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The Unfolded Protein Response in Fatty Liver Disease

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Abstract

The Unfolded Protein Response (UPR) is a protective cellular response activated under conditions of endoplasmic reticulum (ER) stress. The hepatic UPR is activated in several forms of liver disease including nonalcoholic fatty liver disease (NAFLD). Recent data defining the role of the UPR in hepatic lipid metabolism have identified molecular mechanisms that may underlie the association between UPR activation and NAFLD. It has become increasingly evident that the IREα/Xbp1 pathway of the UPR is critical for hepatic lipid homeostasis, and dysregulation of this evolutionarily conserved pathway is associated with human non-alcoholic steatohepatitis (NASH). Although increasing evidence has delineated the importance of UPR pathway signaling in fatty liver disorders, the regulation of the hepatic UPR in normal physiology and fatty liver disorders remains incompletely understood. Understanding the role of the UPR in hepatic lipid metabolism may lead to the identification of novel therapeutic targets for the treatment of NAFLD.

Keywords

unfolded protein response; hepatic lipid metabolism; fatty liver; endoplasmic reticulum stress

Introduction

The unfolded protein response (UPR) is a highly conserved signaling pathway activated in response to endoplasmic reticulum (ER) stress. Recent data indicate that the UPR is activated in NAFLD and may have an important role in the development and/or progression of this disease.^{1–4} The molecular mechanism by which the UPR regulates hepatic lipid metabolism has been an area of intense investigation over the past decade. In this review we will a) provide an overview of the UPR, b) discuss the role of the UPR in the pathogenesis of human liver disease including NAFLD, c) review the data implicating the UPR in the

regulation of hepatic lipid metabolism, and d) identify the UPR as a potential therapeutic target in human NAFLD.

The Unfolded Protein Response

One of the critical functions of the endoplasmic reticulum (ER) is to maintain protein homeostasis by regulating protein synthesis, folding and processing. Under conditions of ER stress, normal ER function becomes compromised leading to the accumulation of unfolded or misfolded proteins. Glucose deprivation, aberrant calcium signaling, viral infection, and disruption of redox regulation are among the many types of cellular disturbances that provoke ER stress.⁵ Such disturbances in ER function trigger an evolutionarily conserved intracellular signal transduction pathway known as the unfolded protein response (UPR).⁶ The UPR initially aims to restore homeostasis in order to allow the cell to adapt to the stressor. Elements of this compensatory response include reducing protein translation and producing molecular chaperones to assist in proper protein folding and trafficking.⁷ If, however, homeostasis is not adequately restored, pathways leading to apoptosis are initiated.^{8, 9}

As depicted in Figure 1, the UPR is mediated through three ER transmembrane receptors, PKR-like ER kinase (PERK), activating transcription factor 6 (ATF6 α), and inositol requiring enzyme 1 α (IRE1 α) and one master chaperone, glucose-regulated protein 78kDa (GRP78, also known as BiP). In the unstressed state, BiP is bound to these transmembrane receptors. However, when unfolded proteins accumulate in the ER, BiP preferentially binds to unfolded proteins, thereby dissociating from PERK, ATF6 α , and IRE1 α .

The IRE1 α Pathway

The IRE1 α pathway is the most highly conserved arm of the UPR. In an unstressed state, IRE1 α is bound by the ER chaperone BiP. In response to accumulation of unfolded proteins, BiP releases IRE1 α allowing its activation by dimerization and autophosphorylation. Activated IRE1 α induces splicing of the mRNA encoding X-box binding protein 1 (XBP1).¹⁰ Spliced (activated) XBP1 is a transcriptional activator that has many targets including ER chaperones and genes involved in ER-associated degradation (ERAD).¹¹

The PERK pathway

Upon dissociation from BiP, PERK forms a dimer leading to its activation by autophosphorylation. Activation of PERK promotes phosphorylation of eukaryotic initiation factor (eIF2 α), leading to a global attenuation of protein translation.^{7, 12} Although eIF2 α primarily serves to halt overall protein translation, eIF2 α increases the translation of select proteins, including activating transcription factor 4 (ATF4). ATF4 functions to increase the production of molecular chaperones and promote ERAD.^{13, 14} ATF4 activation also leads to the activation of C/EBP homologous protein (CHOP).^{15, 16} CHOP, in turn, activates GADD34 which dephosphorylates eIF2 α , allowing protein translation to resume.¹⁵

The ATF6 pathway

ATF6 α is a 90kDa protein bound by BiP. Dissociation of BiP results in the unmasking of two Golgi localization sequences within ATF6.¹⁷ Upon translocation to the Golgi apparatus, ATF6 α is activated by proteolytic cleavage to a 50kDa transcription factor. Activated ATF6 α translocates to the nucleus where it transcriptionally activates ER chaperones (such as BiP and Grp94) and genes associated with ERAD.¹⁸

ER stress-induced apoptosis

The UPR initially aims to restore homeostasis resulting from cellular stressors, however if overwhelming ER stress persists, the UPR initiates apoptosis. The molecular mechanisms governing this critical transition from restoration of homeostasis to initiation of apoptosis remain poorly understood.

The IRE1 α pathway has been implicated in ER stress-induced apoptosis (Figure 2). In addition to activating XBP1, activated IRE1 α also recruits TNFR-associated receptor 2 (TRAF2) leading to activation of the c-Jun N-terminal kinase (JNK).^{19, 20} JNK is a mitogen activated protein kinase (MAPK) that mediates multiple stress signaling pathways and acts to promote inflammation and apoptosis in the liver. Bak and Bax are pro-apoptotic Bcl2 family members which interact with the IRE1 α pathway and may mediate, in part, ER stress-induced apoptosis.²¹ Bak and Bax function in the membranes of both mitochondria and the ER. Within the ER membrane, these proteins associate with IRE1 α to potentiate its activity.²¹ Mice deficient in Bax/Bak are resistant to ER stress-induced apoptosis yet show enhanced liver injury, possibly due to attenuation of IRE1 α activity.²¹ Caspase-12 may also mediate, in part, ER stress-induced apoptosis. Caspase-12 associates with activated IRE1 α , allowing its proteolytic cleavage to active caspase-12. Mice deficient in caspase-12 show resistance to apoptosis in the face of pharmacologic ER stress.²²

CHOP is thought to be an important mediator of ER stress-induced apoptosis.^{23, 24} Studies have shown that CHOP overexpression sensitizes cells to apoptosis whereas CHOP depletion attenuates ER stress-induced apoptosis.^{23, 24} CHOP functions as a transcriptional activator of numerous pro-apoptotic genes including death receptor 5 (DR5), Bim, and tribbles homolog 3 (TRB3).^{25–27}

The Unfolded Protein Response in Liver Disease

The UPR was initially described in yeast almost two decades ago. However, it is only more recently that the UPR has been demonstrated to be important in the pathogenesis of several hepatic diseases. Table 1 describes several liver diseases in which the UPR is important, including both non-alcoholic fatty liver diseases and other hepatic diseases.

It has recently been demonstrated that both NAFLD and NASH are associated with increased phosphorylation of eIF-2 α in the liver, however, there is a failure to activate downstream UPR recovery pathways in these fatty liver disorders. In addition, NASH is associated with the inability to express adequate hepatic XBP-1s protein and JNK phosphorylation.¹ Experimental evidence in alcohol-induced liver injury also indicates that

excessive alcohol ingestion causes ER stress and UPR activation, and thus, the UPR is also likely important in the pathogenesis of alcohol liver disease^{28–35}.

Viral hepatitis causes ER stress and the UPR has been shown to be an important cellular response to infection with hepatitis B and hepatitis C^{36–44}. Experimental evidence indicates that bile salts also are important in regulating ER stress in hepatocytes, as well as intestinal and pancreatic cells^{45–51}. Alpha-1 antitrypsin deficiency is a hepatic disease caused by genetic mutations that result in protein misfolding in hepatocytes. Therefore, it is not surprising that hepatic UPR activation occurs in patients with alpha-1 antitrypsin deficiency and UPR activation is an important response to liver injury and in the disease pathogenesis^{52–58}. Experimental evidence also indicates that the UPR may have an important role in hepatic iron overload states and in ischemia-reperfusion liver injury^{46, 59–66}. Therefore, the UPR response to ischemia reperfusion injury likely has clinical implications for both ischemic liver injury and for ischemia-reperfusion injury during liver transplantation. Finally, ER stress and the UPR is important in the pathogenesis and treatment of hepatocellular carcinoma.^{67–75}

The Unfolded Protein Response and Hepatic Lipid Metabolism

In addition to its role in protein homeostasis, the ER performs several other essential cellular functions. The ER is the major cellular site of calcium storage, the disruption of which alters numerous cellular signaling pathways. The ER contains cytochrome P450 enzymes, which are responsible for drug metabolism among other cellular functions. Lastly, the ER has a primary role in lipid synthesis and cellular membrane biogenesis. Interestingly it has been shown that within liver cells of obese mice, the ER decreases protein synthesis and increases lipid synthesis, which may contribute to the development of hepatic steatosis in obesity.⁷⁶

Although the UPR was initially identified as a mechanism to maintain proper protein folding and processing, it is now clear that the UPR has broader metabolic functions. In particular, it is becoming increasingly evident that a major function of the UPR is to maintain hepatic lipid homeostasis. The interplay between the UPR and hepatic lipid metabolism is complex and incompletely understood. ER stress induces hepatic lipid accumulation but additionally, hepatic lipid accumulation induces ER stress. As such, hepatic lipid accumulation is both a cause and a consequence of ER stress, thus creating a positive feedback loop which may promote the development of hepatic steatosis.^{2, 77, 78}

ER stress induces hepatic lipid accumulation

Numerous studies have shown that both acute and chronic ER stress induce hepatic steatosis in mice. Treating mice with tunicamycin or thapsigargin, two commonly used pharmacologic inducers of ER stress, results in profound hepatic lipid accumulation.^{79, 80} Despite causing significant hepatic steatosis in mice, tunicamycin suppresses hepatic lipid synthesis suggesting that ER stress-induced hepatic steatosis may not result from *de novo* lipogenesis.⁷⁹ Instead, ER stress has been shown to inhibit VLDL secretion,^{78, 81} which may be a primary mechanism by which tunicamycin promotes hepatic steatosis in the setting of suppressed lipogenesis.^{78, 81} Recent data indicate that tunicamycin induces expression of VLDL receptor (VLDLR) in mice and loss of VLDLR protects against tunicamycin-induced

hepatic steatosis. Furthermore, it has been proposed that the effects of tunicamycin on VLDLR expression are mediated by PERK-ATF4 signaling.⁸² Other studies have suggested that ER stress may enhance hepatic lipogenesis.⁸⁰ Pharmacologic induction of ER stress with thapsigargin suppresses the translation of Insig-1, which functions to inhibit the translocation and activation of sterol regulatory element binding protein 1c (SREBP-1c).⁸³ In this model, ER stress promotes hepatic lipogenesis via increased activation of SREBP-1c.

Further highlighting the importance of ER stress on hepatic lipid accumulation is the finding that reducing ER stress in mice attenuates hepatic steatosis.⁸⁴ Tauroursodeoxycholic acid (TUDCA) and 4-phenylbutyric acid (PBA) are chemical chaperones that have been shown to reduce ER stress by facilitating proper protein folding and trafficking.^{85, 86} Inhibiting ER stress using these chemical chaperones in a murine model of hepatic steatosis (*ob/ob* mice) has been shown to reduce hepatic lipid accumulation.⁸⁴

Hepatic lipid accumulation induces ER stress

Obesity induces a chronic state of ER stress which is thought to contribute to metabolic complications of this condition.^{87–90} Hepatic steatosis, which is tightly associated with obesity, is a well-established trigger of ER stress in the liver.^{2, 91, 92} Several studies have shown that palmitate and other saturated fatty acids activate the UPR in the liver, which is characterized by a preferential induction of PERK signaling.^{93, 94} Excess cellular cholesterol is also a potent inducer of ER stress.⁹¹ Furthermore it has been shown that saturated fatty acids and cholesterol work synergistically to promote ER stress.⁹⁵ Conversely, short-term exposure to unsaturated fatty acids appears to attenuate ER stress in the setting of excess palmitate or cholesterol.^{96–98} This effect may be due to more efficient triglyceride synthesis and VLDL secretion by monounsaturated fatty acids. However, chronic exposure to oleic acid, a more physiologically relevant model of metabolic disease, induces ER stress and suppresses VLDL secretion.⁷⁸ Interestingly, the lipid composition of the hepatic ER in obese mice is altered. It has been proposed that this shift in lipid composition promotes ER stress via disruption in ER calcium retention.⁷⁶

Regulation of hepatic lipid homeostasis by the UPR

All three major branches of the UPR have been implicated in lipid homeostasis. Disruption of any of these branches or the master ER chaperone, BiP, is thought to promote hepatic lipid deposition in mice.^{79, 99}

Numerous studies have identified a critical role of the IRE α /XBP1 pathway in hepatic lipid metabolism. Hepatic XBP1 is a transcription factor that has been shown to directly activate key lipogenic genes.⁷⁷ Mice bearing a liver-specific deletion of XBP1 demonstrate decreased *de novo* hepatic lipogenesis and decreased steatosis in response to lipogenic diets.^{77, 100} Hepatocyte-specific IRE1 α -null mice develop profound hepatic steatosis in response to ER stress.¹⁰¹ IRE1 α -deletion results in decreased VLDL secretion attributable, in part, to decrease microsomal triglyceride-transfer protein activity.¹⁰² Unlike liver-specific XBP1-deletion, IRE1 α -deletion does not suppress *de novo* lipogenesis and, in fact, exacerbates diet-induced hepatic steatosis.¹⁰² The molecular mechanisms underlying the discrepancy in metabolic phenotype between IRE α -deficient and XBP1-deficient mice are

incompletely understood and warrant further exploration. Interestingly, it was recently shown that the IRE α /XBP1 axis may function in the postprandial shift from glucose production to glucose assimilation and, as such, serve as a metabolic switch in hepatocytes.¹⁰³

The PERK pathway has also been implicated in the regulation of hepatic lipids. Genetic ablation of eIF2 α exacerbates hepatic steatosis in mice subjected to pharmacologic ER stress.⁷⁹ Mice bearing genetic mutations that alter the phosphorylation of eIF2 α also demonstrate aberrant hepatic lipid metabolism. Transgenic mice overexpressing GADD34, a regulatory protein of eIF2 α phosphatase, are protected from high-fat diet-induced hepatic steatosis.¹⁰⁴ GADD34 transgenic mice show suppression of key lipogenic genes, which is thought to be the mechanism of protection from steatosis. Furthermore, PERK activates the transcription factors C/EBP α and C/EBP β , which regulate hepatic lipogenesis.^{105, 106} ATF4, a downstream target of PERK, has also been implicated in hepatic lipid metabolism. Mice heterozygous for ATF4 deletion are protected from diet-induced hepatic steatosis.¹⁰⁷ In addition to its role in mediating ER stress-induced apoptosis, the ATF4 target CHOP functions as a transcriptional regulator of key genes involved in lipid metabolism.¹⁰⁸

Genetic ablation of ATF6 α in mice results in enhanced hepatic steatosis in response to pharmacologic ER stress.^{79, 109} The primary mechanism by which loss of ATF6 α promotes hepatic steatosis is via a reduction in fatty acid β -oxidation and decreased VLDL formation. Activated ATF6 α has also been shown to associate with SREBP2 thus inhibiting its transcriptional activity, which may reduce hepatic lipid accumulation.¹¹⁰

Genetic manipulation of the ER chaperone BiP, the master regulator of the UPR, also impacts hepatic lipid metabolism. Overexpression of Grp78 in *ob/ob* mice confers protection against ER stress in the liver associated with a reduction in SREBP-1c activation and reduced hepatic steatosis.⁹⁹

Overall, the preponderance of data indicate that the UPR has a critical role in hepatic lipid metabolism. As such, manipulating the UPR may prove to be a promising strategy to treat NAFLD.

Unfolded Protein Response Targets for the Treatment of Fatty Liver Disease

Current pharmacologic therapy for non-alcoholic steatohepatitis remains inadequate, and progressive liver disease from NASH remains a common cause of cryptogenic cirrhosis, end-stage liver disease, need for liver transplantation and death. In addition, due to the epidemic of obesity in the United States and throughout the world, it is anticipated that the prevalence of NASH will increase in the next decades, with an associated increase in morbidity and mortality. There is increasing experimental evidence suggesting that targeting UPR signaling pathways may allow for the rationale development of novel therapeutic approaches to treat fatty liver disorders (Table 2).

Chaperones are cellular proteins that are involved in the folding, unfolding, assembly and disassembly of other cellular proteins. TUDCA and PBA are chemical chaperones that have been shown to be beneficial in several murine models of fatty liver disease^{46, 49, 84}. In light of these data, chemical chaperones have been regarded as highly exciting candidates to treat human NAFLD. UDCA, an effective therapy in various forms of cholestatic liver disease, has been studied in numerous clinical NASH trials over the past decade. Unfortunately, the majority of these trials have shown disappointing results, and the routine use of UDCA in patients with NAFLD cannot be recommended.^{111–113}

Experimental evidence suggests that elevated serum homocysteine levels are associated with fatty liver disorders, although it remains controversial whether the elevated homocysteine levels are the primary cause of liver injury or resultant from the liver injury¹¹⁴³. In fact, homocysteine supplementation reduces UPR activation in an experimental model of NAFLD³. Homocysteine and methionine metabolism is important in experimental models of NAFLD, and these agents and related metabolites may also be potential pharmacologic therapies for fatty liver disease, either alone or in combination with other agents. These drugs include Betaine, S-adenosyl-L-methionine (SAME), taurine and folic acid^{28, 30, 31, 115–126}.

Glucagon-like peptide-1 (GLP-1) analogues, such as exenatide, also show promise as future therapeutic options. The beneficial effects of GLP-1 agonists may be mediated, in part, by modulation of the ER stress response. Exendin-4, a GLP-1 agonist, has been shown to attenuate lipid accumulation in primary human hepatocytes associated with enhanced BiP expression and decreased CHOP expression.¹²⁷

Additional strategies to target the UPR pathways are being developed but are not yet in clinical trials. Genetic approaches including hepatic gene over-expression of hepatic UPR genes or hepatic micro-RNAs also may have future therapeutic roles⁵⁰. Regulators such as BiP protein Inducer X (BIX) or methoxyflavones are pharmacologic agents that has been shown in experimental models of brain ischemia to reduce neurologic injury^{128–131}. Since BiP regulates all three UPR pathways, pharmacologic approaches to regulate BiP expression may provide additional potential therapeutic approaches. Nonetheless, large controlled studies of pharmacologic agents targeting UPR pathways in patients with fatty liver diseases have not yet been performed.

Summary

The Unfolded Protein Response is a protective hepatic signaling pathway that is activated in response to ER stress. The hepatic UPR has been shown to be important in the pathophysiology of several liver diseases, and recent experimental animal and human studies have demonstrated an important role of the UPR in non-alcoholic fatty liver diseases. Although the mechanisms of UPR regulation and dysregulation remain incompletely understood, further investigations into the role of the UPR in fatty liver disorders may allow for the future design of novel, effective therapies to treat fatty liver disorders.

Abbreviations

UPR	unfolded protein response
ER	endoplasmic reticulum
PERK	PKR-like ER kinase
ATF6α	activating transcription factor 6
IRE1α	inositol requiring enzyme 1 α
BiP/Grp78	Binding immunoglobulin protein/78 kDa glucose-regulated protein
XBP1	X-box binding protein 1
ERAD	ER-associated degradation
eIF2α	eukaryotic initiation factor
ATF4	activating transcription factor 4
CHOP	C/EBP homologous protein
TRAF2	TNFR-associated receptor 2
JNK	c-Jun N-terminal kinase
DR5	death receptor 5
Bim	Bcl2 interacting mediator of cell death
TRB3	tribbles homolog 3
VLDLR	VLDL receptor
SREBP-1c	sterol regulatory element binding protein 1c
PBA	4-phenylbutyric acid
TUDCA	Tauroursodeoxycholic acid
BIX	BiP protein Inducer X
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
SAME	S-adenosyl-L-methionine

References

1. Puri P, Mirshahi F, Cheung O, et al. Activation and dysregulation of the unfolded protein response in nonalcoholic fatty liver disease. *Gastroenterology*. Feb; 2008 134(2):568–576. [PubMed: 18082745]
2. Wang D, Wei Y, Pagliassotti MJ. Saturated fatty acids promote endoplasmic reticulum stress and liver injury in rats with hepatic steatosis. *Endocrinology*. Feb; 2006 147(2):943–951. [PubMed: 16269465]
3. Henkel AS, Elias MS, Green RM. Homocysteine supplementation attenuates the unfolded protein response in a murine nutritional model of steatohepatitis. *J Biol Chem*. Nov 13; 2009 284(46):31807–31816. [PubMed: 19762918]

4. Rinella ME, Siddiqui MS, Gardikiotes K, Gottstein J, Elias M, Green RM. Dysregulation of the unfolded protein response in db/db mice with diet-induced steatohepatitis. *Hepatology*. Nov; 54(5): 1600–1609. [PubMed: 21748768]
5. Xu C, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: cell life and death decisions. *J Clin Invest*. Oct; 2005 115(10):2656–2664. [PubMed: 16200199]
6. Zhang K, Kaufman RJ. Signaling the unfolded protein response from the endoplasmic reticulum. *J Biol Chem*. Jun 18; 2004 279(25):25935–25938. [PubMed: 15070890]
7. Wek RC, Cavener DR. Translational control and the unfolded protein response. *Antioxid Redox Signal*. Dec; 2007 9(12):2357–2371. [PubMed: 17760508]
8. Marciniak SJ, Ron D. Endoplasmic reticulum stress signaling in disease. *Physiol Rev*. Oct; 2006 86(4):1133–1149. [PubMed: 17015486]
9. Walter P, Ron D. The unfolded protein response: from stress pathway to homeostatic regulation. *Science*. Nov 25; 334(6059):1081–1086. [PubMed: 22116877]
10. Uemura A, Oku M, Mori K, Yoshida H. Unconventional splicing of XBP1 mRNA occurs in the cytoplasm during the mammalian unfolded protein response. *J Cell Sci*. Aug 15; 2009 122(Pt 16): 2877–2886. [PubMed: 19622636]
11. Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K. XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell*. Dec 28; 2001 107(7):881–891. [PubMed: 11779464]
12. Harding HP, Zhang Y, Ron D. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. *Nature*. Jan 21; 1999 397(6716):271–274. [PubMed: 9930704]
13. Vattem KM, Wek RC. Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells. *Proc Natl Acad Sci U S A*. Aug 3; 2004 101(31):11269–11274. [PubMed: 15277680]
14. Harding HP, Novoa I, Zhang Y, et al. Regulated translation initiation controls stress-induced gene expression in mammalian cells. *Mol Cell*. Nov; 2000 6(5):1099–1108. [PubMed: 11106749]
15. Marciniak SJ, Yun CY, Oyadomari S, et al. CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. *Genes Dev*. Dec 15; 2004 18(24):3066–3077. [PubMed: 15601821]
16. Ma Y, Brewer JW, Diehl JA, Hendershot LM. Two distinct stress signaling pathways converge upon the CHOP promoter during the mammalian unfolded protein response. *J Mol Biol*. May 17; 2002 318(5):1351–1365. [PubMed: 12083523]
17. Shen J, Chen X, Hendershot L, Prywes R. ER stress regulation of ATF6 localization by dissociation of BiP/GRP78 binding and unmasking of Golgi localization signals. *Dev Cell*. Jul; 2002 3(1):99–111. [PubMed: 12110171]
18. Adachi Y, Yamamoto K, Okada T, Yoshida H, Harada A, Mori K. ATF6 is a transcription factor specializing in the regulation of quality control proteins in the endoplasmic reticulum. *Cell Struct Funct*. 2008; 33(1):75–89. [PubMed: 18360008]
19. Urano F, Wang X, Bertolotti A, et al. Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. *Science*. Jan 28; 2000 287(5453):664–666. [PubMed: 10650002]
20. Hu P, Han Z, Couvillon AD, Kaufman RJ, Exton JH. Autocrine tumor necrosis factor alpha links endoplasmic reticulum stress to the membrane death receptor pathway through IRE1alpha-mediated NF-kappaB activation and down-regulation of TRAF2 expression. *Mol Cell Biol*. Apr; 2006 26(8):3071–3084. [PubMed: 16581782]
21. Hetz C, Bernasconi P, Fisher J, et al. Proapoptotic BAX and BAK modulate the unfolded protein response by a direct interaction with IRE1alpha. *Science*. Apr 28; 2006 312(5773):572–576. [PubMed: 16645094]
22. Nakagawa T, Zhu H, Morishima N, et al. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. *Nature*. Jan 6; 2000 403(6765):98–103. [PubMed: 10638761]
23. McCullough KD, Martindale JL, Klotz LO, Aw TY, Holbrook NJ. Gadd153 sensitizes cells to endoplasmic reticulum stress by down-regulating Bcl2 and perturbing the cellular redox state. *Mol Cell Biol*. Feb; 2001 21(4):1249–1259. [PubMed: 11158311]

24. Zinszner H, Kuroda M, Wang X, et al. CHOP is implicated in programmed cell death in response to impaired function of the endoplasmic reticulum. *Genes Dev.* Apr 1; 1998 12(7):982–995. [PubMed: 9531536]
25. Yamaguchi H, Wang HG. CHOP is involved in endoplasmic reticulum stress-induced apoptosis by enhancing DR5 expression in human carcinoma cells. *J Biol Chem.* Oct 29; 2004 279(44):45495–45502. [PubMed: 15322075]
26. Puthalakath H, O'Reilly LA, Gunn P, et al. ER stress triggers apoptosis by activating BH3-only protein Bim. *Cell.* Jun 29; 2007 129(7):1337–1349. [PubMed: 17604722]
27. Ohoka N, Yoshii S, Hattori T, Onozaki K, Hayashi H. TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death. *EMBO J.* Mar 23; 2005 24(6):1243–1255. [PubMed: 15775988]
28. Ji C. Mechanisms of alcohol-induced endoplasmic reticulum stress and organ injuries. *Biochemistry research international.* 2012; 2012:216450. [PubMed: 22110961]
29. Ji C, Mehriani-Shai R, Chan C, Hsu YH, Kaplowitz N. Role of CHOP in hepatic apoptosis in the murine model of intragastric ethanol feeding. *Alcoholism, clinical and experimental research.* Aug; 2005 29(8):1496–1503.
30. Kaplowitz N, Ji C. Unfolding new mechanisms of alcoholic liver disease in the endoplasmic reticulum. *Journal of gastroenterology and hepatology.* Oct; 2006 21(Suppl 3):S7–9. [PubMed: 16958678]
31. Ji C. Dissection of endoplasmic reticulum stress signaling in alcoholic and non-alcoholic liver injury. *Journal of gastroenterology and hepatology.* Mar; 2008 23(Suppl 1):S16–24. [PubMed: 18336657]
32. Galligan JJ, Fritz KS, Tipney H, et al. Profiling impaired hepatic endoplasmic reticulum glycosylation as a consequence of ethanol ingestion. *J Proteome Res.* Apr 1; 2011 10(4):1837–1847. [PubMed: 21319786]
33. Galligan JJ, Smathers RL, Shearn CT, et al. Oxidative Stress and the ER Stress Response in a Murine Model for Early-Stage Alcoholic Liver Disease. *J Toxicol.* 2012; 2012:207594. [PubMed: 22829816]
34. Longato L, Ripp K, Setshedi M, et al. Insulin resistance, ceramide accumulation, and endoplasmic reticulum stress in human chronic alcohol-related liver disease. *Oxid Med Cell Longev.* 2012; 2012:479348. [PubMed: 22577490]
35. Tsuchiya M, Ji C, Kosyk O, et al. Interstrain differences in liver injury and one-carbon metabolism in alcohol-fed mice. *Hepatology (Baltimore, Md).* Jul; 2012 56(1):130–139.
36. Li B, Gao B, Ye L, et al. Hepatitis B virus X protein (HBx) activates ATF6 and IRE1-XBP1 pathways of unfolded protein response. *Virus Res.* Mar; 2007 124(1–2):44–49. [PubMed: 17092596]
37. Li J, Liu Y, Wang Z, et al. Subversion of cellular autophagy machinery by hepatitis B virus for viral envelopment. *J Virol.* Jul; 2011 85(13):6319–6333. [PubMed: 21507968]
38. Lazar C, Macovei A, Petrescu S, Branza-Nichita N. Activation of ERAD pathway by human hepatitis B virus modulates viral and subviral particle production. *PLoS One.* 2012; 7(3):e34169. [PubMed: 22461906]
39. Tardif KD, Mori K, Siddiqui A. Hepatitis C virus subgenomic replicons induce endoplasmic reticulum stress activating an intracellular signaling pathway. *J Virol.* Aug; 2002 76(15):7453–7459. [PubMed: 12097557]
40. Kukiwara H, Moriishi K, Tagawa S, et al. Human VAP-C negatively regulates hepatitis C virus propagation. *J Virol.* Aug; 2009 83(16):7959–7969. [PubMed: 19515777]
41. Li S, Ye L, Yu X, et al. Hepatitis C virus NS4B induces unfolded protein response and endoplasmic reticulum overload response-dependent NF-kappaB activation. *Virology.* Sep 1; 2009 391(2):257–264. [PubMed: 19628242]
42. Asselah T, Bieche I, Mansouri A, et al. In vivo hepatic endoplasmic reticulum stress in patients with chronic hepatitis C. *J Pathol.* Jul; 2010 221(3):264–274. [PubMed: 20527020]
43. Ke PY, Chen SS. Activation of the unfolded protein response and autophagy after hepatitis C virus infection suppresses innate antiviral immunity in vitro. *J Clin Invest.* Jan; 2011 121(1):37–56. [PubMed: 21135505]

44. Merquiol E, Uzi D, Mueller T, et al. HCV causes chronic endoplasmic reticulum stress leading to adaptation and interference with the unfolded protein response. *PLoS One*. 2011; 6(9):e24660. [PubMed: 21949742]
45. Bochkis IM, Rubins NE, White P, Furth EE, Friedman JR, Kaestner KH. Hepatocyte-specific ablation of *Foxa2* alters bile acid homeostasis and results in endoplasmic reticulum stress. *Nat Med*. Aug; 2008 14(8):828–836. [PubMed: 18660816]
46. Ben Mosbah I, Alfany-Fernandez I, Martel C, et al. Endoplasmic reticulum stress inhibition protects steatotic and non-steatotic livers in partial hepatectomy under ischemia-reperfusion. *Cell Death Dis*. 2010; 1:e52. [PubMed: 21364657]
47. Malo A, Kruger B, Seyhun E, et al. Tauroursodeoxycholic acid reduces endoplasmic reticulum stress, trypsin activation, and acinar cell apoptosis while increasing secretion in rat pancreatic acini. *Am J Physiol Gastrointest Liver Physiol*. Oct; 2010 299(4):G877–886. [PubMed: 20671193]
48. Seyhun E, Malo A, Schafer C, et al. Tauroursodeoxycholic acid reduces endoplasmic reticulum stress, acinar cell damage, and systemic inflammation in acute pancreatitis. *Am J Physiol Gastrointest Liver Physiol*. Nov; 2011 301(5):G773–782. [PubMed: 21778463]
49. Jimenez-Castro MB, Elias-Miro M, Mendes-Braz M, et al. Tauroursodeoxycholic acid affects PPARgamma and TLR4 in Steatotic liver transplantation. *Am J Transplant*. Dec; 2012 12(12):3257–3271. [PubMed: 22994543]
50. Dai BH, Geng L, Wang Y, et al. microRNA-199a-5p protects hepatocytes from bile acid-induced sustained endoplasmic reticulum stress. *Cell Death Dis*. 2013; 4:e604. [PubMed: 23598416]
51. Bernstein H, Payne CM, Bernstein C, Schneider J, Beard SE, Crowley CL. Activation of the promoters of genes associated with DNA damage, oxidative stress, ER stress and protein misfolding by the bile salt, deoxycholate. *Toxicol Lett*. Jul 30; 1999 108(1):37–46. [PubMed: 10472808]
52. Lawless MW, Greene CM, Mulgrew A, Taggart CC, O'Neill SJ, McElvaney NG. Activation of endoplasmic reticulum-specific stress responses associated with the conformational disease Z alpha 1-antitrypsin deficiency. *J Immunol*. May 1; 2004 172(9):5722–5726. [PubMed: 15100318]
53. Mencin A, Seki E, Osawa Y, et al. Alpha-1 antitrypsin Z protein (PiZ) increases hepatic fibrosis in a murine model of cholestasis. *Hepatology (Baltimore, Md)*. Nov; 2007 46(5):1443–1452.
54. Scott CM, Kruse KB, Schmidt BZ, Perlmutter DH, McCracken AA, Brodsky JL. ADD66, a gene involved in the endoplasmic reticulum-associated degradation of alpha-1-antitrypsin-Z in yeast, facilitates proteasome activity and assembly. *Mol Biol Cell*. Oct; 2007 18(10):3776–3787. [PubMed: 17634286]
55. Lawless MW, Mankan AK, Gray SG, Norris S. Endoplasmic reticulum stress--a double edged sword for Z alpha-1 antitrypsin deficiency hepatotoxicity. *Int J Biochem Cell Biol*. 2008; 40(8):1403–1414. [PubMed: 18353704]
56. Carroll TP, Greene CM, O'Connor CA, Nolan AM, O'Neill SJ, McElvaney NG. Evidence for unfolded protein response activation in monocytes from individuals with alpha-1 antitrypsin deficiency. *J Immunol*. Apr 15; 2010 184(8):4538–4546. [PubMed: 20228200]
57. Greene CM, McElvaney NG. Z alpha-1 antitrypsin deficiency and the endoplasmic reticulum stress response. *World J Gastrointest Pharmacol Ther*. Oct 6; 2010 1(5):94–101. [PubMed: 21577302]
58. Smith SE, Granell S, Salcedo-Sicilia L, et al. Activating transcription factor 6 limits intracellular accumulation of mutant alpha(1)-antitrypsin Z and mitochondrial damage in hepatoma cells. *J Biol Chem*. Dec 2; 2011 286(48):41563–41577. [PubMed: 21976666]
59. Lawless MW, Mankan AK, White M, O'Dwyer MJ, Norris S. Expression of hereditary hemochromatosis C282Y HFE protein in HEK293 cells activates specific endoplasmic reticulum stress responses. *BMC Cell Biol*. 2007; 8:30. [PubMed: 17650303]
60. Pinto JP, Ramos P, de Almeida SF, et al. Protective role of calreticulin in HFE hemochromatosis. *Free Radic Biol Med*. Jan 1; 2008 44(1):99–108. [PubMed: 18045552]
61. Isom HC, McDevitt EI, Moon MS. Elevated hepatic iron: a confounding factor in chronic hepatitis C. *Biochimica et biophysica acta*. Jul; 2009 1790(7):650–662. [PubMed: 19393721]
62. Lou LX, Geng B, Chen Y, Yu F, Zhao J, Tang CS. Endoplasmic reticulum stress involved in heart and liver injury in iron-loaded rats. *Clin Exp Pharmacol Physiol*. Jul; 2009 36(7):612–618. [PubMed: 19594550]

63. Oliveira SJ, Pinto JP, Picarote G, et al. ER stress-inducible factor CHOP affects the expression of hepcidin by modulating C/EBP α activity. *PLoS One*. 2009; 4(8):e6618. [PubMed: 19672300]
64. Vecchi C, Montosi G, Zhang K, et al. ER stress controls iron metabolism through induction of hepcidin. *Science*. Aug 14; 2009 325(5942):877–880. [PubMed: 19679815]
65. Emadali A, Nguyen DT, Rochon C, Tzimas GN, Metrakos PP, Chevet E. Distinct endoplasmic reticulum stress responses are triggered during human liver transplantation. *J Pathol*. Sep; 2005 207(1):111–118. [PubMed: 15912576]
66. Dara L, Ji C, Kaplowitz N. The contribution of endoplasmic reticulum stress to liver diseases. *Hepatology* (Baltimore, Md). May; 2011 53(5):1752–1763.
67. Dai R, Chen R, Li H. Cross-talk between PI3K/Akt and MEK/ERK pathways mediates endoplasmic reticulum stress-induced cell cycle progression and cell death in human hepatocellular carcinoma cells. *Int J Oncol*. Jun; 2009 34(6):1749–1757. [PubMed: 19424594]
68. Tang J, Guo YS, Zhang Y, et al. CD147 induces UPR to inhibit apoptosis and chemosensitivity by increasing the transcription of Bip in hepatocellular carcinoma. *Cell Death Differ*. Nov; 2012 19(11):1779–1790. [PubMed: 22595757]
69. Xu M, Lu N, Sun Z, et al. Activation of the unfolded protein response contributed to the selective cytotoxicity of oroxylin A in human hepatocellular carcinoma HepG2 cells. *Toxicol Lett*. Jul 20; 2012 212(2):113–125. [PubMed: 22609744]
70. Honma Y, Harada M. Sorafenib enhances proteasome inhibitor-mediated cytotoxicity via inhibition of unfolded protein response and keratin phosphorylation. *Exp Cell Res*. May 31.2013
71. Yi P, Higa A, Taoji S, et al. Sorafenib-mediated targeting of the AAA(+) ATPase p97/VCP leads to disruption of the secretory pathway, endoplasmic reticulum stress, and hepatocellular cancer cell death. *Mol Cancer Ther*. Dec; 2012 11(12):2610–2620. [PubMed: 23041544]
72. Xu M, Lu N, Zhang H, et al. Wogonin induced cytotoxicity in human hepatocellular carcinoma cells by activation of unfolded protein response and inactivation of AKT. *Hepatol Res*. Dec 4.2012
73. Duan Q, Wang X, Gong W, et al. ER stress negatively modulates the expression of the miR-199a/214 cluster to regulates tumor survival and progression in human hepatocellular cancer. *PLoS One*. 2012; 7(2):e31518. [PubMed: 22359598]
74. Yang F, Zhang L, Wang F, et al. Modulation of the unfolded protein response is the core of microRNA-122-involved sensitivity to chemotherapy in hepatocellular carcinoma. *Neoplasia*. Jul; 2011 13(7):590–600. [PubMed: 21750653]
75. Chen R, Dai RY, Duan CY, et al. Unfolded protein response suppresses cisplatin-induced apoptosis via autophagy regulation in human hepatocellular carcinoma cells. *Folia Biol (Praha)*. 2011; 57(3):87–95. [PubMed: 21888831]
76. Fu S, Yang L, Li P, et al. Aberrant lipid metabolism disrupts calcium homeostasis causing liver endoplasmic reticulum stress in obesity. *Nature*. May 26; 473(7348):528–531. [PubMed: 21532591]
77. Lee AH, Scapa EF, Cohen DE, Glimcher LH. Regulation of hepatic lipogenesis by the transcription factor XBP1. *Science*. Jun 13; 2008 320(5882):1492–1496. [PubMed: 18556558]
78. Ota T, Gayet C, Ginsberg HN. Inhibition of apolipoprotein B100 secretion by lipid-induced hepatic endoplasmic reticulum stress in rodents. *J Clin Invest*. Jan; 2008 118(1):316–332. [PubMed: 18060040]
79. Rutkowski DT, Wu J, Back SH, et al. UPR pathways combine to prevent hepatic steatosis caused by ER stress-mediated suppression of transcriptional master regulators. *Dev Cell*. Dec; 2008 15(6): 829–840. [PubMed: 19081072]
80. Lee JS, Mendez R, Heng HH, Yang ZQ, Zhang K. Pharmacological ER stress promotes hepatic lipogenesis and lipid droplet formation. *Am J Transl Res*. 4(1):102–113. [PubMed: 22347525]
81. Liao W, Chan L. Tunicamycin induces ubiquitination and degradation of apolipoprotein B in HepG2 cells. *Biochem J*. Feb 1; 2001 353(Pt 3):493–501. [PubMed: 11171045]
82. Jo H, Choe SS, Shin KC, et al. Endoplasmic reticulum stress induces hepatic steatosis via increased expression of the hepatic very low-density lipoprotein receptor. *Hepatology*. Apr; 2012 57(4): 1366–1377. [PubMed: 23152128]

83. Lee JN, Ye J. Proteolytic activation of sterol regulatory element-binding protein induced by cellular stress through depletion of Insig-1. *J Biol Chem.* Oct 22; 2004 279(43):45257–45265. [PubMed: 15304479]
84. Ozcan U, Yilmaz E, Ozcan L, et al. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science.* Aug 25; 2006 313(5790):1137–1140. [PubMed: 16931765]
85. Xie Q, Khaoustov VI, Chung CC, et al. Effect of tauroursodeoxycholic acid on endoplasmic reticulum stress-induced caspase-12 activation. *Hepatology.* Sep; 2002 36(3):592–601. [PubMed: 12198651]
86. Vilatoba M, Eckstein C, Bilbao G, et al. Sodium 4-phenylbutyrate protects against liver ischemia reperfusion injury by inhibition of endoplasmic reticulum-stress mediated apoptosis. *Surgery.* Aug; 2005 138(2):342–351. [PubMed: 16153446]
87. Ozcan U, Cao Q, Yilmaz E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science.* Oct 15; 2004 306(5695):457–461. [PubMed: 15486293]
88. Nakatani Y, Kaneto H, Kawamori D, et al. Involvement of endoplasmic reticulum stress in insulin resistance and diabetes. *J Biol Chem.* Jan 7; 2005 280(1):847–851. [PubMed: 15509553]
89. Boden G, Duan X, Homko C, et al. Increase in endoplasmic reticulum stress-related proteins and genes in adipose tissue of obese, insulin-resistant individuals. *Diabetes.* Sep; 2008 57(9):2438–2444. [PubMed: 18567819]
90. Sharma NK, Das SK, Mondal AK, et al. Endoplasmic reticulum stress markers are associated with obesity in nondiabetic subjects. *J Clin Endocrinol Metab.* Nov; 2008 93(11):4532–4541. [PubMed: 18728164]
91. Feng B, Yao PM, Li Y, et al. The endoplasmic reticulum is the site of cholesterol-induced cytotoxicity in macrophages. *Nat Cell Biol.* Sep; 2003 5(9):781–792. [PubMed: 12907943]
92. Boden G, Song W, Duan X, et al. Infusion of glucose and lipids at physiological rates causes acute endoplasmic reticulum stress in rat liver. *Obesity (Silver Spring).* Jul; 19(7):1366–1373. [PubMed: 21475143]
93. Wei Y, Wang D, Topczewski F, Pagliassotti MJ. Saturated fatty acids induce endoplasmic reticulum stress and apoptosis independently of ceramide in liver cells. *Am J Physiol Endocrinol Metab.* Aug; 2006 291(2):E275–281. [PubMed: 16492686]
94. Cao J, Dai DL, Yao L, et al. Saturated fatty acid induction of endoplasmic reticulum stress and apoptosis in human liver cells via the PERK/ATF4/CHOP signaling pathway. *Mol Cell Biochem.* May; 364(1–2):115–129. [PubMed: 22246806]
95. Pineau L, Colas J, Dupont S, et al. Lipid-induced ER stress: synergistic effects of sterols and saturated fatty acids. *Traffic.* Jun; 2009 10(6):673–690. [PubMed: 19302420]
96. Listenberger LL, Han X, Lewis SE, et al. Triglyceride accumulation protects against fatty acid-induced lipotoxicity. *Proc Natl Acad Sci U S A.* Mar 18; 2003 100(6):3077–3082. [PubMed: 12629214]
97. Peng G, Li L, Liu Y, et al. Oleate blocks palmitate-induced abnormal lipid distribution, endoplasmic reticulum expansion and stress, and insulin resistance in skeletal muscle. *Endocrinology.* Jun; 152(6):2206–2218. [PubMed: 21505048]
98. Fu S, Watkins SM, Hotamisligil GS. The role of endoplasmic reticulum in hepatic lipid homeostasis and stress signaling. *Cell Metab.* May 2; 15(5):623–634. [PubMed: 22560215]
99. Kammoun HL, Chabanon H, Hainault I, et al. GRP78 expression inhibits insulin and ER stress-induced SREBP-1c activation and reduces hepatic steatosis in mice. *J Clin Invest.* May; 2009 119(5):1201–1215. [PubMed: 19363290]
100. So JS, Hur KY, Tarrio M, et al. Silencing of lipid metabolism genes through IRE1alpha-mediated mRNA decay lowers plasma lipids in mice. *Cell Metab.* Oct 3; 16(4):487–499. [PubMed: 23040070]
101. Zhang K, Wang S, Malhotra J, et al. The unfolded protein response transducer IRE1alpha prevents ER stress-induced hepatic steatosis. *EMBO J.* Apr 6; 30(7):1357–1375. [PubMed: 21407177]

102. Wang S, Chen Z, Lam V, et al. IRE1alpha-XBP1s induces PDI expression to increase MTP activity for hepatic VLDL assembly and lipid homeostasis. *Cell Metab.* Oct 3; 16(4):473–486. [PubMed: 23040069]
103. Deng Y, Wang ZV, Tao C, et al. The Xbp1s/GaE axis links ER stress to postprandial hepatic metabolism. *J Clin Invest.* Jan 2; 123(1):455–468. [PubMed: 23257357]
104. Oyadomari S, Harding HP, Zhang Y, Oyadomari M, Ron D. Dephosphorylation of translation initiation factor 2alpha enhances glucose tolerance and attenuates hepatosteatosis in mice. *Cell Metab.* Jun; 2008 7(6):520–532. [PubMed: 18522833]
105. Schroeder-Gloeckler JM, Rahman SM, Janssen RC, et al. CCAAT/enhancer-binding protein beta deletion reduces adiposity, hepatic steatosis, and diabetes in *Lepr(db/db)* mice. *J Biol Chem.* May 25; 2007 282(21):15717–15729. [PubMed: 17387171]
106. Millward CA, Heaney JD, Sinasac DS, et al. Mice with a deletion in the gene for CCAAT/enhancer-binding protein beta are protected against diet-induced obesity. *Diabetes.* Jan; 2007 56(1):161–167. [PubMed: 17192478]
107. Seo J, Fortuno ES 3rd, Suh JM, et al. Atf4 regulates obesity, glucose homeostasis, and energy expenditure. *Diabetes.* Nov; 2009 58(11):2565–2573. [PubMed: 19690063]
108. Chikka MR, McCabe DD, Tyra HM, Rutkowski DT. C/EBP homologous protein (CHOP) contributes to suppression of metabolic genes during endoplasmic reticulum stress in the liver. *J Biol Chem.* Feb 8; 288(6):4405–4415. [PubMed: 23281479]
109. Yamamoto K, Takahara K, Oyadomari S, et al. Induction of liver steatosis and lipid droplet formation in ATF6alpha-knockout mice burdened with pharmacological endoplasmic reticulum stress. *Mol Biol Cell.* Sep 1; 21(17):2975–2986. [PubMed: 20631254]
110. Zeng L, Lu M, Mori K, et al. ATF6 modulates SREBP2-mediated lipogenesis. *EMBO J.* Feb 25; 2004 23(4):950–958. [PubMed: 14765107]
111. Lindor KD, Kowdley KV, Heathcote EJ, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. *Hepatology.* Mar; 2004 39(3):770–778. [PubMed: 14999696]
112. Wu SD, Li L, Wang JY. Ursodeoxycholic acid for nonalcoholic steatohepatitis. *Eur J Gastroenterol Hepatol.* Nov; 24(11):1247–1253. [PubMed: 22864259]
113. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology.* Jun; 55(6):2005–2023. [PubMed: 22488764]
114. Werstuck GH, Lentz SR, Dayal S, et al. Homocysteine-induced endoplasmic reticulum stress causes dysregulation of the cholesterol and triglyceride biosynthetic pathways. *J Clin Invest.* May; 2001 107(10):1263–1273. [PubMed: 11375416]
115. Chen X, Sebastian BM, Tang H, et al. Taurine supplementation prevents ethanol-induced decrease in serum adiponectin and reduces hepatic steatosis in rats. *Hepatology (Baltimore, Md).* May; 2009 49(5):1554–1562.
116. Gentile CL, Nivala AM, Gonzales JC, et al. Experimental evidence for therapeutic potential of taurine in the treatment of nonalcoholic fatty liver disease. *Am J Physiol Regul Integr Comp Physiol.* Dec; 2011 301(6):R1710–1722. [PubMed: 21957160]
117. Ji C, Kaplowitz N. Hyperhomocysteinemia, endoplasmic reticulum stress, and alcoholic liver injury. *World journal of gastroenterology : WJG.* Jun 15; 2004 10(12):1699–1708. [PubMed: 15188490]
118. Kaplowitz N, Than TA, Shinohara M, Ji C. Endoplasmic reticulum stress and liver injury. *Seminars in liver disease.* Nov; 2007 27(4):367–377. [PubMed: 17979073]
119. Zhang XM, Wang XT, Cai H, Leung SW, Guggino SE. Characterization of endogenous betaine gamma-amino-n-butyric acid cotransporter glycoform and its hyperosmotic regulation in MDCK cells. *Pflügers Archiv : European journal of physiology.* Apr; 2007 454(1):143–153. [PubMed: 17186307]
120. Esfandiari F, You M, Villanueva JA, Wong DH, French SW, Halsted CH. S-adenosylmethionine attenuates hepatic lipid synthesis in micropigs fed ethanol with a folate-deficient diet. *Alcoholism, clinical and experimental research.* Jul; 2007 31(7):1231–1239.

121. Ou X, Yang H, Ramani K, et al. Inhibition of human betaine-homocysteine methyltransferase expression by S-adenosylmethionine and methylthioadenosine. *The Biochemical journal*. Jan 1; 2007 401(1):87–96. [PubMed: 16953798]
122. Akoglu B, Schrott M, Bolouri H, et al. The folic acid metabolite L-5-methyltetrahydrofolate effectively reduces total serum homocysteine level in orthotopic liver transplant recipients: a double-blind placebo-controlled study. *European journal of clinical nutrition*. Jun; 2008 62(6): 796–801. [PubMed: 17522618]
123. Hirsch S, Poniachick J, Avendano M, et al. Serum folate and homocysteine levels in obese females with non-alcoholic fatty liver. *Nutrition (Burbank, Los Angeles County, Calif)*. Feb; 2005 21(2):137–141.
124. Papandreou D, Rousso I, Malindretos P, Makedou A, Arvanitidou M. Effects of oral folate supplementation on serum total homocysteine and cholesterol levels in hyperhomocysteinemic children. *Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition*. Aug; 2010 25(4):390–393. [PubMed: 20702844]
125. Symons JD, Zaid UB, Athanassious CN, Mullick AE, Lentz SR, Rutledge JC. Influence of folate on arterial permeability and stiffness in the absence or presence of hyperhomocysteinemia. *Arteriosclerosis, thrombosis, and vascular biology*. Apr; 2006 26(4):814–818.
126. Woo CW, Prathapasinghe GA, Siow YL, OK. Hyperhomocysteinemia induces liver injury in rat: Protective effect of folic acid supplementation. *Biochimica et biophysica acta*. Jul; 2006 1762(7): 656–665. [PubMed: 16837172]
127. Sharma S, Mells JE, Fu PP, Saxena NK, Anania FA. GLP-1 analogs reduce hepatocyte steatosis and improve survival by enhancing the unfolded protein response and promoting macroautophagy. *PLoS One*. 2011; 6(9):e25269. [PubMed: 21957486]
128. Kudo T. Therapeutic strategies for Alzheimer disease based on endoplasmic reticulum stress. *Nihon shinkei seishin yakurigaku zasshi = Japanese journal of psychopharmacology*. Aug; 2010 30(4):163–168. [PubMed: 20857693]
129. Inokuchi Y, Nakajima Y, Shimazawa M, et al. Effect of an inducer of BiP, a molecular chaperone, on endoplasmic reticulum (ER) stress-induced retinal cell death. *Investigative ophthalmology & visual science*. Jan; 2009 50(1):334–344. [PubMed: 18757512]
130. Takano K, Tabata Y, Kitao Y, et al. Methoxyflavones protect cells against endoplasmic reticulum stress and neurotoxin. *American journal of physiology. Cell physiology*. Jan; 2007 292(1):C353–361. [PubMed: 16971492]
131. Gorbatyuk MS, Gorbatyuk OS. The Molecular Chaperone GRP78/BiP as a Therapeutic Target for Neurodegenerative Disorders: A Mini Review. *Journal of genetic syndrome & gene therapy*. Mar 11.2013 4(2)

Figure 1. Overview of the Unfolded Protein Response (UPR)

In the unstressed state, IRE1α, PERK, and ATF6α are bound by the ER chaperone Grp78. In response to ER stress, Grp78 dissociates from these receptors to bind to unfolded proteins. IRE1α is activated by dimerization and autophosphorylation. Activated IRE1α induces splicing of XBP1. Spliced (activated) XBP1s translocates to the nucleus where it functions as a potent transcription factor. Upon dissociation from Grp78, PERK forms a dimer leading to its activation by autophosphorylation. Activation of PERK promotes phosphorylation of eIF2α leading to a global attenuation of protein translation. Phosphorylated eIF2α increases the translation of ATF4. Dissociation of Grp78 from ATF6 results in the unmasking of two Golgi localization sequences within ATF6. Upon translocation to the Golgi apparatus, ATF6α is activated by proteolytic cleavage to a 50kDa transcription factor. Activated XBP1s, ATF4, and ATF6α all translocate to the nucleus where they transcriptionally activate numerous genes including ER chaperones, CHOP, and genes associated with ERAD.

Figure 2. Proposed mechanisms of ER stress-induced apoptosis

Activated IRE1 α recruits TNFR-associated receptor 2 (TRAF2) leading to activation of the c-Jun N-terminal kinase (JNK). Caspase-12 associates with activated IRE1 α , allowing its proteolytic cleavage to active caspase-12. Within the ER membrane, Bak and Bax associate with IRE1 α to potentiate its activity. Activated ATF4 increases transcription of CHOP, which functions as a transcriptional activator of numerous pro-apoptotic genes including death receptor 5 (DR5), Bim, and tribbles homolog 3 (TRB3).

Table 1

Liver Diseases involving the Unfolded Protein Response (UPR)

Liver Disease	References
Non-alcoholic Fatty Liver Disease	1, 84
Alcohol-Related Fatty Liver Disease	28–35
Hepatitis B	36–38
Hepatitis C	39–44
Cholestatic Liver Disease	45, 50, 51
Alpha-1 Antitrypsin Deficiency	52–58
Iron Overload	59–64
Ischemia-Reperfusion	46, 65, 66
Hepatocellular Carcinoma	67–75

Table 2

Potential Unfolded Protein Response (UPR) Therapeutic Targets for Fatty Liver Diseases

Potential Future Therapies	References
Tauroursodeoxycholic acid (TUDCA)	46, 49, 84
4-phenylbutyric acid (PBA)	46, 84
Betaine	30, 31, 114–116
S-adenosyl-L-methionine (SAME)	28, 30, 117, 118
Taurine	112, 113
Folic Acid	119–123
GLP-1 analogues	124
micro-RNAs	50, 69, 73, 74
Grp78/BiP regulators	125–128