Research Progress on Endoplasmic Reticulum Stress in Liver Diseases: Postprint

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Abstract

Numerous studies have confirmed that endoplasmic reticulum stress (ERS) is intimately associated with the occurrence and development of liver diseases; however, the mechanistic link between ERS and liver disease progression remains to be fully elucidated and warrants further exploration. Many studies have revealed that moderate ERS can activate the unfolded protein response (UPR) to protect cells, while severe or persistent ERS induces cellular apoptosis. Therefore, exploring the role of ERS in the pathogenesis of liver diseases may help identify novel therapeutic strategies. This review thus discusses the current state of research on ERS and UPR in various liver diseases and their potential therapeutic strategies.

Full Text

Advances in Endoplasmic Reticulum Stress in Liver Diseases

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Abstract

A large body of research has confirmed that endoplasmic reticulum stress (ERS) is closely associated with the development and progression of liver diseases, though the precise mechanisms linking ERS to disease progression remain to

be fully elucidated. Numerous studies have demonstrated that moderate ERS can activate the unfolded protein response (UPR) to protect cells, whereas severe or persistent ERS induces apoptosis. Therefore, investigating the role of ERS in the pathogenesis of liver diseases may facilitate the discovery of novel therapeutic strategies. This review describes the current research status and potential therapeutic strategies targeting ERS and UPR in various liver diseases.

Keywords: Liver disease; Endoplasmic reticulum stress; Unfolded protein response; Cell apoptosis; Inflammation

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The endoplasmic reticulum (ER) is a vital cellular organelle that facilitates proper folding of linear polypeptides and proteins. In addition, the ER serves as a critical site for synthesis of various substances and maintains intracellular Ca^{2+} homeostasis. When physiological or pathological factors disrupt cellular homeostasis, unfolded and/or misfolded proteins accumulate in the ER lumen, triggering endoplasmic reticulum stress (ERS). ERS activates the unfolded protein response (UPR), which restores ER homeostasis by inhibiting new protein synthesis and enhancing degradation of unfolded proteins. However, if ERS persists and ER homeostasis cannot be restored in a timely manner, UPR activates intracellular apoptotic signals. Accumulating evidence has revealed that ERS is intimately involved in the pathogenesis of diverse liver diseases, making it a clinically significant area of investigation.

1. ERS

The ER is a highly sensitive organelle present in all eukaryotic cells, and any adverse factor can disrupt its internal equilibrium. Under normal conditions, ER molecular chaperones such as glucose-regulating protein 78 (GRP78) remain inactive through tight binding to ER membrane proteins, thereby maintaining ER stability. During ERS, accumulated unfolded and misfolded proteins competitively bind GRP78, thereby activating UPR. Eukaryotic cells utilize the UPR system to alleviate ERS or prevent apoptosis. Following mild to moderate ERS, UPR is initiated to correct unfolded or misfolded proteins and restore ER homeostasis; this protective UPR is termed "adaptive or cytoprotective" UPR. Conversely, during severe or persistent ERS, UPR becomes overactivated, triggering apoptotic signaling pathways; this pathological form is termed "maladaptive or terminal" UPR.

2. ERS Signaling Pathways

In mammalian cells, UPR signaling is initiated by three ER transmembrane proteins that serve as the three branches of UPR sensors: activating transcription factor 6 (ATF6), protein kinase R-like ER kinase (PERK), and inositol-requiring enzyme 1 (IRE1). Activation of ATF6, PERK, and IRE1 modulates transcription of multiple downstream genes, thereby promoting proper protein folding

and restoring ER homeostasis.

2.1 ATF6 Pathway

ATF6 is a transmembrane protein with two isoforms in mammals: ATF6α and ATF6β, which contain distinct transcriptional activation domains. Under physiological conditions, ATF6α and ATF6β exist as 90 kD and 110 kD proteins, respectively. During ERS, they are cleaved into 50 kD and 60 kD fragments that dissociate from GRP78. In the Golgi apparatus, ATF6 is processed by proteases S1P and S2P, and the cleaved active fragment translocates to the nucleus where it induces expression of ER chaperones including glucose-regulated protein 94 (GRP94), C/EBP-homologous protein (CHOP), X-box binding protein 1 (XBP1), and GRP78. Additionally, complex crosstalk exists among ATF6, PERK, and IRE1α during UPR activation. When ERS occurs, accumulated unfolded or misfolded proteins bind GRP78, activating all three UPR branches and initiating their respective signaling cascades. While PERK and IRE1α dimerization and phosphorylation promote cell survival through the PERK-EIF2α-ATF4 and IRE1α-spliced XBP1 pathways, ATF6 is recruited to the Golgi for processing. If adaptive UPR fails to restore ER homeostasis, severe or persistent ERS induces terminal UPR, activating PERK-EIF2α-ATF4-CHOP, ATF6-CHOP, and IRE1α-TRAF2-ASK1-JNK1 pathways that ultimately lead to cell death.

2.2 IRE1 Pathway

IRE1 exists as two isoforms in mammals: IRE1α and IRE1β. IRE1α is ubiquitously expressed and mediates downstream signaling through its kinase and cytoplasmic endoribonuclease domains. Following dissociation from GRP78, IRE1α undergoes oligomerization and autophosphorylation, inducing conformational changes that activate its ribonuclease domain. Additionally, misfolded or unfolded proteins can directly bind IRE1α to induce structural changes. IRE1β mRNA has been detected in intestinal epithelial cells, suggesting its involvement in digestive tissue-specific expression. IRE1 also regulates various biological processes including protein folding, ER-associated degradation (ERAD), and lipid synthesis. Notably, IRE1α activation can lead to activation of c-Jun N-terminal kinase (JNK) and ER-specific caspase-12, thereby inducing apoptosis.

2.3 PERK Pathway

PERK is a transmembrane protein whose primary substrate is the eukaryotic initiation factor 2α (EIF2α). The UPR activation mechanism of PERK is similar to that of IRE1. During ERS, PERK autophosphorylates and activates EIF2α, reducing protein translation and folding in the ER and thereby decreasing protein synthesis. PERK also promotes translation of transcription factor ATF4, which is associated with various stress pathways, UPR-related inflammatory signals, ER chaperone transport, antioxidant responses, and autophagy.

ATF4 can induce expression of the downstream CHOP gene, which is considered a key pro-apoptotic factor downstream of EIF2α and ATF4 and is closely implicated in liver disease pathogenesis. During ERS activation, ATF4 overexpression increases transcription of growth arrest and DNA damage-inducible factors, with CHOP showing the most prominent upregulation. Overexpression of CHOP not only inhibits anti-apoptotic gene expression but also activates pro-apoptotic genes, leading to hepatocyte apoptosis.

3. ERS and Liver Diseases

3.1 ERS and Alcoholic Liver Disease (ALD)

Alcoholic liver disease results from chronic heavy alcohol consumption and typically progresses from hepatic steatosis to alcoholic hepatitis, fibrosis, cirrhosis, and potentially hepatocellular carcinoma. Previous studies have shown that lipid metabolism disorders in ALD patients cause ceramide accumulation, which induces ERS and insulin resistance. Excess hepatic iron can activate IRE1α and PERK to induce ERS, rendering hepatocytes more susceptible to injury. Alcohol-fed mice exhibit PERK activation and ATF4-dependent upregulation of nicotinamide N-methyltransferase (NNMT), indicating that the PERK-ATF4-NNMT axis contributes to alcohol-induced steatosis. Recent research has demonstrated that betulinic acid alleviates alcohol-induced liver injury by suppressing ERS and reducing expression of phosphorylated EIF2α, GRP78, GRP94, p-IRE1α, and p-PERK, thereby attenuating hepatocyte apoptosis and liver damage. These findings suggest that further investigation of the relationship between ERS and ALD pathogenesis may yield important clinical therapeutic implications.

3.2 ERS and Non-alcoholic Fatty Liver Disease (NAFLD)

NAFLD is characterized by hepatic lipid accumulation with insulin resistance, with hepatic fat content reaching 5-10%. The disease spectrum includes simple steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and eventual progression to hepatocellular carcinoma. Recently, scholars have proposed renaming NAFLD as metabolic-associated fatty liver disease (MAFLD). The pathogenesis of MAFLD remains incompletely understood, though studies have shown that ERS and UPR participate in steatosis, inflammation, and fibrosis. IRE1α signaling is implicated in MAFLD through XBP1 production and regulated IRE1-dependent decay (RIDD). Interestingly, hepatocyte-specific IRE1α knockout exacerbates liver fibrosis and inflammation, suggesting a protective role for IRE1α in NASH. Sulforaphane (SFN) ameliorates NAFLD induced by high-fat and high-fructose diets through gut-liver axis modulation. Empagliflozin has been shown to attenuate NAFLD progression by inhibiting Caspase-8 cleavage and reducing apoptosis, possibly through decreasing ERS-related protein levels. Insulin resistance and type 2 diabetes are critically linked to NAFLD pathogenesis; for instance, glucagon-like peptide-1 (GLP-1) can inhibit ERS activation via ER protein 46 (ERp46), slowing NAFLD

development. Recent studies have also shown that nuclear factor of activated T-cells 1 accelerates NAFLD progression by activating ERS and UPR to induce hepatocyte injury and inflammation. Additionally, α-linolenic acid ester of plant sterol (ALA-PS) protects against ERS-induced hepatocyte apoptosis in high-fat diet mouse models, likely by inhibiting the IRE1α/TRAF2/NK signaling pathway through AMP-activated protein kinase (AMPK) activation.

3.3 ERS and Drug-Induced Liver Injury

As a major metabolic organ, the liver metabolizes and excretes various drugs and toxins, with the ER serving as a critical site for biotransformation. This process can disrupt ER homeostasis and activate ERS. Carbon tetrachloride (CCl_4) is metabolized via the ER CYP2E1 pathway to generate highly reactive trichloromethyl free radicals that damage lipids and proteins, causing lipid peroxidation and protein aggregation. CCl_4 also disrupts Golgi metabolism and intracellular calcium homeostasis, ultimately leading to hepatocyte death. In acetaminophen (APAP)-induced acute liver injury models, overexpression of ATF6, CHOP, and Caspase-12 indicates that ERS plays an important role in toxic liver injury. Recent studies have shown that cadmium activates the PERK-EIF2α-ATF4-CHOP, IRE1α-XBP1, and ATF6-CHOP ERS signaling pathways, causing overexpression of ERS-related factors including GRP78, PERK, EIF2α, ATF4, CHOP, IRE1α, XBP1, and ATF6 at both mRNA and protein levels. Avicularin has been found to ameliorate lead-induced hepatic glucose metabolism disorders by inhibiting ERS. These findings collectively suggest that ERS is intimately involved in the pathogenesis of drug-induced liver injury.

3.4 ERS and Viral Hepatitis

In China, hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common forms of viral hepatitis. Previous studies have shown that massive accumulation of HBV replication products in the ER lumen activates UPR, and when UPR cannot cope with ERS, hepatocyte death ensues. Mutations in HBV surface antigen and e antigen, as well as development of anti-HBV drug resistance, may be associated with ERS. HCV encodes two envelope proteins, E1 and E2, which can specifically activate CHOP through PERK, causing hepatocyte injury. During HBV surface antigen accumulation, interferon can reduce UPR-induced ERS and decrease associated protein expression, thereby reducing cell death. Recent research has demonstrated that anti-CCDC88A/GIV polyclonal antibodies are significantly expressed in liver tissues of chronic HBV-infected patients, promoting HBV replication and secretion and causing excessive accumulation in the ER lumen, which triggers ERS and activates UPR. Liver biopsies from hepatitis C patients show upregulated ATF4 and CHOP protein levels. Additionally, HBV surface antigen (SHBs) can activate IRE1, PERK, and ATF6 pathways, leading to overexpression and secretion of vascular endothelial growth factor A (VEGFA), which may further promote hepatocellular

carcinoma development. In summary, chronic viral infection leads to massive accumulation of viral proteins in the ER, potentially causing UPR dysfunction and exacerbating hepatic inflammation, highlighting the importance of early intervention in HBV infection.

3.5 ERS and Liver Fibrosis/Cirrhosis

Liver fibrosis is a pathological condition characterized by extracellular collagen accumulation, often accompanied by inflammation that can progress to cirrhosis and hepatocellular carcinoma. Under normal conditions, hepatocytes rapidly regenerate to repair liver injury. However, when damage is persistent or severe, hepatic stellate cells (HSCs) transdifferentiate into myofibroblasts, representing a critical step in fibrosis pathogenesis. During fibrosis, type I procollagen transcription is induced, with secretion into the extracellular matrix via the Golgi apparatus. Angiotensin II (Ang-II) promotes fibrosis progression by mediating inflammatory cytokine production, collagen synthesis, cell proliferation, and mitotic activity. Maier et al. found that deletion of TANGO1, a protein involved in type I collagen secretion, causes type I procollagen retention in the ER, promoting UPR-mediated HSC apoptosis and attenuating liver fibrosis in mouse and human tissue samples. This study also revealed that IRE1α-XBP1s can induce TANGO1 upregulation following transforming growth factor-β (TGF-β) treatment, indicating that TANGO1 is essential for HSC homeostasis in fibrosis. Both CCl_4-induced mouse liver fibrosis and thioacetamide-induced rat cirrhosis are accompanied by ERS and activation of all three UPR branches, with therapeutic effects confirmed by specific anti-inflammatory inhibitor TPPU. Additionally, Su et al. demonstrated that celecoxib attenuates ERS and effectively alleviates liver fibrosis and cirrhosis progression. These findings suggest that liver fibrosis and cirrhosis are associated with severe ERS that activates UPR, promoting disease progression. Targeting this pathway may represent a novel therapeutic strategy.

3.6 ERS and Liver Failure

Liver failure is an end-stage liver disease characterized by severe impairment of hepatic synthetic, detoxification, metabolic, and immune functions under multiple insults. In acute-on-chronic liver failure (ACLF) patients, ERS-related protein levels and gene expression (e.g., GRP78, PERK, ATF4) are altered compared to cirrhotic patients, with upregulated XBP1, caspase-3, caspase-8, and TNF-α protein levels. Electron microscopy of hepatocytes from HBV-related ACLF patients reveals ER structural dilation and disruption, with all three UPR branches activated, suggesting ERS involvement in ACLF pathogenesis. Recent studies have shown that caffeine reduces hepatocyte apoptosis by inhibiting GRP78 and blocking lipopolysaccharide-induced ERS. Additionally, tauroursodeoxycholic acid attenuates APAP-induced liver injury by suppressing upregulation of ERS-related proteins including CHOP, XBP1, and p-EIF2α, thereby reducing tissue damage. These observations indicate that ERS partici-

pates in the pathophysiology of liver failure, and ERS inhibitors may alleviate hepatic injury and reduce hepatocyte apoptosis by suppressing relevant signaling pathways, preserving liver function. Further investigation into the mechanisms linking ERS and liver failure may provide new clinical insights.

3.7 ERS and Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, with ERS evident across various cancers. HBV infection is a well-established risk factor for HCC in China. The UPR pathways activated by ERS, particularly ATF6α and IRE1α, may play important roles in hepatocarcinogenesis. Recent studies have shown that the IRE1α signaling pathway is crucial in HCC development, and short-term inhibition of ATF6α may be an effective therapeutic approach for NASH and HCC. In a diethylnitrosamine model, specific knockdown of hepatic IRE1 effectively attenuated HCC progression. Lee et al. found that combining tumor necrosis factor superfamily member 10 (TNFSF10) with the non-steroidal anti-inflammatory drug celecoxib in TNFSF10/CD44-expressing HCC cells reversed resistance to TNFSF10, enhancing clinical efficacy potentially through celecoxib-induced ERS-dependent autophagy. Additionally, the deubiquitinase inhibitor b-AP15 induces ERS, blocks Wnt/Notch1 signaling, disrupts cell cycle progression, reduces cell survival, and ultimately causes apoptosis. Yang et al. discovered that a novel N-heterocyclic carbene silver(I) complex derived from 4,5-diarylimidazole (compound 4C) induces immunogenic cell death in HCC cells, demonstrating excellent efficacy in tumor-targeted therapy and antitumor activity. However, the precise mechanisms by which ERS induces HCC cell apoptosis remain unclear, and whether ERS ultimately inhibits or promotes tumor growth is still undetermined, necessitating further research.

In recent years, ERS has garnered increasing attention in liver disease research. ERS represents a self-protective mechanism wherein mild ERS activates adaptive UPR, whereas severe ERS triggers terminal UPR leading to apoptosis. Terminal UPR not only participates in liver disease pathogenesis but is also implicated in metabolic diseases and tumorigenesis. Therefore, research on ERS in liver diseases remains in its early stage, and its precise mechanistic roles in disease development require further investigation.

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Figure 1 Schematic diagram of adaptive unfolded protein response and maladaptive unfolded protein response

Note: ER = endoplasmic reticulum, ERS = endoplasmic reticulum stress, Grp78 = glucose-regulated protein 78, PERK = protein kinase R-like ER kinase, IRE1α = inositol-requiring enzyme 1, ATF6 = activating transcription factor 6, EIF2α = eukaryotic translation initiation factor 2α, ATF4 = activating transcription factor 4, XBP1s = spliced X-box binding protein 1, ATF6α = activating transcription factor 6α, ATF6β = activating transcription factor 6β, CHOP = C/EBP-homologous protein, ASK1 = apoptosis signal-regulating kinase 1, BCL2 = B-cell lymphoma 2, ERAD = ER-associated degradation, JNK1 = Jun N-terminal kinase 1, TRAF2 = tumor necrosis factor receptor-associated factor 2, CAMK II = Ca^{2+}/calmodulin-dependent protein kinase II, IP3R1 = inositol 1,4,5-trisphosphate receptor type 1, Nucleus = cell nucleus, Autophagy = autophagy, Apoptosis = apoptosis

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Note: Figure translations are in progress. See original paper for figures.