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Endoplasmic reticulum stress and liver diseases

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Abstract

Endoplasmic reticulum (ER) stress occurs when ER homeostasis is perturbed with accumulation of unfolded/misfolded protein or calcium depletion. The unfolded protein response (UPR), comprising of inositol-requiring enzyme 1α (IRE1α), PKR-like ER kinase (PERK) and activating transcription factor 6 (ATF6) signaling pathways, is a protective cellular response activated by ER stress. However, UPR activation can also induce cell death upon persistent ER stress. The liver is susceptible to ER stress given its synthetic and other biological functions. Numerous studies from human liver samples and animal disease models have indicated a crucial role of ER stress and UPR signaling pathways in the pathogenesis of liver diseases, including non-alcoholic fatty liver disease, alcoholic liver disease, alpha-1 antitrypsin deficiency, cholestatic liver disease, drug-induced liver injury, ischemia/reperfusion injury, viral hepatitis and hepatocellular carcinoma. Extensive investigations have demonstrated the potential underlying mechanisms of the induction of ER stress and the contribution of UPR pathways during the development of the diseases. Moreover ER stress and the UPR proteins and genes have become emerging therapeutic targets to treat liver diseases.

Keywords

ER stress; UPR; IRE1α; PERK; ATF6; liver diseases

1. Introduction

Endoplasmic reticulum (ER) is a cellular organelle present in all eukaryote cells that carries out many essential cell functions including protein synthesis and processing, lipid synthesis and calcium storage. ER stress occurs when there is excessive accumulation of unfolded and misfolded protein in the ER or when ER calcium is depleted. The liver is a vital organ with important metabolic, secretory and excretory functions. Hepatocytes are the predominant cell type in the liver and are responsible for producing large amounts of secretory proteins including albumin, alpha-1 antitrypsin and lipoproteins. Given the large requirement for protein synthesis and folding, hepatocytes are enriched in ER and susceptible to ER perturbation and ER stress. Upon ER stress, an adaptive cellular response termed the

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unfolded protein response (UPR) is activated to restore ER homeostasis and promote cell survival. However, when restoration fails, prolonged ER stress and UPR activation trigger cell death. ER stress and the UPR have been implicated in the pathogenesis of human diseases, including liver diseases.[1] This review discusses the contribution of ER stress and three UPR pathways in major liver disorders with a focus on non-alcoholic fatty liver disease, and current therapeutic approaches targeting ER stress.

2. UPR pathways

The UPR is an adaptive response to ER stress.[2,3] The UPR is comprised of three transmembrane ER stress sensor proteins, including inositol-requiring enzyme 1α (IRE1α), PKR-like ER kinase (PERK) and activating transcription factor 6 (ATF6) (Figure 1). The N-terminus of these proteins is positioned in the ER lumen and the C-terminus is in the cytosol, thus connecting the two cellular compartments. When ER homeostasis is perturbed and excess unfolded/misfolded proteins accumulate in the ER, the three ER sensors are activated via dissociation of the ER luminal protein chaperone binding immunoglobulin protein (BIP) and/or by direct association with unfolded/misfolded protein, initiating the downstream UPR signaling cascades.[4–6]

Among the three ER sensors, IRE1α is a type I ER transmembrane protein and is the evolutionarily most conserved component of the UPR. When ER stress occurs, IRE1α dimerizes and auto-phosphorylates to activate its kinase and endoribonuclease activities. The endoribonuclease property of IRE1α is responsible for the unconventional splicing of X-box binding protein 1 (XBP1) mRNA, removing a 26-nucleotide sequence from unspliced XBP1 (XBP1u) mRNA and causing a translational frameshift to produce the transcriptionally active XBP1 spliced (XBP1s). XBP1s regulates downstream target genes to promote protein folding and ER-associated degradation (ERAD). The cytosolic kinase domain of IRE1α recruits TNF receptor associated factor 2 (TRAF2) and apoptosis signal-regulating kinase 1 (ASK1) to mediate the activation of c-jun N-terminal kinase (JNK) and nuclear factor kappa B (NF-κB) pathways. The ribonuclease activity of IRE1α also negatively regulates gene expression through a process termed regulated IRE1α-dependent decay of mRNA (RIDD). RIDD targets include IRE1α mRNA and mRNAs of several genes involved in lipid metabolism.

PERK is also a type I transmembrane protein and a member of the eukaryotic initiation factor 2α (eIF2α) kinase family. Upon activation by ER stress, PERK phosphorylates eIF2α, which in turn attenuates translation initiation, thus blocking global protein translation to reduce the ER protein folding load. The phosphorylation status of eIF2α is also tightly regulated by growth arrest and DNA damage-inducible protein 34 (GADD34) and constitutive repressor of eIF2α phosphorylation (CReP), which interact with protein phosphatase 1 (PP1) and promote PP1-mediated de-phosphorylation of eIF2α.[7] In addition to protein translation inhibition, phosphorylated-eIF2α (p-eIF2α) also selectively increases translation of a number of mRNAs, such as activating transcription factor 4 (ATF4). ATF4 promotes adaptation to ER stress by activating UPR target genes encoding proteins necessary for antioxidant responses and amino acid synthesis and transport. ATF4 also transcriptionally activates CCAAT-enhancer-binding protein homologous protein (CHOP),

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which plays a critical role in ER-stress mediated apoptosis. Interestingly CHOP is also regulated at the translational level by p-eIF2α. In addition, PERK signaling is part of the integrated stress response (ISR), which will be discussed in the end of this review.

ATF6 is a type II transmembrane protein and a basic Leucine zipper transcription factor. Upon ER stress, ATF6 dissociates with BIP and translocates from the ER to the Golgi apparatus where it is cleaved by site-1 protease (S1P) and site-2 protease (S2P) to generate an active N-terminus cytosolic fragment (ATF6N). ATF6N then translocates into the nucleus to transcriptionally regulate expression of a collection of ER stress target genes, including XBP1, CHOP and protein chaperones such as BIP. ATF6 also forms a heterodimer with XBP1 to activate genes involved in ERAD.[8]

These three UPR branches orchestrate a response to restore ER homeostasis resulting from various cellular stresses. However unmitigated ER stress and prolonged UPR activation may lead to cell apoptosis. Multiple mechanisms have been proposed for ER stress-induced apoptosis.[9–11] CHOP is a major mediator for ER stress-induced apoptosis. CHOP deletion attenuates ER stress-induced apoptosis whereas CHOP overexpression sensitizes cells to apoptosis.[12,13] CHOP transcriptionally activates a number of pro-apoptotic genes including death receptor 5 (DR5), Bcl-2-like protein 11 (BIM), GADD34 and tribbles homolog 3 (TRB3) and represses the expression of anti-apoptotic B-cell lymphoma 2 (BCL2), thus inducing apoptosis during ER stress. ER oxidase 1α (ERO1α) is a downstream target of CHOP and has a role in reactive oxygen species (ROS) generation. CHOP induces ERO1α expression which enhances the ROS production and stimulates inositol-1,4,5-trisphosphate receptor (IP_3R)-mediated Ca^{2+} release from the ER, triggering cell death.[14] In addition, a recent study shows CHOP promotes cell apoptosis through inhibiting autophagy.[15] IRE1α contributes to ER stress-induced apoptosis through JNK activation which mediates multiple stress signaling pathways and promotes inflammation and apoptosis in the liver. ER resident pro-caspase 12 associates with TRAF2 and mediates ER stress-induced apoptosis.[16] Mice lacking caspase-12 are resistant to apoptosis induced by pharmacologic ER stress.[17] Persistent ER stress also induces apoptosis through RIDD-mediated degradation of pre-microRNAs and mRNAs encoding pro-survival proteins.[18,19] Interestingly proapoptotic Bcl-2-associated X protein (BAX) and BCL2 antagonist/killer 1 (BAK) directly interact with IRE1α and modulate the UPR, providing a physical connection between the core apoptotic pathway to the UPR.[20]

3. ER and Hepatic Steatosis

The ER is the major site of lipid metabolism in hepatocytes and a major function of the UPR is to maintain hepatic lipid homeostasis. The master transcription factors regulating fatty acid synthesis and sterol synthesis, sterol regulatory element-binding protein 1c (SREBP1c) and SREBP2 respectively, are localized in ER membrane and get activated by S1P in a manner similar to ATF6 activation. Triglycerides are synthesized from fatty acid and glycerol mainly in the ER. The ER is also the location where very low-density lipoprotein (VLDL) is assembled before trafficking to the Golgi. Therefore, ER homeostasis is closely related to lipid metabolism. Previous studies have shown that ER stress induces hepatic steatosis in mice.[21–27] Multiple mechanisms have been proposed including SREBP

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activation[22–24], reduced VLDL secretion[25,26], increased expression of VLDL receptor (VLDLR)[27] and decreased fatty acid oxidation[28]. On the other hand, lipid accumulation triggers ER stress. Palmitate and other saturated fatty acids have been shown to activate the UPR (PERK, XBP1s) in the liver and in cell cultures.[29–31] Interestingly the lipid composition of the hepatic ER is altered in obese mice and this shift of lipid composition promotes ER stress through disruption of ER calcium homeostasis.[32] The ER stress transducers can also directly sense membrane lipid saturation and activate the UPR.[33] This two-way interaction between ER stress and lipid metabolism creates a positive feedback loops to promote hepatic steatosis. UPR activation is protective from transient ER stress-induced hepatic steatosis, unresolved ER stress and defective UPR activation further aggravate ER-stress induced hepatic steatosis.[21,34]

4. Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is currently the most common cause of abnormal liver chemistry tests in the United States and western world. NAFLD represents a spectrum of diseases associated with the accumulation of triglycerides in hepatocytes, ranging from isolated hepatic steatosis to progressive non-alcoholic steatohepatitis (NASH) that can cause progressive liver injury, fibrosis and cirrhosis.[35] With the rapid rise in the prevalence of obesity and the metabolic syndrome, the prevalence of NAFLD is estimated to be approximately 24% globally and 21–24% in the United States.[36] Approximately 20% of NAFLD patients will develop NASH, with up to 5% developing cirrhosis. In fact, NASH is expected to be the leading indication for liver transplantation in the United States within the next ten years.[37,38] The mechanisms underlying the progression from isolated hepatic steatosis to NASH are poorly understood although proinflammatory cytokines[39], oxidative stress, mitochondrial dysfunction[40] and genetic factors are believed to contribute to the pathogenesis. ER stress and dysregulation of UPR proteins have been implicated in human NAFLD and NASH.[41–43] In fact, NASH is associated with increased p-eIF2α and the inability to adequately express XBP1s[41], although other data show increased expression of XBP1s and its target genes in NASH liver biopsies[42,44]. Studies from animal models of NAFLD also support the important role of the three UPR pathways in the development and progression of NAFLD.[45]

The hepatic IRE1α/XBP1 pathway is important for lipid metabolism through regulation of hepatic lipid synthesis and VLDL assembly and secretion.[46] Hepatic deficiency of IRE1α causes modest elevation of basal liver lipid contents and exacerbates pharmacologic ER stress-induced liver steatosis through increasing lipogenic genes (including CCAAT-enhancer-binding protein β (C/EBPβ), C/EBPδ and peroxisome proliferator-activated receptor gamma (PPARγ)) and reducing VLDL secretion.[47] Loss of hepatocyte IRE1α aggravates high-fat diet-induced steatosis, in part by up-regulating miR-200 and miR-34 and down-regulating their targets (PPARα and sirtuin 1 (SIRT1)).[48] However, mice with hyperactive IRE1α RNase activity induced by deleting the negative IRE1α regulator bax inhibitor-1 (BI-1) are more vulnerable to pharmacologic ER stress activator tunicamycin- or high fat diet-induced hepatosteatosis, as well as hepatocellular injury with enhanced inflammasome signaling and cell death.[49] In addition, overexpressing BI-1 protects from obesity-associated insulin resistance by down-regulating genes involved in lipid metabolism

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(C/EBPα, SREBP1 and peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC1α)).[50] On the other hand, XBP1s transcriptionally regulates fibroblast growth factor 21 (FGF21) to protect from ER stress-induced hepatic steatosis.[51] XBP1 overexpression using adenovirus leads to reduced hepatic triglyceride and diacylglycerol in diet-induced and genetically obese mice, which is associated with decreased hepatic fatty acid synthesis rate and enhanced macrolipophagy.[52] Loss of hepatic XBP1 results in lower serum triglyceride and cholesterol level due to reduced hepatic *de novo* lipogenesis.[53] XBP1 directly regulates a subset of lipid metabolism genes (such as *Fdps*, *Hsd17b7*).[54,55] However multiple key lipogenic genes (*Dgat2*, *Angptl3*, and etc) have also been shown to be primarily regulated by RIDD. The activation of RIDD pathway in XBP1 deficient mice and subsequent degradation of the mRNA of these key lipogenic genes contributes to the hypolipidemic phenotype in these mice.[55] Mice with hepatic XBP1 deficiency have decreased hepatic steatosis when fed lipogenic diets, however, these mice can be protected or predisposed to diet-induced liver injury under different diet compositions and strain backgrounds.[31,55] Given that XBP1 deletion causes a feedback activation of IRE1α, whether the observed modulation of liver injury is a direct effect of XBP1 deficiency and/or IRE1α activation is yet to be fully determined.

The PERK/p-eIF2α/ATF4 arm of the UPR also regulates lipid homeostasis. The PERK/ATF4 pathway is essential for tunicamycin-induced VLDLR expression, which mediates pharmacologic ER stress-induced hepatic steatosis.[27] Genetic ablation of eIF2α in the liver exacerbates tunicamycin-induced lipid accumulation in the liver.[21] GADD34 transgenic mice, which have defective p-eIF2α-mediated UPR signaling, have lower expression of C/EBPα. C/EBPβ, their downstream target PPARγ and improved glucose tolerance in response to a high fat diet, and are protected from high fat diet-induced hepatic steatosis.[56] ATF4 null mice are protected from high fructose or high-carbohydrate diet-induced liver steatosis.[57,58] ATF4 overexpression induces early onset of hyperlipidaemia and hepatic steatosis in zebrafish.[59]

ATF6 null mice demonstrate aggravated hepatic steatosis in response to tunicamycin, which is associated with sustained expression of CHOP, inhibition of C/EBPα, decreased fatty acid β oxidation, reduced VLDL formation and enhanced lipid droplet formation.[21,60] Hepatocyte ATF6 enhances fatty acid oxidation through interacting with PPARα and increasing PPARα transcriptional activity. Overexpression of dominant negative ATF6 exacerbates diet-induced hepatic steatosis and insulin resistance, whereas overexpression of active ATF6 protects against diet-induced hepatic steatosis.[61] ATF6 inhibits hepatic gluconeogenesis by disrupting the cAMP response element binding protein (CREB) and CREB regulated transcription coactivator 2 (CRTC2) interaction and thereby improving glucose metabolism.[62] Active ATF6α also interacts and suppresses SREBP2-mediated transcription of lipogenic genes in cultured hepatocyte.[63]

5. Alcoholic Liver Disease

Alcoholic liver disease (ALD) is a major cause of chronic liver disease worldwide. ALD can cause simple steatosis or can progress to steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma.[64] Multiple factors associated with alcohol consumption can trigger ER stress,

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including increased hepatic cytochrome P450 2E1 (CYP2E1) expression, alcohol-induced accumulation of ROS, reduced liver S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH) ratio, excessive serum homocysteine level and epigenetic regulation.[65–67] Indeed, ER stress and UPR pathway activation are observed both in livers of patients with chronic ALD[68] and in many experimental ALD models[67]. Intragastric alcoholic feeding in mice up-regulates UPR genes, such as BIP and CHOP.[69] In ALD, ER stress contributes to steatosis by activating lipogenic pathways in hepatocytes through SREBP induction.[22,69] Alcohol-induced ER stress also plays a role in inflammation through NF-κB and JNK pathway activation. In addition, enhanced ER stress also induces apoptosis via CHOP and interferon regulatory factor 3 (IRF3) pathway. Loss of hepatic BIP causes ER damage and aggravates alcohol-induced liver injury.[70] CHOP-null mice are protected from alcohol-induced hepatocellular apoptosis, but not fatty liver, ER stress or hyperhomocysteinemia.[71] ATF6 expression is significantly increased in zebrafish model of ALD and blocking ATF6 prevents alcohol-induced hepatic steatosis whereas overexpressing ATF6N induces steatosis in a SREBP-independent/fatty acid synthetase (FASN)-dependent manner.[72] Recent studies have shown that ATF4 expression is upregulated by alcohol and liver-specific ATF4 deficient mice are protected from ethanol-induced hepatosteatosis through activating AMP-activated protein kinase (AMPK) signaling.[73] The precise role of the IRE1α branch of the UPR in ALD is yet to be determined, though it is anticipated that the IRE1α/XBP1 pathway may modulate ALD-induced hepatic steatosis.

6. Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin (AAT) deficiency (AATD) is a genetic disorder caused by mutations in the AAT-encoding SERPINA1 gene, which results in the retention of the mutant AAT protein in the liver and decreased serum AAT levels. AATD can cause lung disease due to the lack of the protease inhibitor activity in the lung and can be treated by replacement therapy. In contrast, replacement therapy is ineffective for the liver disease, since the liver injury occurs due to the accumulation of the misfolded protein in the liver. The most frequent liver disease-associated “Z” allele mutation leads to conformational change and polymerization of the Z-AAT protein. While most of this mutated protein is degraded through ERAD and autophagy, a large amount of this protein accumulates in the ER of hepatocytes and other AAT-producing cells, stimulating ER stress. Therefore AATD is considered a prototypic protein misfolding and ER stress disease. The retention of mutant Z-AAT protein in hepatocytes leads to hepatocyte damage and predisposes to cirrhosis and hepatocellular carcinoma.[74] Studies from liver biopsy samples of AATD patients demonstrate dilated and abnormal ER structures, supporting the existence of ER stress.[75] However, the activation of UPR in AATD is inconsistent. Studies using cell line expressing mutant AAT or transgenic mice with liver-specific inducible expression of mutant AAT show no evidence of UPR activation, but specific activation of caspase-12 and NF-κB pathway.[76] Whereas other data have shown that BIP promoter and protein expression is increased in cells expressing AAT mutant protein and treated with pharmacologic ER stress inducer thapsigargin.[77] UPR activation is observed with accumulation of nonpolymerogenic null Hong Kong (NHK) AAT mutant, which cannot fold properly.[76,78] Recently mutant AAT proteins have been shown to interact with IRE1α and induce ATF6 binding responsive

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reporter activity.[79] These suggest that the activation of UPR is context- and cell type-specific. Indeed, the UPR activation is observed in monocytes from individuals with AATD, providing a connection between ER stress and inflammatory response in AATD.[80] Nonetheless, one of the current therapeutic approaches is to enhance ERAD and autophagy to decrease ER load of mutant Z-AAT. Activation of the ATF6 pathway is shown to attenuate Z-AAT accumulation and mitochondrial damage in liver cells through promoting ERAD.[81] Recently nor-ursodeoxycholic acid (nor-UDCA), a synthetic bile acid under investigation for treatment of cholangiophathies, is shown to be protective in a mouse model of AATD.[82]

7. Cholestatic Liver Diseases

Cholestatic liver diseases including primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), genetic liver diseases and biliary obstruction are highly prevalent causes of progressive liver diseases that are characterized by the impairment of bile formation and bile flow. ER stress markers BIP and protein disulfide isomerase (PDI) expression increase in small bile ducts in PBC patients, indicating a possible involvement of ER stress in PBC.[83] Excess accumulation of toxic bile acids in the liver has been shown to induce ER stress *in vivo* and *in vitro*. Feeding mice bile acid increases hepatic expression of UPR genes (*Xbp1s*, *Bip* and *Chop*).[84,85] In a genetic model of intrahepatic cholestasis, liver-specific *Foxa2* ablation results in accumulated bile acids with resultant ER stress, dilated ER and increased BIP expression.[85] In α-naphthyl isothiocyanate (ANIT) model of intrahepatic cholestasis, expression of UPR genes (*Bip*, *Perk*, *eIF2α*, *Ire1α* and *Atf6*) and proteins (BIP, p-IRE1α) is up-regulated.[86] Wild-type mice subjected to bile duct ligation, a model of obstructive cholestasis, demonstrate robust and transient ER stress with increased hepatic expression of IRE1α, XBP1s, p-PERK and CHOP.[84,87,88] CHOP deficiency attenuates obstructive cholestatic liver injury and fibrosis and CHOP-deficient hepatocytes display decreased cell death in response to the bile acid glycochenodeoxycholic acid (GCDCA).[89] The hepatoprotective role of global CHOP knockout mice subjected to bile duct ligation may also be due, in part, to suppression of intestinal stem cell proliferation and intestinal epithelial cell regeneration. CHOP can disrupt intestinal barrier tight junction, increase intestinal bacteria translocation, kupffer cell activation and inflammatory responses, supporting the liver-gut axis in the pathogenesis of cholestatic liver injury.[88] Treating HepG2 cells with the bile acid sodium deoxycholate induces promoter activity of BIP and CHOP.[90] Hepatocytes treated with various bile acids also demonstrate increased expression of BIP, XBP1s and CHOP, ER-related calcium release and mitochondria oxidative stress.[84,91–94] Interestingly ER stress and the UPR have been shown to regulate bile acid homeostasis, which may serve as a feedback mechanism to modulate the cellular response to cholestasis.[95,96]

8. Viral Hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) cause chronic infection that can progress to fibrosis, cirrhosis and eventually hepatocellular carcinoma. ER stress occurs during viral infection as the ER in the host cells is utilized to synthesize a large amount of viral proteins over a short period, which leads to perturbation of the ER homeostasis. The activation of UPR by HBV and HCV infection has been shown in human liver tissues.[97,98]

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The role of ER stress and UPR activation by HBV and HCV infection is also well described *in vivo* and *in vitro*.[99–101] The multifunctional regulatory protein of HBV, hepatitis B x protein (HBx) activates IRE1α/XBP1 and ATF6 pathways of the UPR to promote HBV replication and expression in liver cells, contributing to liver disease pathogenesis.[102] HBx also activates the PERK/ATF4 pathway to induce cyclooxygenase-2 (COX-2) expression which mediates inflammation.[103] However other data have shown that HBx represses PERK/ATF4 pathway to inhibit cell apoptosis to promote HBV-associated carcinogenesis.[104] In addition, pre-S mutant proteins have been shown to accumulate in the ER and can trigger ER stress to induce oxidative DNA damage and genomic instability.[105,106] Recently the middle S protein has been shown to initiate ER stress and activate the p38/NF-kB pathway to produce IL-6.[107] HCV infection in Huh7 cells induces an acute and sustained activation of all three UPR pathways.[108] However, in a liver-specific Huh7 line stably expressing HCV replicons, XBP1s transcriptional activity and its downstream ERAD pathway are repressed (even though XBP1s expression is increased), allowing the viral proteins to escape degradation and accumulate in the cells.[109] A number of HCV proteins triggers ER stress. Expression of HCV envelope proteins in Hela cells induces PERK/ATF4-depedent CHOP expression and XBP1 splicing.[110] HCV core protein is processed in the ER and expressing HCV core protein elicits ER stress and calcium depletion leading to apoptosis.[111] Nonstructural HCV protein NS4B modulates the UPR by inducing ATF6 cleavage and XBP1 splicing, though the expression of XBP1s downstream ERAD target gene EDEM is repressed to favor HCV replication.[112,113] Viral infection-induced ER stress and adaptive UPR pathway are essential for viral productive life cycles; however chronic ER stress induced by hepatic virus contribute to hepatic inflammation and the progression of liver diseases. Pharmacologic inhibition of ER stress by administration of 4-phenylbutyric acid (4-PBA) or the specific IRE1α inhibitor 4μ8C impaired the HBV production induced by cisplatin treatment.[114]

9. Ischemia/Reperfusion Injury

Liver ischemia/reperfusion (I/R) injury can occur during systemic hypotension, vascular occlusion, and surgery including liver transplantation. I/R injury in the donor liver is a major determinant for clinical outcomes. I/R injury causes liver damage through oxidative stress, inflammation, calcium release from the ER and apoptosis.[115,116] ER stress and activation of the UPR have been shown to play a role in I/R injury. In ischemic and reperfused human livers, UPR activation, as assessed by expression of BIP, CHOP, GADD34, XBP1s, p-PERK and p-eIF2α, occurs in a biphasic manner.[117] Similar UPR activation is also observed in cold preserved liver grafts[118] and mouse models of I/R injury. Hepatic XBP1 splicing and increased BIP expression occur in a traumatic-hemorrhagic shock model[119] and cleaved ATF6 expression increases in ischemic mice livers and promotes ER stress-medicated inflammatory responses.[120,121] I/R induces cytoprotective protein BI-1 expression and loss of BI-1 enhances IRE1α and ATF6 activation and increases hepatic liver damage.[122] The involvement of ER stress in IR injury is further supported by the protective effect of chemical chaperone 4-PBA and tauroursodeoxycholic acid (TUDCA) against I/R injury.[123,124]

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10. Drug-Induced Liver Injury

The majority of drugs and xenobiotics are metabolized in the liver and drug-induced liver injury (DILI) is often a dose-limiting side effect for many medications. The pathogenesis of DILI is complex, including hepatocyte apoptosis, inflammatory response activation, mitochondrial dysfunction and bile duct injury.[125] The smooth ER of the hepatocyte is the primary site of drug metabolism and ER stress has recently been shown to have an important role in DILI[126,127], and has been linked to the adverse events of many drugs[128]. Acetaminophen (APAP) overdose is the most common cause of acute liver failure, and APAP causes hepatocellular injury by depleting glutathione level and altering the redox balance in the ER. APAP toxicity results in increased expression of p-eIF2α and CHOP and mice with CHOP deficiency are protected from APAP-induced liver damage, with decreased liver necrosis and increased survival.[129] A sublethal dose of APAP also induces ATF6 and transient caspase12 activation in mouse liver.[130] Liver-specific XBP1 deficiency protects the mice from APAP-induced hepatotoxicity through IRE1α/RIDD-mediated down-regulation of *Cyp1a2* and *Cyp2e1*.[131] The role of ER stress in APAP-induced liver injury is further supported by the evidence that treating mice with 4-PBA decreases APAP-induced hepatocyte apoptosis/necrosis.[132] In addition to APAP, HIV protease inhibitors (PI) increase ER stress and UPR activation in hepatocytes, intestinal epithelial cells, macrophages and adipocytes contributing to PI-induced hepatocyte injury and metabolic syndrome.[133–136]

11. Hepatocellular Carcinoma

ER stress occurs when the microenvironment changes in cancer cells and has been implicated in many forms of cancer including hepatocellular carcinoma (HCC). In the United States, the incidence and mortality from HCC is rising and HCC occurs predominantly in the presence of pre-existing cirrhosis. HBV can cause HCC in the absence of cirrhosis, and is a common cause of liver cancer death worldwide. In addition, recent data indicate that HCC may occur in non-alcoholic steatohepatitis prior to the development of cirrhosis.[137] Activated gene expression of the ATF6, XBP1s and BIP has been reported in human HCC[138] and UPR pathways are activated at different stage of tumorigenesis in an orthotopic mouse model of HCC[139]. IRE1α signaling may be crucial during HCC initiation. Liver-specific IRE1α deficient mice have decreased HCC incidence in diethylnitrosamine (DEN)-treated mice irrespective of their adiposity status. This is associated with STAT3 activation and decreased hepatocyte proliferation, in spite of increased hepatic apoptosis, and reduced production of tumor necrosis factor α (TNFα) and interleukin 6 (IL-6).[140] CHOP also has a role in ER stress-induced HCC cell apoptosis through inhibiting autophagy.[15] The activation of the UPR in response to tumorigenesis-induced ER stress is a protective mechanism for cancer cells survival, adaptation to adverse environmental conditions, and resistance to conventional chemotherapy. Therefore, the UPR may serves as a therapeutic target for cancer treatment. Ongoing clinical studies are investigating the role of XBP1 inhibitors in multiple myeloma and other malignancies.

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12. Modulators of ER Stress and UPR in Liver Diseases

ER stress and UPR activation are implicated in the etiology of many liver diseases; therefore modulators of ER stress and the UPR are of interest for treatment of liver diseases.[141,142] Several compounds have been developed either targeting a single UPR pathway or acting as protein chaperones in order to modulate ER stress. Ursodeoxycholic acid (UDCA) and 4-PBA are chemical chaperones that promote protein folding and assembly and are FDA-approved to treat primary biliary cholangitis and urea-cycle disorder, respectively. TUDCA and 4-PBA have been shown to be beneficial in several murine models of fatty liver diseases.[143,144] 4-PBA has also been shown to increase secretion of the mutant AAT protein[145], while TUDCA inhibits apoptosis induced by mutant AAT protein[146] and reduces hepatocarcinogenesis in a diethylnitrosamine (DEN) model of HCC[147]. Berberine, a natural plant alkaloid, has been shown to prevent the progression from steatosis and steatohepatitis by reducing ER stress.[148] The IRE1α inhibitor 4μ8C suppresses carbon tetrachloride (CCl_4)-induced liver injury and fibrosis.[149] Similarly PERK pathway modulator salubrinal prevents eIF2α dephosphorylation and improves HepG2 cell viability in response to tunicamycin.[139] Other small inhibitors of UPR pathways are currently being developed for several liver and other benign and malignant diseases.

13. Integrated Stress Response

The integrated stress response (ISR) is an adaptive response to cellular stress, including ER stress and UPR pathways are important in the ISR. In addition to PERK, the ISR comprises three additional eIF2α kinases, general control nonrepressed 2 kinase (GCN2), dsRNA activated protein kinase (PKR) and heme-regulated eIF2α kinase (HRI), that phosphorylate eIF2α under different stress conditions.[150] Similar to the UPR, transient activation of the ISR is considered pro-survival, whereas prolonged ISR activation can lead to induction of cell death. The activation of ISR promotes ATF6 activation during ER stress.[151] The ISR is important in cardiovascular disease[152], lung disease[153], inherited retinal degeneration[154] and central nervous system injury[155]. Recently ISR has been connected to metabolic disease through FGF21 induction in diet-induced obesity and insulin resistance.[156] The activation of the ISR has been implicated in the pathogenesis of liver steatosis.[56–58] The role of ISR in host of liver diseases remains unclear, providing avenues for future research in liver diseases.

14. Conclusion

ER stress and subsequent adaptive UPR activation are important in the pathogenesis of many liver disorders. The three UPR pathways are not only essential to restore ER homeostasis and promote cell survival, but also have important roles in regulating metabolic functions including glucose and lipid metabolism. ER stress often occurs initially as a result of the pathological conditions, and then subsequent defective UPR activation or prolonged ER stress can predispose the system to further injury. ER stress also occurs concomitantly with oxidative stress, mitochondrial dysfunction and autophagy. The complex interplay between these hepatic signaling pathways may collectively determine the overall response to the injurious stimuli. The causative or resultant role of ER stress in liver diseases and the precise contribution of each individual UPR pathways are incompletely understood. Further

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investigation on the mechanisms of ER stress and UPR activation during hepatic diseases may allow for the identification of novel, effective therapeutic targets to treat liver diseases.

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Abbreviations:

4-PBA	4-phenylbutyric acid
AAT	alpha-1 antitrypsin
AATD	alpha-1 antitrypsin deficiency
ALD	alcoholic liver disease
AMPK	AMP-activated protein kinase
ANIT	α-naphthyl isothiocyanate
APAP	acetaminophen
ASK1	apoptosis signal-regulating kinase 1
ATF4	activating transcription factor 4
ATF6	activating transcription factor 6
BAK	Bcl2 antagonist/killer 1
BAX	Bcl2-associated X protein
BCL2	B-cell lymphoma 2
BI-1	bax inhibitor-1
BIM	Bcl-2-like protein 11
BIP	binding immunoglobulin protein
CCl_4	carbon tetrachloride
C/EBPα	CCAAT-enhancer-binding protein α
C/EBPβ	CCAAT-enhancer-binding protein β
C/EBPδ	CCAAT-enhancer-binding protein δ
CHOP	CCAAT-enhancer-binding protein homologous protein
COX-2	Cyclooxygenase-2
CREB	cAMP response element binding protein
CReP	constitutive repressor of eIF2α phosphorylation

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CRTC2	CREB regulated transcription coactivator 2
CYP2E1	cytochrome P450 2E1
DEN	diethylnitrosamine
DILI	drug-induced liver injury
DR5	death receptor 5
eIF2α	eukaryotic initiation factor 2α
ER	endoplasmic reticulum
ERAD	ER-associated degradation
ERO1α	ER oxidase 1α
FASN	fatty acid synthetase
FGF21	fibroblast growth factor 21
GADD34	growth arrest and DNA damage-inducible protein 34
GCDCA	glycochenodeoxycholic acid
GCN2	general control nonrepressed 2 kinase
HBV	hepatitis B virus
HBx	hepatitis B x protein
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HRI	heme-regulated eIF2α kinase
IL-6	interleukin 6
I/R	ischemia/reperfusion
IP_3R	inositol-1,4,5-trisphosphate receptor
IRE1α	inositol-requiring enzyme 1α
IRF3	interferon regulatory factor 3
ISR	integrated stress response
JNK	c-jun N-terminal kinase
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NF-κB	nuclear factor kappa B

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NHK	null Hong Kong
nor-UDCA	nor-ursodeoxycholic acid
p-eIF2α	phosphorylated-eIF2α
PBC	primary biliary cholangitis
PDI	protein disulfide isomerase
PERK	PKR-like ER kinase
PGC1α	peroxisome proliferator-activated receptor-gamma coactivator 1α
PI	protease inhibitor
PKR	dsRNA activated protein kinase
PP1	protein phosphatase 1
PPARα	peroxisome proliferator-activated receptor α
PPARγ	peroxisome proliferator-activated receptor γ
PSC	primary sclerosing cholangitis
RIDD	regulated IRE1α-dependent decay of mRNA
ROS	reactive oxygen species
S1P	site-1 protease
S2P	site-2 protease
SAH	S-adenosylhomocysteine
SAM	S-adenosylmethionine
SIRT1	sirtuin 1
SREBP1c	sterol regulatory element-binding protein 1c
SREBP2	sterol regulatory element-binding protein 2
TNFα	tumor necrosis factor α
TRAF2	TNF receptor associated factor 2
TRB3	tribbles homolog 3
TUDCA	tauroursodeoxycholic acid
UPR	unfolded protein response
VLDL	very low-density lipoprotein
VLDLR	very low-density lipoprotein receptor

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XBP1	X-box binding protein 1
XBP1s	XBP1 spliced
XBP1u	XBP1 unspliced

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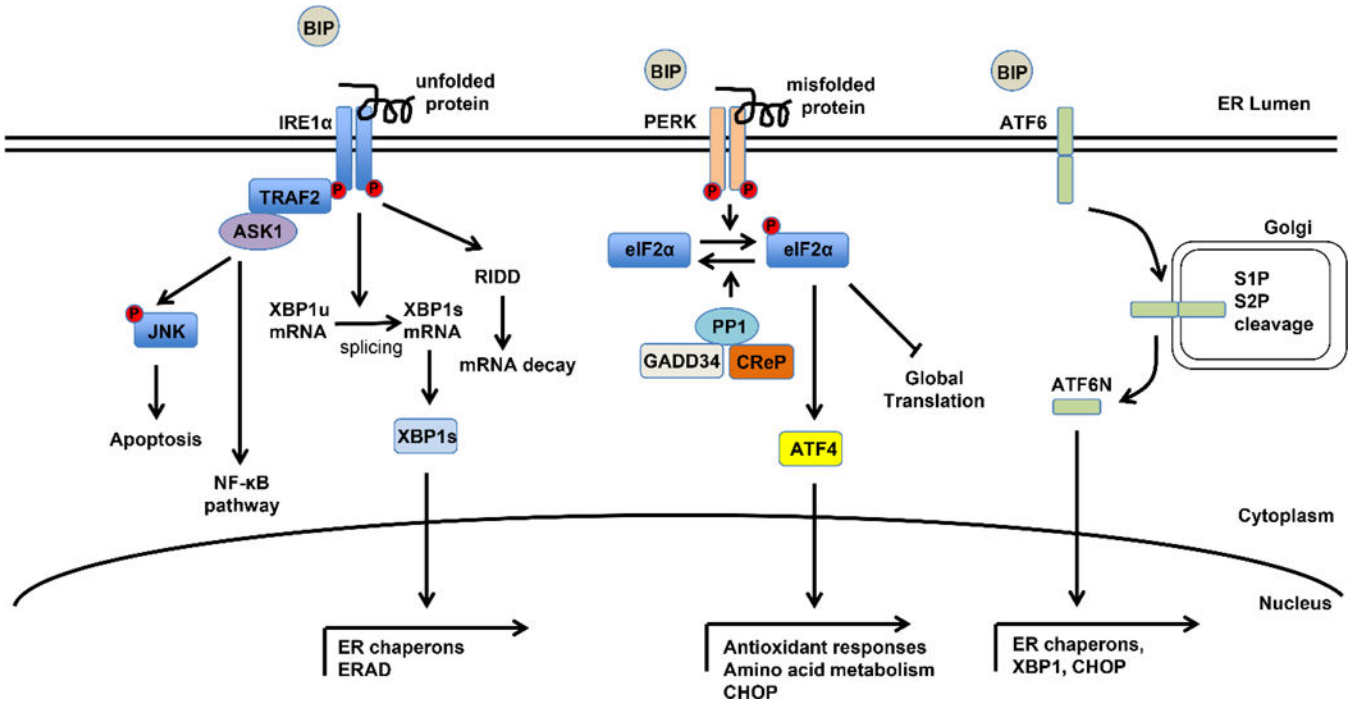

Figure 1.

The unfolded protein response pathways.

During ER stress, the three ER sensors are activated via dissociation of the ER protein chaperon BIP and/or direct association with unfolded/misfolded protein. IRE1α dimerizes and auto-phosphorylates to activate its kinase and endoribonuclease activities. Activated IRE1α induces transcriptionally active XBP1s by an atypical splicing mechanism and XBP1s translocates to the nucleus and regulates downstream target genes including ER chaperones and genes involved in ERAD. IRE1α also recruits TRAF2 and ASK1 to mediate the activation of JNK and NF-κB pathways. The ribonuclease activity of IRE1α also negatively regulates gene expression through RIDD-mediated mRNA decay. ER stress causes PERK dimerization and auto-phosphorylation to phosphorylate eIF2α and inhibit global protein translation. The phosphorylation status of eIF2α is also tightly regulated by GADD34 and CReP, which interact and promotes PP1-mediated de-phosphorylation of eIF2α. Phosphorylated-eIF2α also selectively increases translation of a number of mRNAs, such as ATF4. ATF4 promotes adaptation to ER stress by activating UPR target genes encoding proteins necessary for antioxidant responses and amino acid metabolism. ATF4 also transcriptionally activates CHOP, which plays a critical role in ER-stress mediated apoptosis. Dissociation of BIP from ATF6 causes ATF6 translocation from the ER to the Golgi apparatus where it is cleaved by S1P and S2P to generate an active N-terminus cytosolic fragment (ATF6N). ATF6N then translocates into the nucleus to transcriptionally regulate expression of a collection of ER stress target genes. Abbreviations: ER, endoplasmic reticulum; BIP, binding immunoglobulin protein; IRE1α, inositol-requiring enzyme 1α; XBP1s, X-box binding protein 1 spliced; ERAD, ER-associated degradation; TRAF2, TNF receptor associated factor 2; ASK1, apoptosis signal-regulating kinase 1; JNK, c-jun N-terminal kinase; NF-κB, nuclear factor kappa B; RIDD, regulated IRE1α-dependent decay of mRNA; PERK, PKR-like ER kinase; eIF2α, eukaryotic initiation factor 2α;

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GADD34, growth arrest and DNA damage-inducible protein 34; CReP, constitutive repressor of eIF2α phosphorylation; PP1, protein phosphatase 1; ATF4, activating transcription factor 4; UPR, unfolded protein response; CHOP, CCAAT-enhancer-binding protein homologous protein; ATF6, activating transcription factor 6; S1P, site-1 protease; S2P, site-2 protease.

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Table 1.

Human studies of the involvement of hepatic ER stress and UPR activation in liver diseases.

Liver disease	Findings	Reference(s)
Non-alcoholic fatty liver disease/	↓XBP1s	41
Non-alcoholic steatohepatitis	↑p-eIF2α	41
	↑XBP1s and targets	42–44
	↓BIP, PDI	43
Alcoholic liver disease	↑BIP	68
	↑IRE1α	68
	↑PERK, p-PERK, ATF4, CHOP	68
Alpha-1 antitrypsin deficiency	Dilated and abnormal ER	75
Primary biliary cholangitis	↑BIP, PDI	83
Hepatitis B	↑BIP, XBP1s	97
Hepatitis C	Abnormal ER	98
	↑XBP1s, ATF6 and PERK, ATF4 pathway	98
	↑BIP	97
Ischemia/reperfusion injury	↑BIP, CHOP, GADD34, XBP1s, p-PERK and p-eIF2α	117
Hepatocellular carcinoma	↑ATF6, XBP1s and BIP	138

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Table 2.

UPR pathways in experimental models of liver diseases.

Liver Disease	UPR component	Functions	Ref
Non-alcoholic fatty liver disease/	IRE1α	Regulates hepatic lipogenesis through RIDD	55
Non-alcoholic steatohepatitis	IRE1α	Prevents tunicamycin-induced hepatic steatosis	47
	IRE1α	Protects from diet-induced steatosis	48
	IRE1α	Promotes the progression of NAFLD to NASH	49
	XBP1	Protects from steatosis	51,52
	XBP1	Protects from diet-induced liver injury	31
	XBP1	Regulates hepatic lipogenesis	53–55
	XBP1	Contributes to diet-induced liver injury	55
	PERK/ATF4	Essential for tunicamycin-induced hepatic steatosis	27
	ATF4	Contributes to diet-induced hepatic steatosis	57,58
	ATF4	Induces early onset of steatosis in zebrafish	59
	eIF2α	Protects from tunicamycin-induced fatty liver	21
	GADD34	Protects from diet-induced steatosis	56
	ATF6	Protects from tunicamycin-induced fatty liver	21,60
	ATF6	Protects from diet-induced steatosis	61
Alcoholic liver disease	BIP	Protects from alcohol-induced liver injury	70
	ATF4	Responsible for alcohol-induced hepatic steatosis	73
	CHOP	Promotes alcohol-induced liver injury	71
	ATF6	Induces alcohol-induced hepatic steatosis	72
Alpha-1 antitrypsin deficiency	IRE1α	Interacts with mutant AAT to induce ATF6 activity	79
	ATF6	Attenuates liver mitochondrial damage through promoting ERAD	81
Cholestasis	IRE1α/XBP1	Increases with bile acids treatment or bile duct ligation	84–87
	IRE1α/XBP1	Regulates bile acid metabolism	95
	PERK	Phosphorylation increases with bile duct ligation	87
	CHOP	Increases with bile duct ligation	87,88
	CHOP	Promotes cholestatic cell death and liver injury	88,89
Hepatitis B	IRE1α/XBP1	Activated by HBx to promote HBV replication	102
	PERK/ATF4	Activated by HBx to induce inflammation mediator COX-2	103

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Liver Disease	UPR component	Functions	Ref
	PERK/ATF4	Repressed by HBx to inhibit apoptosis	104
	ATF6	Activated by HBx to promote HBV replication	102
Hepatitis C	IRE1α/XBP1	Activated by HCV protein	108, 110
	IRE1α/XBP1	Transcriptional activity repressed by HCV	109, 112, 113
	PERK/ATF4	Activated by HCV protein	110
	ATF6	Activated by HCV protein	112, 113
Ischemia/reperfusion injury	XBP1s	Increases in mouse model of Ischemia/reperfusion injury	119
	ATF6	Increases in ischemic mouse livers	120
	ATF6	Promotes ER stress-medicated inflammatory responses	120
Acetaminophen overdose	IRE1α	Protects from acetaminophen toxicity through RIDD	131
	p-eIF2α	Increased with acetaminophen toxicity	129
	CHOP	Increased with acetaminophen toxicity	129
	CHOP	Mediates acetaminophen toxicity-induced liver injury	129
	ATF6	Activated by a sublethal dose of Acetaminophen	130
Hepatocellular carcinoma	IRE1α/XBP1s	Increases in HCC model, promotes HCC development	139,140
	PERK/ATF4	Increases in HCC model	139
	CHOP	Increases in HCC model, promotes HCC cell apoptosis	15
	ATF6	Downstream targets increase in HCC model	139