency [81]. However, in this case the initial cause for ER stress will remain, and the ER function will not recover. Several models show that persistent ER dysfunction will lead to critical changes in the liver metabolism, such as steatosis, fibrosis, leading to liver cell damage and finally cell death [35,82,83]. All these observations show that ER stress results in a disturbed protein and lipid metabolism, thus representing cellular dysfunction, but does not induce cell death by itself. The cell death is triggered by the UPR. Thus, persisting ER stress will ultimately result in liver dysfunction, either due to an increased cell death, or by the unresolved cellular dysfunction. This persistent cellular dysfunction can be linked to inflammatory responses in the liver.

4. Inflammatory pathways in liver pathophysiology

Besides its central role in metabolism, the liver also plays important immunological roles. Foreign antigens deriving from the gastrointestinal tract require an appropriate reaction, an innate immune response in the case of infectious or toxic material, or immunological tolerance for the majority of harmless material. PAMPs, such as bacterial products, and DAMPs, components, which derive from the host itself and which may be released following increased tissue damage, activate pattern recognition receptors, such as the Toll-like receptor family (TLRs) and intracellular receptors that initiate the inflammasome assembly, nucleotide-binding domain and leucine-rich repeat receptors (NLRs). Activation of these receptors is an integral part of the immune response of the innate immune system and sets in motion complex signaling cascades, which lead to the secretion of pro-inflammatory cytokines and other inflammatory mediators that coordinate the elimination of pathogens, infected cells and induce the restoration of tissue homeostasis [84]. However, in the liver inappropriate TLR signaling may result in activation of hepatic immune and stellate cells, and excessive secretion of inflammatory modulators leading to chronic liver inflammation, injury and fibrosis [85,86].

Below we consider TLR3 and 4 signaling cascades, which are particularly important for induction of the inflammatory response in liver.

TLR4 signaling includes two major pathways, which recruit different adaptor proteins, a MyD88 (myeloid-differentiation-primary-response-gene-88)-dependent and a MyD88 independent/TRIF (Toll/IL-1R resistance (TIR) domain-containing adapter-inducing IFN-β) dependent pathway [87]. MyD88 is an essential part of the signaling cascade of all TLRs except for TLR3. Deficiency in TLR4 and the adaptor protein MyD88 renders mice fully resistant to induction of septic shock by *E. coli* [88]. The adaptor protein MyD88 induces TRAF6 –mediated activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [89], resulting in the transcription of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β. The MyD88-independent/TRIF-dependent pathway is unique to TLR3 and TLR4 signaling and results in interferon (IFN)-β production and a delayed activation of NF-κB. TLR3 and TLR4, upon ligand-binding, are moved to the endolysosome for degradation, where they interact with TRIF residing at the lysosomal membrane [90]. TRIF associates with the receptor-interacting serine–threonine kinase (RIPK)-1 leading also to an activation of NF-κB, however, with much slower kinetics [90].

The most effective mediators of inflammation are pro-inflammatory cytokines. Cytokines activate different effector functions and therefore act as communicators between the various cell populations residing in the liver, such as hepatocytes, endothelial cells, liver-resident macrophage (Kupffer cell), lymphocyte populations (mainly natural killer T cells), hepatic stellate cells, and the immune cells which enter the liver via hepatic arteries and portal vein branches. The cytokines most commonly associated with hepatic disorders are the pro-inflammatory cytokines TNF-α, IL-1, IL-6, and transforming growth factor (TGF)-β. In the liver TNF-α plays an important role for cellular homeostasis, since it either induces a pro-death signal by activating the apoptotic caspase cascade, or a pro-survival signal that involves activation of NF-κB [7]. The IL-1 family is fundamental to innate immunity, as their receptors intimately share components of the signaling cascade used by TLRs. IL-1 signaling is essential for activating the NF-κB family and is therefore primarily associated with acute and chronic inflammation [91], as it may constitute a feed forward inflammatory vicious cycle. IL-6 is the most important activator of the acute phase protein expression in hepatocytes, which is shaped in cooperation with members of the IL-1-family and other cytokines [92,93].

TLR4 is expressed in several cells of the healthy liver. However, despite the constant challenge with gut-derived LPS, the normal liver does not show signs of inflammation. This is achieved by the decreased expression of TLR4 and downstream components of the TLR signaling cascade, such as the adaptor protein MyD88, in liver residing innate immune cells compared to other organs and due to the particular ability to modulate TLR4 signaling [94]. Kupffer cells express TLR4 and are responsive to LPS and produce TNF-α, IL-1β, IL-6, IL-12, IL-18, and the anti-inflammatory cytokine IL-10 [95]. Chronic triggering of Kupffer cells by elevated levels of LPS upregulates TLR4 and enhances TNF-α production [96]. LPS/TLR4 signaling may also play a role in the pathogenesis of both alcoholic liver injury and non-alcoholic fatty liver disease (NAFLD). Apparently, in alcoholic fatty liver disease as well as in NAFLD hepatocyte injury is mediated by TLR4 signaling and MyD88 enhanced TNF-α levels from Kupffer cells, likely via enhanced ROS production leading to chronic liver inflammation [97].

Activation of Kupffer cells with DAMPs, particularly if primed via TLR4, also triggers assembly of the inflammasome complex, especially nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3), which lead to an increased production of IL-1β via activation of caspase 1 [98]. NLRP3 inflammasome activation involves TNF-α and IL-17, which perpetuate liver damage [99], and is therefore of particular importance in the amplification of liver inflammation and fibrosis associated with various liver diseases [100]. In stellate cells TLR4 signaling appears to be critically involved in liver fibrosis occurring in nearly all liver diseases associated with chronic inflammation. TGF-β is an important regulator of the synthesis of extracellular matrix proteins by these cells. Activated hepatic stellate cells express TLR4 and CD14 and respond to LPS [101].

Activation of the acute phase response is perhaps the most important link between inflammatory response and ER function. Via the acute phase proteins hepatocytes contribute to the control of inflammation at systemic level, since the acute phase proteins constitute a first-line and non-specific defence of the organism against invading pathogens. As stated earlier, this early systemic response requires STAT3 and the p65 subunit of NF-κB. In fact, STAT3 was first described as an IL-6-inducible DNA-binding factor that specifically interacts with enhancer elements located in the regulatory regions of genes encoding positive acute phase proteins [102]. Besides IL-6 family members STAT3 activation is achieved also in response to other cytokines, a variety of interferons or members of the IL-10-family and other stimuli including growth factors and hormones [103]. While the involvement of NF-κB expression exerts an inhibitory effect on the STAT3-dependent expression of γ-fibrinogen and α2-macroglobulin, for other acute phase proteins, such as C-reactive protein (CRP), or α1-acid glycoprotein [104] a synergistic or cooperative effect was shown. In addition, a direct role for STAT3 regulating the synthesis of components of the secretory pathway during the acute phase response of the liver was shown as well [27].

The most intriguing association of inflammation mediated ER stress is the discovery of the role of cyclic AMP responsive element-binding protein (CREBH), an ER-localized transcription factor. Similarly to ATF6 CREBH travels to the Golgi in response to ER stress. Interestingly, cytokines (IL-1β, IL-6 and TNF-α), but also metabolic signals trigger this transit, where it is cleaved by S1P and S2P processing enzymes. However, cleaved CREBH does not activate transcription of UPR genes, but transcription of acute-phase response genes, such as C-reactive protein and murine serum amyloid P component [105].

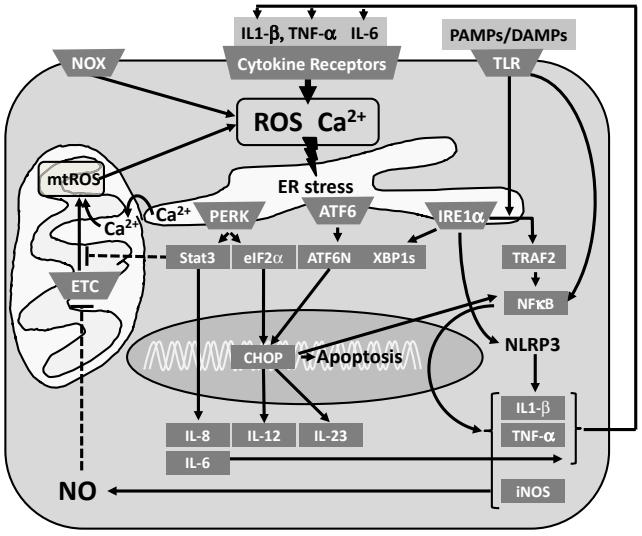

Fig. 2. Interaction between inflammation and ER stress in liver. In the initial phase of inflammation PAMPs/DAMPs activate ER stress, predominantly via IRE1α-TRAF2 pathway of UPR. TNF-α and IL-1β synthetized and released by this pathway in turn activate ER stress in liver cells in Ca^{2+}/ROS dependent manner. Another inflammatory gene up-regulated by NF-κB-pathway is iNOS. NO generated by iNOS blocks electron transport chain (ETC) in mitochondria, elevates mitochondrial ROS (mtROS) production, impairs Ca^{2+} homeostasis. The changes in ROS/Ca^{2+} levels activate all three branches of ER stress. Increased IL-6 expression downstream of the PERK pathway of UPR further aggravates UPR.

5. Induction of inflammation by ER stress and UPR (Fig. 2)

Proper protein synthesis is essential for cells with a demanding secretory activity. Thus ER stress triggered by metabolic derangements may be considered as intracellular danger signals, which are sensed by specialized structures of the innate immunity. Recent years have shown that the interaction of different UPR branches occur with microbe sensing structures, which have the potential to activate inflammatory cytokine production. In macrophages loaded with cholesterol, which disturbs the ER membrane homeostasis, ER stress induces both, apoptosis and secretion of TNF-α and IL-6 [106,107]. However, the underlying mechanisms are not fully elucidated, including the contribution of the three arms of the UPR. Most evidence points towards a role for IRE1α signalling through TNF-α-receptor-associated factor 2 (TRAF2) and PERK signaling through STAT3 in linking ER stress/UPR and inflammation.

Apart from its signalling through the splicing of XBP1 mRNA, IRE1α can also signal through an alternative IRE1α-TRAF2 pathway. It has been suggested that mild ER stress accompanied by the formation of IRE1α dimers predominantly catalyzes splicing of XBP1, while upon additional stress stimuli IRE1α oligomers can be formed which activate IRE1α-TRAF2 pathway [108]. Phosphorylation of IRE1α creates binding sites for TRAF2, which leads to JNK activation [109,109]. The IRE1α–TRAF2 complex can recruit IκB kinase (IKK), which phosphorylates IκB, leading to the degradation of IκB and the nuclear translocation of NF-κB [33], and the expression of NF-κB-dependent cytokines, and other downstream targets, such as inducible nitric oxide synthase (iNOS). Additionally, irremediable ER stress hyperactivates the RNase domain of IRE1α by *trans*-phosphorylation, which leads to massive degradation of ER-localized mRNAs, a mechanism called regulated IRE1-dependent decay (RIDD) [110,111]. Additionally, JNK is phosphorylated by the kinase activity of IRE1α to promote apoptosis [112]. Recent reports have adressed the involvement of RIDD in liver diseases [110]. By this mechanism also inflammation is induced, since persistent activation of IRE1α facilitates the degradation of miR17, which leads to the stabilization of thioredoxin-interacting protein (TXNIP) mRNA and a downstream activation of the NLRP3 inflammasome [113]. As outlined above, NLRP3 inflammasome plays a key role in liver inflammation and fibrosis [99]. In addition, RIDD has recently been linked to the translational activation of retinoic acid-inducible gene 1 (RIG1), a member of intracellular receptors that sense RNA viruses [114,115]. Activation of these receptors lead to enhanced production of INF-β, via NF-κB signalling elements [116], a mechanism which was shown to be inhibited by hepatitis C virus [117]. Thus, enhanced immune surveillance and viral stress response may be an important consequence of activated IRE1α-RIDD-RIG1 pathway.

The PERK branch of UPR can undergo two pathways. The classical pathway is mediated by elF2α (PERK-elF2α pathway) and may serve as a mechanism eliminating dysfunctional liver cells under physiological conditions, but it can also aggravate liver diseases. PERK-elF2α pathway induces the death signaling molecule C/EBP homologous protein (CHOP). CHOP also can modulate immune response activating the release of IL-23, which is important in controlling immune responses by T cells. Knockdown of CHOP significantly reduced the expression of IL-23 in response to bacterial infection [118]. On the other hand CHOP has been shown to play a critical role in the induction of liver diseases, such as steatohepatitis [119]. CHOP is an important mediator of liver injury induced by IL-1β. Consequently, IL-1β deficiency ameliorates liver inflammation via decreased CHOP expression and hepatocyte injury [120]. There are differences in the action of CHOP in different species. CHOP has been shown to activate NF-κB pathway in human hepatocytes, but not in mouse hepatocytes [121]. CHOP-mediated cell death is a mechanism of action of a number of drugs used in chemotherapy for hepatocellular carcinoma [68]. ER stress induced during the acute phase response in hepatocytes was shown to activate STAT3 [27], possibly mediated by PERK (PERK-STAT3 pathway), as was recently described in other cell types [122]. It is not clear yet which mechanism controls the balance between PERK-elF2α and PERK-STAT3 interaction. However, it appears that PERK-STAT3 pathway rather than PERK-elF2α pathway is associated with aggravation of the pathological situation. Activation of PERK-STAT3 signalling accelerates inflammatory response via p38 and ERK resulting in the release of IL-6 and IL-8 [123].

6. Induction of ER stress and UPR by inflammatory mediators (Fig. 2)

While UPR transducers can induce an inflammatory response, the converse can also be observed, specifically the induction of ER stress by several inflammatory mediators. The ER of hepatocytes is particularly challenged during the acute phase response, which is triggered by the inflammatory triad, IL-6, TNF-α and IL-1β, as outlined before. The changes in protein synthesis demand an increased folding capacity of the ER. It has been shown that the induction of an ER stress response is essential for the enhanced expression of acute phase response proteins [105]. Also, it was shown that an inflammatory stimulus provokes a phase of elevated ER stress in hepatocytes [58,124]. Although some studies showed that an appropriate hepatic ER stress response is beneficial in certain inflammatory models, evidence exists that sustained ER stress and UPR, or failure to return to ER homeostasis, may enhance hepatic inflammation [125–128].

It appears that inflammatory mediators particularly impact cells with high protein production rates. Treatment of human beta cells, which were exposed to IL-1β, TNF-α and IFN-γ, with the chemical chaperone TUDCA, or suppression of CHOP (or JNK) resulted in protection against cytokine-induced apoptosis. It was shown that the induced ER stress contributed to human beta cell death, at least in part via JNK activation [129]. The pro-inflammatory cytokines IL-6, IL-1β and TNF-α may activate the ER-bound liver-specific transcription factor CREBH that interacts with components of the UPR, in particular with the ER stress sentinel ATF6, which is required to synergistically induce major acute phase response genes, such as serum amyloid P-component and C-reactive protein [105].

Upon inflammation iNOS is up-regulated, especially in macrophages, which can generate high amounts of nitric oxide (NO). NO was shown to increase ROS production [130], by inhibiting mitochondrial respiration through nitrosylation of cytochrome *c* oxidase, or protein disulphide isomerase (PDI) [131,132]. As was outlined in detail elsewhere, ER is not only responding to, but also is a significant source of oxidative stress within the cell [133]. In hepatocytes the ER resident cytochrome P450 system is considered to be a significant, if not the most relevant source of ROS production [134], which is modulated under stressful conditions. An unbalanced ROS generation activate the UPR through multiple mechanisms [133]. ROS production and disturbance of the Ca^{2+} flux between mitochondria and ER [135] constitute a major risk of detrimental crosstalk between both organelles [136]. Therefore ROS trigger ER stress, which activate particularly the PERK branch of UPR and elicit an anti-oxidative stress response. Increased NO levels result in enhanced expression of pro-apoptotic CHOP, probably through disturbance of Ca^{2+} homeostasis in the ER [137] or via changes of the Ca^{2+} flux in mitochondria, which involves ATF6 activation [138]. Possibly NO activates the upstream proteases, which result in cleavage of ATF6 [139].

TLR2- and TLR4-mediated signalling, involved in the host defence against bacterial pathogens, has been shown to specifically activate IRE1α-XBP-1 signaling [140,141]. TLRs undergo chaperone-mediated trafficking involving ER-resident proteins, such as PRAT4 and gp96 [142]. We have found that treatment of rats with LPS led to an increased ER stress response in liver tissue accompanied by morphological changes in the ER [58]. In macrophages, stimulation with LPS has also been shown to selectively activate IREα-XBP1 signalling [143,144], which subsequently leads to an increased synthesis of IFN-β

via the MyD88 independent/TRIF dependent TLR4 signalling pathway [145]. The mechanism selectively activating IRE1α-XBP1 pathway is not completely understood; several reports suggest that it can be due to inhibition of two other branches of UPR rather than isolated activation of the IRE1α-XBP1 pathway [146,147].

7. Feed forward loop comprising secretion of inflammatory mediators and UPR in liver

The data described above show that inflammation in the liver as well as the activation of ER stress result in complex intracellular processes, which have several points of intersection and crosstalk. They also indicate that there is a feed forward loop between inflammatory mediators and branches of the UPR. This loop can be initiated by inflammation with the help of immune cells. TLRs on immune cells activate IRE1α-TRAF2 signalling leading to NF-κB mediated production and secretion of variety of inflammatory mediators. The cytokines TNF-α and IL-1β, together with iNOS play a particularly important role in this phase. TNF-α and IL-1β can interact with nearly all classes of liver cells inducing elevated levels of intracellular ROS and disturbance in Ca^{2+} homeostasis. Mitochondria rather than the ER are the source of increased generation of intracellular ROS in the inflammatory response [148]. In addition NADPH-oxidase, activated by IL-1β may further contribute to the elevated ROS levels in liver cells [149]. Elevated levels of ROS and disruption of Ca^{2+} metabolism can induce ER stress resulting in activation of all three UPR branches. This induction is so strong, that not only canonical elF2α, ATF6 and XBP1-dependent UPR pathways are activated, but also STAT3 and TRAF2-mediated signaling pathways. The latter two further aggravate the inflammatory response and ER stress. The pro-inflammatory cytokine triad TNF-α, IL-1β and IL-6 plays a predominant role in this process. Apart from this mechanism the up-regulation of iNOS by NF-κB stimulates the production of NO, which has been shown to elevate mitochondrial ROS (mitoROS) production in hepatocytes. Further mitoROS were shown to up-regulate iNOS, which produce a ROS-NOS feed forward cycle [130]. It was shown that besides its main role as a transcription factor for inflammatory cytokine production, a portion of STAT3 is localized to mitochondria, where it controls the electron transport chain and limits mitoROS production [150]. However, oxidative stress or inflammatory cytokines lead to a rapid depletion of mitochondrial STAT3 [151]. Further, very recently STAT3 was shown to decrease Ca^{2+} release from ER and protect against ER/mitochondrial Ca^{2+} flux modulated apoptosis [152]. Thus, besides its role as transcription factor STAT3 turns out to have important roles in the regulation of mitochondrial and ER functions.

There are three possible scenarios to overcome the vicious cycle of compromised ER stress and inflammation described above and rescue cells: (i) Activation of the adaptive branch of the UPR, which would interrupt this vicious cycle at the level of the ER, thus precluding downstream organ dysfunction. (ii) Activation of the death branch of the UPR, causing cells to die via apoptosis, which would result in organ dysfunction due to reduced cell number. (iii) Signaling by the UPR is blocked such that the ER stress remains unresolved and organ dysfunction occurs due to accumulation of live but non-functional or dysfunctional cells. Only the first scenario prevents organ dysfunction and thus therapies that could promote adaptive UPR signaling may be beneficial. Similarly, in the second scenario rescue of cells from undergoing cell death may also be achieved by promoting adaptive UPR signaling. In the latter scenario, therapies to interfere with the crosstalk between ER stress and inflammation may block the vicious cycle.

8. Therapy targeting UPR in liver diseases

Compounds targeting ER stress/UPR in liver consist of two general classes - those acting at the level of the ER luminal chaperones, irrespective of the specific branches of UPR, and those working at the level of specific UPR branches as inhibitors or activators. Since different branches of UPR can serve as either pro-survival or pro-apoptotic signaling the manipulation of ER stress and UPR may either kill or rescue the cells. There are substances regulating expression of natural chaperones. Acetylshikonin activates expression of GRP78/BiP, while berberine and geldanamycine inhibit expression of chaperones. Another class of substances consist of chemical chaperones, which interact directly with misfolded proteins, such as TUDCA. Salubrinal and sinulariolide modulate the PERK branch, acting as inhibitor or activator respectively. Salicylamide analog and resveratrol were shown to inhibit IRE1α signaling while querzitine activates this branch of UPR. Baicalein and apigenin have been shown to up-regulate ATF6 and consequently activate this branch of UPR. Acetylshikonin (a derivative of shikonin) induces ER stress and causes apoptosis in hepatocellular carcinoma cells [153]. Berberine has been shown to ameliorate the progression of hepatic steatosis to steatohepatitis and fibrosis by reducing ER stress [154]. 17-allylamino-17-demethoxygeldanamycin (17AAG), a geldanamycin derivative, has been shown to inhibit the viability of hepatocellular carcinoma cells lines with various levels of metastatic potential [155]. TUDCA, which has been shown to attenuate ER stress and protect the liver from hypoxia induced injury [156], reverts liver fibrosis in a model of cholestatic liver disease [157], attenuates hepatocarcinogenesis by suppressing carcinogen-induced ER stress-mediated cell death, and inflammation without stimulating tumor progression [158], and it could improve graft survival in liver transplantation [159]. Salubrinal has been shown to diminish cell death in hepatocellular carcinoma [160,161]. In contrast sinulariolide accelerated cell death in hepatocellular carcinoma [160]. Resveratrol has been shown to prevent hepatic steatosis and alleviate hepatocellular apoptosis [162]. Resveratrol also attenuates ethanol-induced hepatocyte apoptosis [163]. In contrast, quercetin induced apoptosis and ER stress, but to our best knowledge it was not tested in hepatocytes, but in other cell types, such as cervical carcinoma [164] and pancreatic cells [165]. Finally, baicalein has been shown to induce apoptosis and autophagy via ER stress in hepatocellular carcinoma cells [166].

9. Conclusion (Fig. 3)

Considering the importance of proper protein synthesis, ER stress, which may be induced by adverse metabolic conditions, can be understood as an internal danger signal for liver cells with a high secretory activity. In accordance with the severity of this stress condition several options must be available to correct the occurring problem. A fine-tuned response is achieved by redundancy of the three UPR branches, which allow amplification on the one hand (all three UPR branches activate ERSE-containing genes) and cooperation of the signals on the other hand (PERK pathway mediates a translational arrest and IRE1α activation stimulates endonuclease activity to degrade ER associated RNA). In some situations ER stress is caused by pathogenic (PAMPs) or injury derived material (DAMPs). Therefore the UPR intersects at several points with signalling of the innate immune response to induce or enhance inflammation. If resolution of ER stress or resolution of inflammation is impaired, ER stress is aggravated and moves UPR from a physiological to a dangerous pathological response, via a feed forward loop which enhances inflammation. The understanding of the interaction sites of UPR and inflammatory pathways is essential for our understanding of mechanism underlying the transformation of the physiological UPR into a feed forward loop appearing as a vicious cycle causing liver dysfunction. A body of literature suggests that inflammatory cytokines (i.e., TNF-α, IL-1β, IL-6) and two branches of UPR (IRE1α and PERK) play a critical role in this transition. This vicious cycle can be started either by adverse metabolic conditions or by mediators of inflammation and may be interrupted by anti-inflammatory drugs on the one hand and by drugs affecting UPR on the other. In the past, anti-inflammatory therapies were almost exclusively was used to treat liver diseases associated with inflammation. However,

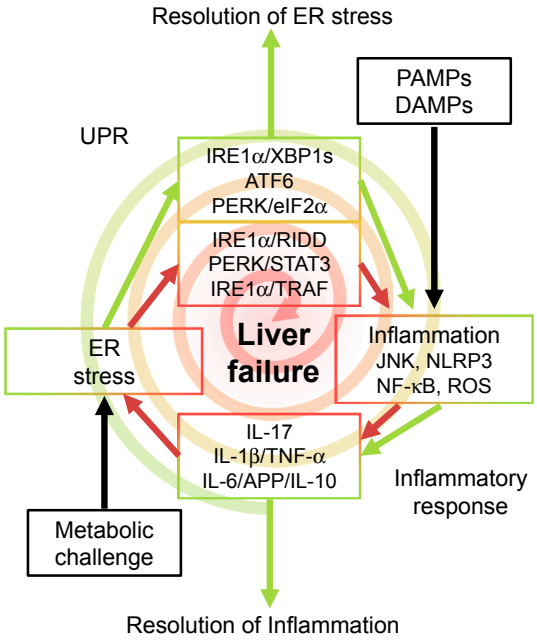

Fig. 3. Feed forward loop consisting of ER stress, UPR and inflammation. Initially this loop can be started by inducers of inflammation (PAMPs and DAMPs) or/and by metabolic changes affecting ER function. Moderate ER stress induces three "classical branches" of UPR, IRE1α/XBP1, ATF6 and PERK/eIF2α. Activation of these branches leads to the resolution of ER stress, rather than to its aggravation. Severe ER stress results in activation of PERK/STAT3 and IRE1α/TRAF2 signalling, which feed several inflammatory pathways, JNK, NLRP3, NF-κB. These pathways generate inflammatory cytokines, which subsequently can either resolve inflammation (IL-10) or further aggravate ER stress (IL-1β, TNF-α, IL-6) accelerating the feed forward loop and causing liver failure. IRE1α/RIDD pathway is likely contributing to both pathological and physiological pathways.

in the last decade many UPR targeted drugs have been developed, which now offer the opportunity to treat liver diseases by targeting the UPR side. Such a combined therapy targeting inflammation and UPR together may result in a breakthrough in therapeutic strategies for liver diseases.

Acknowledgement

Andreia Luis was funded by grant from EU H2020 MSCA ITN-675448 (TRAINERS).

References

[1] B. Chazaud, Macrophages: supportive cells for tissue repair and regeneration, Immunobiology 219 (2014) 172–178.
[2] M.O. Freire, T.E. Van Dyke, Natural resolution of inflammation, Periodontol 2000 (63) (2013) 149–164.
[3] Z. Kmiec, Cooperation of liver cells in health and disease, Adv. Anat. Embryol. Cell Biol. 161 (2001) III-151.
[4] O.P. Kulkarni, J. Lichtnekert, H.J. Anders, S.R. Mulay, The immune system in tissue environments regaining homeostasis after injury: is "Inflammation" always inflammation? Mediators Inflamm. 2016 (2016) 2856213.
[5] C. Brenner, L. Galluzzi, O. Kepp, G. Kroemer, Decoding cell death signals in liver inflammation, J. Hepatol. 59 (2013) 583–594.
[6] M.W. Robinson, C. Harmon, C. O'Farrelly, Liver immunology and its role in inflammation and homeostasis, Cell. Mol. Immunol. 13 (2016) 267–276.
[7] F. Tacke, T. Luedde, C. Trautwein, Inflammatory pathways in liver homeostasis and liver injury, Clin. Rev. Allergy Immunol. 36 (2009) 4–12.
[8] K.R. Porter, A. Claude, E.F. Fullam, A study of tissue culture cells by electron microscopy: methods and preliminary observations, J. Exp. Med. 81 (1945) 233–246.
[9] A. Almanza, A. Carlesso, C. Chintha, S. Creedican, D. Doultsinos, B. Leuzzi, A. Luis, N. McCarthy, L. Montibeller, S. More, A. Papaioannou, F. Puschel, M.L. Sassano, J. Skoko, P. Agostinis, B.J. de, L.A. Eriksson, S. Fulda, A.M. Gorman, S. Healy, A. Kozlov, C. Munoz-Pinedo, M. Rehm, E. Chevet, A. Samali, Endoplasmic reticulum stress signalling - from basic mechanisms to clinical applications 1, FEBS J. (2018).
[10] E. Szegezdi, S.E. Logue, A.M. Gorman, A. Samali, Mediators of endoplasmic reticulum stress-induced apoptosis 1, EMBO Rep. 7 (2006) 880–885.
[11] Q.L. Ahmed, S. Manzoor, M. Tariq, M. Khalid, W. Ashraf, F. Parvaiz, M. Imran, Hepatitis C virus infection in vitro triggers endoplasmic reticulum stress and downregulates insulin receptor substrates 1 and 2 through upregulation of cytokine signaling suppressor 3, Acta Virol. 58 (2014) 238–244.
[12] A. Baiceanu, P. Mesdom, M. Lagouge, F. Foufelle, Endoplasmic reticulum proteostasis in hepatic steatosis, Nat. Rev. Endocrinol. 12 (2016) 710–722.
[13] S. Fu, S.M. Watkins, G.S. Hotamisligil, The role of endoplasmic reticulum in hepatic lipid homeostasis and stress signaling, Cell Metab. 15 (2012) 623–634.
[14] G.J. Quinlan, G.S. Martin, T.W. Evans, Albumin: biochemical properties and therapeutic potential, Hepatology 41 (2005) 1211–1219.
[15] N. Semiane, F. Foufelle, P. Ferre, I. Hainault, S. Ameddah, A. Mallek, A. Khalkhal, Y. Dahmani, High carbohydrate diet induces nonalcoholic steato-hepatitis (NASH) in a desert gerbil, C. R. Biol. 340 (2017) 25–36.
[16] D.L. Howarth, A.M. Vacaru, O. Tsedensodnom, E. Mormone, N. Nieto, L.M. Costantini, E.L. Snapp, K.C. Sadler, Alcohol disrupts endoplasmic reticulum function and protein secretion in hepatocytes, Alcohol. Clin. Exp. Res. 36 (2012) 14–23.
[17] R. Khachatoorian, S.W. French, Chaperones in hepatitis C virus infection, World J. Hepatol. 8 (2016) 9–35.
[18] H. Malhi, R.J. Kaufman, Endoplasmic reticulum stress in liver disease, J. Hepatol. 54 (2011) 795–809.
[19] S. Wang, R.J. Kaufman, How does protein misfolding in the endoplasmic reticulum affect lipid metabolism in the liver? Curr. Opin. Lipidol. 25 (2014) 125–132.
[20] H.L. Kammoun, I. Hainault, P. Ferre, F. Foufelle, Nutritional related liver disease: targeting the endoplasmic reticulum stress, Curr. Opin. Clin. Nutr. Metab. Care 12 (2009) 575–582.
[21] E.S. Wires, K.A. Trychta, S. Back, A. Sulima, K.C. Rice, B.K. Harvey, High fat diet disrupts endoplasmic reticulum calcium homeostasis in the rat liver, J. Hepatol. 67 (2017) 1009–1017.
[22] S. Lee, S. Kim, S. Hwang, N.J. Cherrington, D.Y. Ryu, Dysregulated expression of proteins associated with ER stress, autophagy and apoptosis in tissues from nonalcoholic fatty liver disease, Oncotarget 8 (2017) 63370–63381.
[23] N.U. Ashraf, T.A. Sheikh, Endoplasmic reticulum stress and Oxidative stress in the pathogenesis of Non-alcoholic fatty liver disease, Free Radic. Res. 49 (2015) 1405–1418.
[24] M.A. Hickman, Q.R. Rogers, J.G. Morris, Effect of diet on Heinz body formation in kittens, Am. J. Vet. Res. 51 (1990) 475–478.
[25] M.J. Pagliassotti, Endoplasmic reticulum stress in nonalcoholic fatty liver disease, Annu. Rev. Nutr. 32 (2012) 17–33.
[26] H. Zhou, R. Liu, ER stress and hepatic lipid metabolism, Front. Genet. 5 (2014) 112.
[27] A.N. Ahyi, L.J. Quinton, M.R. Jones, J.D. Ferrari, Z.A. Pepper-Cunningham, J.R. Mella, D.G. Remick, J.P. Mizgerd, Roles of STAT3 in protein secretion pathways during the acute-phase response, Infect. Immun. 81 (2013) 1644–1653.
[28] J.G. Bode, U. Albrecht, D. Haussinger, P.C. Heinrich, F. Schaper, Hepatic acute phase proteins–regulation by IL-6- and IL-1-type cytokines involving STAT3 and its crosstalk with NF-kappaB-dependent signaling, Eur. J. Cell Biol. 91 (2012) 496–505.
[29] C. He, Y. Qiu, P. Han, Y. Chen, L. Zhang, Q. Yuan, T. Zhang, T. Cheng, L. Yuan, C. Huang, S. Zhang, Z. Yin, X.E. Peng, D. Liang, X. Lin, Y. Lin, Z. Lin, N. Xia, ER stress regulating protein phosphatase 2A–B56gamma, targeted by hepatitis B virus X protein, induces cell cycle arrest and apoptosis of hepatocytes, Cell Death Dis. 9 (2018) 762.
[30] H. Moshage, Cytokines and the hepatic acute phase response, J. Pathol. 181 (1997) 257–266.
[31] S. Jain, V. Gautam, S. Naseem, Acute-phase proteins: as diagnostic tool, J. Pharm. Bioallied Sci. 3 (2011) 118–127.
[32] C. Trautwein, K. Boker, M.P. Manns, Hepatocyte and immune system: acute phase reaction as a contribution to early defence mechanisms, Gut 35 (1994) 1163–1166.
[33] K. Zhang, R.J. Kaufman, From endoplasmic-reticulum stress to the inflammatory response, Nature 454 (2008) 455–462.
[34] H. Barle, B. Nyberg, P. Essen, K. Andersson, M.A. McNurlan, J. Wernerman, P.J. Garlick, The synthesis rates of total liver protein and plasma albumin determined simultaneously in vivo in humans, Hepatology 25 (1997) 154–158.
[35] F.P. De, P. Lucidi, Liver protein synthesis in physiology and in disease states, Curr. Opin. Clin. Nutr. Metab. Care 5 (2002) 47–50.
[36] W. Yao, H. Cai, X. Li, T. Li, L. Hu, T. Peng, Endoplasmic reticulum stress links hepatitis C virus RNA replication to wild-type PGC-1alpha/liver-specific PGC-1alpha upregulation, J. Virol. 88 (2014) 8361–8374.
[37] Y. Wang, L. Vera, W.H. Fischer, M. Montminy, The CREB coactivator CRTC2 links hepatic ER stress and fasting gluconeogenesis, Nature 460 (2009) 534–537.
[38] J. Lee, M.A. Salazar Hernandez, T. Auen, P. Mucka, J. Lee, U. Ozcan, PGC-1alpha functions as a co-suppressor of XBP1s to regulate glucose metabolism, Mol. Metab. 7 (2018) 119–131.
[39] Y. Zhou, J. Lee, C.M. Reno, C. Sun, S.W. Park, J. Chung, J. Lee, S.J. Fisher, M.F. White, S.B. Biddinger, U. Ozcan, Regulation of glucose homeostasis through a XBP-1-FoxO1 interaction, Nat. Med. 17 (2011) 356–365.
[40] P. Ferre, F. Foufelle, Hepatic steatosis: a role for de novo lipogenesis and the transcription factor SREBP-1c, Diabetes Obes. Metab. 12 (Suppl 2) (2010) 83–92.
[41] L. Rui, Energy metabolism in the liver, Compr. Physiol. 4 (2014) 177–197.
[42] H. Remmer, The role of theliver in drug metabolism, Am. J. Med. 49 (1970)

617–629.
[43] L. Dara, C. Ji, N. Kaplowitz, The contribution of endoplasmic reticulum stress to liver diseases, Hepatology 53 (2011) 1752–1763.
[44] N.L. ali-Furet, M. Chami, L. Houel, G.F. De, F. Vernejoul, D. Lagorce, L. Buscail, R. Bartenschlager, F. Ichas, R. Rizzuto, P. Paterlini-Brechot, Hepatitis C virus core triggers apoptosis in liver cells by inducing ER stress and ER calcium depletion, Oncogene 24 (2005) 4921–4933.
[45] E.S. Ali, G.Y. Rychkov, G.J. Barritt, Metabolic disorders and cancer: hepatocyte store-operated Ca(2+) channels in nonalcoholic fatty liver disease, Adv. Exp. Med. Biol. 993 (2017) 595–621.
[46] Y. Wei, D. Wang, C.L. Gentile, M.J. Pagliassotti, Reduced endoplasmic reticulum luminal calcium links saturated fatty acid-mediated endoplasmic reticulum stress and cell death in liver cells, Mol. Cell. Biochem. 331 (2009) 31–40.
[47] S. Ding, L. Yu, B. An, G. Zhang, P. Yu, Z. Wang, Combination effects of airborne particulate matter exposure and high-fat diet on hepatic fibrosis through regulating the ROS-endoplasmic reticulum stress-TGFbeta/SMADs axis in mice, Chemosphere 199 (2018) 538–545.
[48] Y. Gao, H.C. Feng, K. Walder, K. Bolton, T. Sunderland, N. Bishara, M. Quick, L. Kantham, G.R. Collier, Regulation of the selenoprotein SelS by glucose deprivation and endoplasmic reticulum stress - SelS is a novel glucose-regulated protein, FEBS Lett. 563 (2004) 185–190.
[49] A. Agouni, N. Mody, C. Owen, A. Czopek, D. Zimmer, M. tires-Alj, K.K. Bence, M. Delibegovic, Liver-specific deletion of protein tyrosine phosphatase (PTP) 1B improves obesity- and pharmacologically induced endoplasmic reticulum stress, Biochem. J. 438 (2011) 369–378.
[50] T. Asselah, I. Bieche, A. Mansouri, I. Laurendeau, D. Cazals-Hatem, G. Feldmann, P. Bedossa, V. Paradis, M. Martinot-Peignoux, D. Lebrec, C. Guichard, E. Ogier-Denis, M. Vidaud, Z. Tellier, V. Soumelis, P. Marcellin, R. Moreau, In vivo hepatic endoplasmic reticulum stress in patients with chronic hepatitis C, J. Pathol. 221 (2010) 264–274.
[51] K. Kawasaki, R. Ushioda, S. Ito, K. Ikeda, Y. Masago, K. Nagata, Deletion of the collagen-specific molecular chaperone Hsp47 causes endoplasmic reticulum stress-mediated apoptosis of hepatic stellate cells, J. Biol. Chem. 290 (2015) 3639–3646.
[52] J.C. Duvigneau, A.V. Kozlov, C. Zifko, A. Postl, R.T. Hartl, I. Miller, L. Gille, K. Staniek, R. Moldzio, W. Gregor, S. Haindl, T. Behling, H. Redl, S. Bahrami, Reperfusion does not induce oxidative stress but sustained endoplasmic reticulum stress in livers of rats subjected to traumatic-hemorrhagic shock 1, Shock 33 (2010) 289–298.
[53] B. Jian, C.H. Hsieh, J. Chen, M. Choudhry, K. Bland, I. Chaudry, R. Raju, Activation of endoplasmic reticulum stress response following trauma-hemorrhage, BBA 1782 (2008) 621–626.
[54] A. Blas-Garcia, N. Apostolova, V. Valls-Belles, J.V. Esplugues, Endoplasmic reticulum and mitochondria: independent roles and crosstalk in fatty liver diseases and hepatic inflammation, Curr. Pharm. Des. 22 (2016) 2607–2618.
[55] A.V. Kozlov, J.C. Duvigneau, I. Miller, S. Nurnberger, B. Gesslbauer, A. Kungl, W. Ohlinger, R.T. Hartl, L. Gille, K. Staniek, W. Gregor, S. Haindl, H. Redl, Endotoxin causes functional endoplasmic reticulum failure, possibly mediated by mitochondria 1, BBA 1792 (2009) 521–530.
[56] O.K. Kim, W. Jun, J. Lee, Mechanism of ER stress and inflammation for hepatic insulin resistance in obesity, Ann. Nutr. Metab. 67 (2015) 218–227.
[57] C. Lebeaupin, E. Proics, C.H. de Bieville, D. Rousseau, S. Bonnafous, S. Patouraux, G. Adam, V.J. Lavallard, C. Rovere, T.O. Le, M.C. Saint-Paul, R. Anty, A.S. Schneck, A. Iannelli, J. Gugenheim, A. Tran, P. Gual, B. Bailly-Maitre, ER stress induces NLRP3 inflammasome activation and hepatocyte death, Cell Death Dis. 6 (2015) e1879.
[58] S. Nurnberger, I. Miller, J.C. Duvigneau, E.T. Kavanagh, S. Gupta, R.T. Hartl, O. Hori, B. Gesslbauer, A. Samali, A. Kungl, H. Redl, A.V. Kozlov, Impairment of endoplasmic reticulum in liver as an early consequence of the systemic inflammatory response in rats, Am. J. Physiol. Gastrointest. Liver Physiol. 303 (2012) G1373–G1383.
[59] G.E. Karagoz, D. costa-Alvear, H.T. Nguyen, C.P. Lee, F. Chu, An unfolded protein-induced conformational switch activates mammalian IRE1, Elife (2017).
[60] K.P. Lee, M. Dey, D. Neculai, C. Cao, T.E. Dever, F. Sicheri, Structure of the dual enzyme Ire1 reveals the basis for catalysis and regulation in nonconventional RNA splicing, Cell 132 (2008) 89–100.
[61] K. Ma, K.M. Vattem, R.C. Wek, Dimerization and release of molecular chaperone inhibition facilitate activation of eukaryotic initiation factor-2 kinase in response to endoplasmic reticulum stress, J. Biol. Chem. 277 (2002) 18728–18735.
[62] W. Rozpedek, D. Pytel, B. Mucha, H. Leszczynska, J.A. Diehl, I. Majsterek, The Role of the PERK/eIF2alpha/ATF4/CHOP signaling pathway in tumor progression during endoplasmic reticulum stress, Curr. Mol. Med. 16 (2016) 533–544.
[63] R. Ye, D.Y. Jung, J.Y. Jun, J. Li, S. Luo, H.J. Ko, J.K. Kim, A.S. Lee, Grp78 heterozygosity promotes adaptive unfolded protein response and attenuates diet-induced obesity and insulin resistance, Diabetes 59 (2010) 6–16.
[64] R. Chen, R.Y. Dai, C.Y. Duan, Y.P. Liu, S.K. Chen, D.M. Yan, C.N. Chen, M. Wei, H. Li, Unfolded protein response suppresses cisplatin-induced apoptosis via autophagy regulation in human hepatocellular carcinoma cells, Folia Biol. (Praha) 57 (2011) 87–95.
[65] C. Ji, N. Kaplowitz, Hyperhomocysteinemia, endoplasmic reticulum stress, and alcoholic liver injury, World J. Gastroenterol. 10 (2004) 1699–1708.
[66] Z.L. Jin, W. Yan, M. Qu, C.Z. Ge, X. Chen, S.F. Zhang, Cinchonine activates endoplasmic reticulum stress-induced apoptosis in human liver cancer cells, Exp. Ther. Med. 15 (2018) 5046–5050.
[67] E.H. Kim, P.H. Park, Globular adiponectin protects rat hepatocytes against acetaminophen-induced cell death via modulation of the inflammasome activation and ER stress: critical role of autophagy induction, Biochem. Pharmacol. 154 (2018) 278–292.
[68] Y. Lei, S. Wang, B. Ren, J. Wang, J. Chen, J. Lu, S. Zhan, Y. Fu, L. Huang, J. Tan, CHOP favors endoplasmic reticulum stress-induced apoptosis in hepatocellular carcinoma cells via inhibition of autophagy, PLoS One 12 (2017) e0183680.
[69] Y. Inaba, T. Furutani, K. Kimura, H. Watanabe, S. Haga, Y. Kido, M. Matsumoto, Y. Yamamoto, K. Harada, S. Kaneko, S. Oyadomari, M. Ozaki, M. Kasuga, H. Inoue, Growth arrest and DNA damage-inducible 34 regulates liver regeneration in hepatic steatosis in mice, Hepatology 61 (2015) 1343–1356.
[70] Y. Xie, A. Ramachandran, D.G. Breckenridge, J.T. Liles, M. Lebofsky, A. Farhood, H. Jaeschke, Inhibitor of apoptosis signal-regulating kinase 1 protects against acetaminophen-induced liver injury, Toxicol. Appl. Pharmacol. 286 (2015) 1–9.
[71] C. Wang, K. Chen, Y. Xia, W. Dai, F. Wang, M. Shen, P. Cheng, J. Wang, J. Lu, Y. Zhang, J. Yang, R. Zhu, H. Zhang, J. Li, Y. Zheng, Y. Zhou, C. Guo, N-acetylcysteine attenuates ischemia-reperfusion-induced apoptosis and autophagy in mouse liver via regulation of the ROS/JNK/Bcl-2 pathway, PLoS One 9 (2014) e108855.
[72] L.L. Gu, Z.L. Shen, Y.L. Li, Y.Q. Bao, H. Lu, Oxymatrine causes hepatotoxicity by promoting the phosphorylation of JNK and induction of endoplasmic reticulum stress mediated by ROS in LO2 cells, Mol. Cells 41 (2018) 401–412.
[73] O.A. Smirnova, A.V. Ivanov, O.N. Ivanova, V.T. Valuev-Ellison, S.N. Kochetkov, Cellular defense systems against oxidative and ER stresses: mechanisms of regulation and influence of hepatitis C virus, Mol. Biol. (Mosk) 45 (2011) 127–141.
[74] H.C. Wang, W. Huang, M.D. Lai, I.J. Su, Hepatitis B virus pre-S mutants, endoplasmic reticulum stress and hepatocarcinogenesis, Cancer Sci. 97 (2006) 683–688.
[75] G. Waris, K.D. Tardif, A. Siddiqui, Endoplasmic reticulum (ER) stress: hepatitis C virus induces an ER-nucleus signal transduction pathway and activates NF-kappaB and STAT-3, Biochem. Pharmacol. 64 (2002) 1425–1430.
[76] D. Imrie, K.C. Sadler, Stress management: how the unfolded protein response impacts fatty liver disease, J. Hepatol. 57 (2012) 1147–1151.
[77] C.L. Gentile, M.A. Frye, M.J. Pagliassotti, Fatty acids and the endoplasmic reticulum in nonalcoholic fatty liver disease, BioFactors 37 (2011) 8–16.
[78] N. Kaplowitz, C. Ji, Unfolding new mechanisms of alcoholic liver disease in the endoplasmic reticulum, J. Gastroenterol. Hepatol. 21 (Suppl 3) (2006) S7–S9.
[79] J. Han, R.J. Kaufman, The role of ER stress in lipid metabolism and lipotoxicity, J. Lipid Res. 57 (2016) 1329–1338.
[80] M. Schroder, R.J. Kaufman, ER stress and the unfolded protein response, Mutat. Res. 569 (2005) 29–63.
[81] N. Tamaki, E. Hatano, K. Taura, M. Tada, Y. Kodama, T. Nitta, K. Iwaisako, S. Seo, A. Nakajima, I. Ikai, S. Uemoto, CHOP deficiency attenuates cholestasis-induced liver fibrosis by reduction of hepatocyte injury, Am. J. Physiol. Gastrointest. Liver Physiol. 294 (2008) G498–G505.
[82] D.T. Rutkowski, J. Wu, S.H. Back, M.U. Callaghan, S.P. Ferris, J. Iqbal, R. Clark, H. Miao, J.R. Hassler, J. Fornek, M.G. Katze, M.M. Hussain, B. Song, J. Swathirajan, J. Wang, G.D. Yau, R.J. Kaufman, UPR pathways combine to prevent hepatic steatosis caused by ER stress-mediated suppression of transcriptional master regulators, Dev. Cell 15 (2008) 829–840.
[83] K. Zhang, S. Wang, J. Malhotra, J.R. Hassler, S.H. Back, G. Wang, L. Chang, W. Xu, H. Miao, R. Leonardi, Y.E. Chen, S. Jackowski, R.J. Kaufman, The unfolded protein response transducer IRE1alpha prevents ER stress-induced hepatic steatosis, EMBO J. 30 (2011) 1357–1375.
[84] O. Takeuchi, S. Akira, Pattern recognition receptors and inflammation 1, Cell 140 (2010) 805–820.
[85] V. Bieghs, C. Trautwein, The innate immune response during liver inflammation and metabolic disease 1, Trends Immunol. 34 (2013) 446–452.
[86] E. Seki, D.A. Brenner, Toll-like receptors and adaptor molecules in liver disease: update 1, Hepatology 48 (2008) 322–335.
[87] S. Akira, K. Takeda, Toll-like receptor signalling 1, Nat. Rev. Immunol. 4 (2004) 499–511.
[88] T. Roger, C. Froidevaux, R.D. Le, M.K. Reymond, A.L. Chanson, D. Mauri, K. Burns, B.M. Riederer, S. Akira, T. Calandra, Protection from lethal gram-negative bacterial sepsis by targeting Toll-like receptor 4 1, Proc. Natl. Acad. Sci. USA 106 (2009) 2348–2352.
[89] H. Wesche, W.J. Henzel, W. Shillinglaw, S. Li, Z. Cao, MyD88: an adapter that recruits IRAK to the IL-1 receptor complex 1, Immunity 7 (1997) 837–847.
[90] M. Yamamoto, S. Sato, H. Hemmi, K. Hoshino, T. Kaisho, H. Sanjo, O. Takeuchi, M. Sugiyama, M. Okabe, K. Takeda, S. Akira, Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway 1, Science 301 (2003) 640–643.
[91] C.A. Dinarello, Interleukin-1 in the pathogenesis and treatment of inflammatory diseases 1, Blood 117 (2011) 3720–3732.
[92] K. Hagihara, T. Nishikawa, Y. Sugamata, J. Song, T. Isobe, T. Taga, K. Yoshizaki, Essential role of STAT3 in cytokine-driven NF-kappaB-mediated serum amyloid A gene expression 1, Genes Cells 10 (2005) 1051–1063.
[93] F. Kramer, J. Torzewski, J. Kamenz, K. Veit, V. Hombach, J. Dedio, Y. Ivashchenko, Interleukin-1beta stimulates acute phase response and C-reactive protein synthesis by inducing an NFkappaB- and C/EBPbeta-dependent autocrine interleukin-6 loop 1, Mol. Immunol. 45 (2008) 2678–2689.
[94] J.B. Soares, P. Pimentel-Nunes, R. Roncon-Albuquerque, A. Leite-Moreira, The role of lipopolysaccharide/toll-like receptor 4 signaling in chronic liver diseases 1, Hepatol. Int. 4 (2010) 659–672.
[95] E. Seki, H. Tsutsui, H. Nakano, N. Tsuji, K. Hoshino, O. Adachi, K. Adachi, S. Futatsugi, K. Kuida, O. Takeuchi, H. Okamura, J. Fujimoto, S. Akira, K. Nakanishi, Lipopolysaccharide-induced IL-18 secretion from murine Kupffer cells independently of myeloid differentiation factor 88 that is critically involved in induction of production of IL-12 and IL-1beta 1, J. Immunol. 166 (2001) 2651–2657.

[96] T. Gustot, A. Lemmers, C. Moreno, N. Nagy, E. Quertinmont, C. Nicaise, D. Franchimont, H. Louis, J. Deviere, M.O. Le, Differential liver sensitization to toll-like receptor pathways in mice with alcoholic fatty liver 1, Hepatology 43 (2006) 989–1000.
[97] A. Spruss, G. Kanuri, S. Wagnerberger, S. Haub, S.C. Bischoff, I. Bergheim, Toll-like receptor 4 is involved in the development of fructose-induced hepatic steatosis in mice 1, Hepatology 50 (2009) 1094–1104.
[98] S.M. Man, T.D. Kanneganti, Regulation of inflammasome activation, Immunol. Rev. 265 (2015) 6–21.
[99] A. Wree, M.D. McGeough, M.E. Inzaugarat, A. Eguchi, S. Schuster, C.D. Johnson, C.A. Pena, L.J. Geisler, B.G. Papouchado, H.M. Hoffman, A.E. Feldstein, NLRP3 inflammasome driven liver injury and fibrosis: roles of IL-17 and TNF in mice, Hepatology (2017).
[100] P. Kubes, C. Jenne, Immune responses in the liver, Annu. Rev. Immunol. 36 (2018) 247–277.
[101] Y.H. Paik, R.F. Schwabe, R. Bataller, M.P. Russo, C. Jobin, D.A. Brenner, Toll-like receptor 4 mediates inflammatory signaling by bacterial lipopolysaccharide in human hepatic stellate cells 1, Hepatology 37 (2003) 1043–1055.
[102] U.M. Wegenka, J. Buschmann, C. Lutticken, P.C. Heinrich, F. Horn, Acute-phase response factor, a nuclear factor binding to acute-phase response elements, is rapidly activated by interleukin-6 at the posttranslational level 1, Mol. Cell. Biol. 13 (1993) 276–288.
[103] C. Schindler, D.E. Levy, T. Decker, JAK-STAT signaling: from interferons to cytokines 1, J. Biol. Chem. 282 (2007) 20059–20063.
[104] Y.M. Lee, L.H. Miau, C.J. Chang, S.C. Lee, Transcriptional induction of the alpha-1 acid glycoprotein (AGP) gene by synergistic interaction of two alternative activator forms of AGP/enhancer-binding protein (C/EBP beta) and NF-kappaB or Nopp140 6, Mol. Cell. Biol. 16 (1996) 4257–4263.
[105] K. Zhang, X. Shen, J. Wu, K. Sakaki, T. Saunders, D.T. Rutkowski, S.H. Back, R.J. Kaufman, Endoplasmic reticulum stress activates cleavage of CREBH to induce a systemic inflammatory response, Cell 124 (2006) 587–599.
[106] B. Feng, P.M. Yao, Y. Li, C.M. Devlin, D. Zhang, H.P. Harding, M. Sweeney, J.X. Rong, G. Kuriakose, E.A. Fisher, A.R. Marks, D. Ron, I. Tabas, The endoplasmic reticulum is the site of cholesterol-induced cytotoxicity in macrophages, Nat. Cell Biol. 5 (2003) 781–792.
[107] Y. Li, R.F. Schwabe, T. Vries-Seimon, P.M. Yao, M.C. Gerbod-Giannone, A.R. Tall, R.J. Davis, R. Flavell, D.A. Brenner, I. Tabas, Free cholesterol-loaded macrophages are an abundant source of tumor necrosis factor-alpha and interleukin-6: model of NF-kappaB- and map kinase-dependent inflammation in advanced atherosclerosis, J. Biol. Chem. 280 (2005) 21763–21772.
[108] J. Wu, G.T. He, W.J. Zhang, J. Xu, Q.B. Huang, IRE1alpha signaling pathways involved in mammalian cell fate determination, Cell. Physiol. Biochem. 38 (2016) 847–858.
[109] F. Urano, X. Wang, A. Bertolotti, Y. Zhang, P. Chung, H.P. Harding, D. Ron, Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1, Science 287 (2000) 664–666.
[110] H.O. Rashid, H.K. Kim, R. Junjappa, H.R. Kim, H.J. Chae, Endoplasmic reticulum stress in the regulation of liver diseases: involvement of Regulated IRE1alpha and beta-dependent decay and miRNA, J. Gastroenterol. Hepatol. 32 (2017) 981–991.
[111] A.B. Tam, A.C. Koong, M. Niwa, Ire1 has distinct catalytic mechanisms for XBP1/HAC1 splicing and RIDD, Cell Rep. 9 (2014) 850–858.
[112] D. Han, A.G. Lerner, W.L. Vande, J.P. Upton, W. Xu, A. Hagen, B.J. Backes, S.A. Oakes, F.R. Papa, IRE1alpha kinase activation modes control alternate endoribonuclease outputs to determine divergent cell fates, Cell 138 (2009) 562–575.
[113] A.G. Lerner, J.P. Upton, P.V. Praveen, R. Ghosh, Y. Nakagawa, A. Igbaria, S. Shen, V. Nguyen, B.J. Backes, M. Heiman, N. Heintz, P. Greengard, S. Hui, Q. Tang, A. Trusina, S.A. Oakes, F.R. Papa, IRE1alpha induces thioredoxin-interacting protein to activate the NLRP3 inflammasome and promote programmed cell death under irremediable ER stress, Cell Metab. 16 (2012) 250–264.
[114] Y.M. Loo, M. Gale Jr., Immune signaling by RIG-I-like receptors, Immunity 34 (2011) 680–692.
[115] T. Matsumiya, T. Imaizumi, H. Yoshida, K. Satoh, Antiviral signaling through retinoic acid-inducible gene-I-like receptors, Arch. Immunol. Ther. Exp. (Warsz) 59 (2011) 41–48.
[116] W.I. Lencer, H. DeLuca, M.J. Grey, J.A. Cho, Innate immunity at mucosal surfaces: the IRE1-RIDD-RIG-I pathway, Trends Immunol. 36 (2015) 401–409.
[117] A. Breiman, N. Grandvaux, R. Lin, C. Ottone, S. Akira, M. Yoneyama, T. Fujita, J. Hiscott, E.F. Meurs, Inhibition of RIG-I-dependent signaling to the interferon pathway during hepatitis C virus expression and restoration of signaling by IKKepsilon, J. Virol. 79 (2005) 3969–3978.
[118] J.C. Goodall, C. Wu, Y. Zhang, L. McNeill, L. Ellis, V. Saudek, J.S. Gaston, Endoplasmic reticulum stress-induced transcription factor, CHOP, is crucial for dendritic cell IL-23 expression, Proc. Natl. Acad. Sci. USA 107 (2010) 17698–17703.
[119] C.D. Fuchs, T. Claudel, H. Scharnagl, T. Stojakovic, M. Trauner, FXR controls CHOP expression in steatohepatitis 1, FEBS Lett. 591 (2017) 3360–3368.
[120] M. Kandel-Kfir, T. Almog, A. Shaish, G. Shlomai, L. Anafi, C. Avivi, I. Barshack, I. Grosskopf, D. Harats, Y. Kamari, Interleukin-1alpha deficiency attenuates endoplasmic reticulum stress-induced liver damage and CHOP expression in mice, J. Hepatol. 63 (2015) 926–933.
[121] J.A. Willy, S.K. Young, J.L. Stevens, H.C. Masuoka, R.C. Wek, CHOP links endoplasmic reticulum stress to NF-kappaB activation in the pathogenesis of nonalcoholic steatohepatitis, Mol. Biol. Cell 26 (2015) 2190–2204.
[122] G.P. Meares, Y. Liu, R. Rajbhandari, H. Qin, S.E. Nozell, J.A. Mobley, J.A. Corbett, E.N. Benveniste, PERK-dependent activation of JAK1 and STAT3 contributes to endoplasmic reticulum stress-induced inflammation, Mol. Cell. Biol. 34 (2014) 3911–3925.
[123] V. Mijosek, F. Lasitschka, A. Warth, H. Zabeck, A.H. Dalpke, M. Weitnauer, Endoplasmic reticulum stress is a danger signal promoting innate inflammatory responses in bronchial epithelial cells, J. Innate Immun. 8 (2016) 464–478.
[124] N. Hiramatsu, A. Kasai, K. Hayakawa, J. Yao, M. Kitamura, Real-time detection and continuous monitoring of ER stress in vitro and in vivo by ES-TRAP: evidence for systemic, transient ER stress during endotoxemia, Nucleic Acids Res. 34 (2006) e93.
[125] M. Maurel, A. Samali, E. Chevet, Endoplasmic reticulum stress: at the crossroads of inflammation and metabolism in hepatocellular carcinoma development, Cancer Cell 26 (2014) 301–303.
[126] S.M. Rahman, J.M. Schroeder-Gloeckler, R.C. Janssen, H. Jiang, I. Qadri, K.N. Maclean, J.E. Friedman, CCAAT/enhancing binding protein beta deletion in mice attenuates inflammation, endoplasmic reticulum stress, and lipid accumulation in diet-induced nonalcoholic steatohepatitis, Hepatology 45 (2007) 1108–1117.
[127] J. Rao, S. Yue, Y. Fu, J. Zhu, X. Wang, R.W. Busuttil, J.W. Kupiec-Weglinski, L. Lu, Y. Zhai, ATF6 mediates a pro-inflammatory synergy between ER stress and TLR activation in the pathogenesis of liver ischemia-reperfusion injury, Am. J. Transplant. 14 (2014) 1552–1561.
[128] F. Ren, L. Zhou, X. Zhang, T. Wen, H. Shi, B. Xie, Z. Li, D. Chen, Z. Wang, Z. Duan, Endoplasmic reticulum stress-activated glycogen synthase kinase 3beta aggravates liver inflammation and hepatotoxicity in mice with acute liver failure, Inflammation 38 (2015) 1151–1165.
[129] F. Brozzi, T.R. Nardelli, M. Lopes, I. Millard, J. Barthson, M. Igoillo-Esteve, F.A. Grieco, O. Villate, J.M. Oliveira, M. Casimir, M. Bugliani, F. Engin, G.S. Hotamisligil, P. Marchetti, D.L. Eizirik, Cytokines induce endoplasmic reticulum stress in human, rat and mouse beta cells via different mechanisms, Diabetologia 58 (2015) 2307–2316.
[130] A. Weidinger, A. Mullebner, J. Paier-Pourani, A. Banerjee, I. Miller, L. Lauterbock, J.C. Duvigneau, V.P. Skulachev, H. Redl, A.V. Kozlov, Vicious inducible nitric oxide synthase-mitochondrial reactive oxygen species cycle accelerates inflammatory response and causes liver injury in rats 4, Antioxid. Redox Signal. 22 (2015) 572–586.
[131] P. Sarti, E. Forte, D. Mastronicola, A. Giuffre, M. Arese, Cytochrome c oxidase and nitric oxide in action: molecular mechanisms and pathophysiological implications, BBA 1817 (2012) 610–619.
[132] T. Uehara, T. Nakamura, D. Yao, Z.Q. Shi, Z. Gu, Y. Ma, E. Masliah, Y. Nomura, S.A. Lipton, S-nitrosylated protein-disulphide isomerase links protein misfolding to neurodegeneration, Nature 441 (2006) 513–517.
[133] J.D. Malhotra, R.J. Kaufman, Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? Antioxid. Redox Signal. 9 (2007) 2277–2293.
[134] E.T. Morgan, Regulation of cytochrome p450 by inflammatory mediators: why and how? Drug Metab. Dispos. 29 (2001) 207–212.
[135] S. Marchi, M. Bittremieux, S. Missiroli, C. Morganti, S. Patergnani, L. Sbano, A. Rimessi, M. Kerkhofs, J.B. Parys, G. Bultynck, C. Giorgi, P. Pinton, Endoplasmic reticulum-mitochondria communication through Ca(2+) signaling: the importance of mitochondria-associated membranes (MAMs), Adv. Exp. Med. Biol. 997 (2017) 49–67.
[136] A. Gorlach, K. Bertram, S. Hudecova, O. Krizanova, Calcium and ROS: a mutual interplay, Redox Biol. 6 (2015) 260–271.
[137] T. Gotoh, M. Mori, Nitric oxide and endoplasmic reticulum stress, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 1439–1446.
[138] W. Xu, L. Liu, I.G. Charles, S. Moncada, Nitric oxide induces coupling of mitochondrial signalling with the endoplasmic reticulum stress response, Nat. Cell Biol. 6 (2004) 1129–1134.
[139] T. Gotoh, S. Oyadomari, K. Mori, M. Mori, Nitric oxide-induced apoptosis in RAW 264.7 macrophages is mediated by endoplasmic reticulum stress pathway involving ATF6 and CHOP, J. Biol. Chem. 277 (2002) 12343–12350.
[140] F. Martinon, X. Chen, A.H. Lee, L.H. Glimcher, TLR activation of the transcription factor XBP1 regulates innate immune responses in macrophages, Nat. Immunol. 11 (2010) 411–418.
[141] L.R. Peters, M. Raghavan, Endoplasmic reticulum calcium depletion impacts chaperone secretion, innate immunity, and phagocytic uptake of cells 1, J. Immunol. 187 (2011) 919–931.
[142] Y. Yang, B. Liu, J. Dai, P.K. Srivastava, D.J. Zammit, L. Lefrancois, Z. Li, Heat shock protein gp96 is a master chaperone for toll-like receptors and is important in the innate function of macrophages 10, Immunity 26 (2007) 215–226.
[143] M. Endo, M. Mori, S. Akira, T. Gotoh, C/EBP homologous protein (CHOP) is crucial for the induction of caspase-11 and the pathogenesis of lipopolysaccharide-induced inflammation, J. Immunol. 176 (2006) 6245–6253.
[144] S.H. Park, H.J. Choi, H. Yang, K.H. Do, J. Kim, D.W. Lee, Y. Moon, Endoplasmic reticulum stress-activated C/EBP homologous protein enhances nuclear factor-kappaB signals via repression of peroxisome proliferator-activated receptor gamma, J. Biol. Chem. 285 (2010) 35330–35339.
[145] L. Zeng, Y.P. Liu, H. Sha, H. Chen, L. Qi, J.A. Smith, XBP-1 couples endoplasmic reticulum stress to augmented IFN-beta induction via a cis-acting enhancer in macrophages 1, J. Immunol. 185 (2010) 2324–2330.
[146] H.R. van, J.L. Martindale, M. Gorospe, N.J. Holbrook, P58IPK, a novel endoplasmic reticulum stress-inducible protein and potential negative regulator of eIF2alpha signaling 1, J. Biol. Chem. 278 (2003) 15558–15564.
[147] W. Yan, C.L. Frank, M.J. Korth, B.L. Sopher, I. Novoa, D. Ron, M.G. Katze, Control of PERK eIF2alpha kinase activity by the endoplasmic reticulum stress-induced molecular chaperone P58IPK 1, Proc. Natl. Acad. Sci. USA 99 (2002)

15920–15925.
[148] A.V. Kozlov, L. Gille, I. Miller, C. Piskernik, S. Haindl, K. Staniek, H. Nohl, S. Bahrami, W. Ohlinger, M. Gemeiner, H. Redl, Opposite effects of endotoxin on mitochondrial and endoplasmic reticulum functions 1, Biochem. Biophys. Res. Commun. 352 (2007) 91–96.
[149] Y.H. Paik, J. Kim, T. Aoyama, M.S. De, R. Bataller, D.A. Brenner, Role of NADPH oxidases in liver fibrosis 1, Antioxid. Redox Signal. 20 (2014) 2854–2872.
[150] K. Szczepanek, Q. Chen, M. Derecka, F.N. Salloum, Q. Zhang, M. Szelag, J. Cichy, R.C. Kukreja, J. Dulak, E.J. Lesnefsky, A.C. Larner, Mitochondrial-targeted Signal transducer and activator of transcription 3 (STAT3) protects against ischemia-induced changes in the electron transport chain and the generation of reactive oxygen species, J. Biol. Chem. 286 (2011) 29610–29620.
[151] J.A. Meier, M. Hyun, M. Cantwell, A. Raza, C. Mertens, V. Raje, J. Sisler, E. Tracy, S. Torres-Odio, S. Gispert, P.E. Shaw, H. Baumann, D. Bandyopadhyay, K. Takabe, A.C. Larner, Stress-induced dynamic regulation of mitochondrial STAT3 and its association with cyclophilin D reduce mitochondrial ROS production 1, Sci Signal 10 (2017).
[152] L. Avalle, A. Camporeale, G. Morciano, N. Caroccia, E. Ghetti, V. Orecchia, D. Viavattene, C. Giorgi, P. Pinton, V. Poli, STAT3 localizes to the ER, acting as a gatekeeper for ER-mitochondrion Ca(2+) fluxes and apoptotic responses, Cell Death Differ. (2018).
[153] J. Moon, S.S. Koh, W. Malilas, I.R. Cho, C. Kaewpiboon, S. Kaowinn, K. Lee, B.H. Jhun, Y.W. Choi, Y.H. Chung, Acetylshikonin induces apoptosis of hepatitis B virus X protein-expressing human hepatocellular carcinoma cells via endoplasmic reticulum stress 1, Eur. J. Pharmacol. 735 (2014) 132–140.
[154] Z. Zhang, B. Li, X. Meng, S. Yao, L. Jin, J. Yang, J. Wang, H. Zhang, Z. Zhang, D. Cai, Y. Zhang, G. Ning, Berberine prevents progression from hepatic steatosis to steatohepatitis and fibrosis by reducing endoplasmic reticulum stress 1, Sci. Rep. 6 (2016) 20848.
[155] Y. Cui, W. Wu, Y. Zhou, Q. Xie, T. Liu, J. Jin, K. Liu, HSP27 expression levels are associated with the sensitivity of hepatocellular carcinoma cells to 17-allylamino-17-demethoxygeldanamycin 1, Future Oncol. 9 (2013) 411–418.
[156] Y. Hou, H. Yang, Z. Cui, X. Tai, Y. Chu, X. Guo, Tauroursodeoxycholic acid attenuates endoplasmic reticulum stress and protects the liver from chronic intermittent hypoxia induced injury 1, Exp. Ther. Med. 14 (2017) 2461–2468.
[157] A. Paridaens, S. Raevens, L. Devisscher, E. Bogaerts, X. Verhelst, A. Hoorens, V.H. Van, L.A. van Grunsven, A. Geerts, I. Colle, Modulation of the unfolded protein response by tauroursodeoxycholic acid counteracts apoptotic cell death and fibrosis in a mouse model for secondary biliary liver fibrosis 1, Int. J. Mol. Sci. 18 (2017).
[158] Y.P. Vandewynckel, D. Laukens, L. Devisscher, A. Paridaens, E. Bogaerts, X. Verhelst, B.A. Van den, S. Raevens, S.C. Van, T.M. Van, C. Ampe, B. Descamps, C. Vanhove, O. Govaere, A. Geerts, V.H. Van, Tauroursodeoxycholic acid dampens oncogenic apoptosis induced by endoplasmic reticulum stress during hepatocarcinogen exposure 1, Oncotarget 6 (2015) 28011–28025.
[159] H. Lu, L. Lu, Z.C. Xu, Y.J. Lu, B. Zhao, L. Zhuang, B.B. Hao, F. Zhang, Tauroursodeoxycholic acid and 4-phenyl butyric acid alleviate endoplasmic reticulum stress and improve prognosis of donation after cardiac death liver transplantation in rats 1, Hepatobiliary Pancreat. Dis. Int. 13 (2014) 586–593.
[160] Y.J. Chen, J.H. Su, C.Y. Tsao, C.T. Hung, H.H. Chao, J.J. Lin, M.H. Liao, Z.Y. Yang, H.H. Huang, F.J. Tsai, S.H. Weng, Y.J. Wu, Sinulariolide induced hepatocellular carcinoma apoptosis through activation of mitochondrial-related apoptotic and PERK/eIF2alpha/ATF4/CHOP pathway 1, Molecules 18 (2013) 10146–10161.
[161] R. Hu, P. Zhou, Y.B. Peng, X. Xu, J. Ma, Q. Liu, L. Zhang, X.D. Wen, L.W. Qi, N. Gao, P. Li, 6-Shogaol induces apoptosis in human hepatocellular carcinoma cells and exhibits anti-tumor activity in vivo through endoplasmic reticulum stress 1, PLoS One 7 (2012) e39664.
[162] F. Li, Y. Yang, L. Yang, K. Wang, X. Zhang, Y. Zong, Y. Ding, C. Wang, L. Zhang, G. Ji, Resveratrol alleviates FFA and CCl4 induced apoptosis in HepG2 cells via restoring endoplasmic reticulum stress 1, Oncotarget 8 (2017) 43799–43809.
[163] L.Q. Liu, Z.Q. Fan, Y.F. Tang, Z.J. Ke, The resveratrol attenuates ethanol-induced hepatocyte apoptosis via inhibiting ER-related caspase-12 activation and PDE activity in vitro 1, Alcohol. Clin. Exp. Res. 38 (2014) 683–693.
[164] X.M. Li, J. Liu, F.F. Pan, D.D. Shi, Z.G. Wen, P.L. Yang, Quercetin and aconitine synergistically induces the human cervical carcinoma HeLa cell apoptosis via endoplasmic reticulum (ER) stress pathway 1, PLoS One 13 (2018) e0191062.
[165] J.H. Lee, H.B. Lee, G.O. Jung, J.T. Oh, D.E. Park, K.M. Chae, Effect of quercetin on apoptosis of PANC-1 cells 1, J. Kor. Surg. Soc. 85 (2013) 249–260.
[166] Z. Wang, C. Jiang, W. Chen, G. Zhang, D. Luo, Y. Cao, J. Wu, Y. Ding, B. Liu, Baicalein induces apoptosis and autophagy via endoplasmic reticulum stress in hepatocellular carcinoma cells 1, Biomed. Res. Int. 2014 (2014) 732516.