

Chapter 2

ER Stress in Drug-Induced Liver Injury

Michael Hinton, Yunzhou Li, Eric Kwong, and Huiping Zhou

Abbreviations

3'UTR	3'-untranslated region
ABCB1	ATP-binding cassette sub-family B member 1
ABCC2	ATP-binding cassette sub-family C member 2
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AP	Alkaline phosphatase
ATF	Activating transcription factor
AIDS	Acquired human immunodeficiency syndrome
BiP/GRP78	Binding immunoglobulin protein/78 kDa glucose-regulated protein
CHOP	CCAAT enhancer-binding protein homologous protein
CYP3A	Cytochrome P450 3A4
CYP7A1	Cholesterol 7 alpha-hydroxylase
DILI	Drug-induced liver injury
eIF2 α	Eukaryotic initiation factor 2 alpha
ER	Endoplasmic reticulum
ERAD	ER-associated degradation
FDA	The Food and Drug Administration
HAART	Highly active anti-retroviral therapy
HIV-1	Human immunodeficiency virus-1
Insig	The insulin-induced gene
IRE1 α	Inositol requiring enzyme 1 α
LPS	Lipopolysaccharide

M. Hinton • Y. Li • E. Kwong • H. Zhou (✉)

Department of Microbiology and Immunology, Medical College of Virginia Campus,
Virginia Commonwealth University, Richmond, VA 23298, USA

McGuire VA Medical Center, Richmond, VA 23249, USA

e-mail: huiping.zhou@vcuhealth.org

© Springer International Publishing AG 2017

W.-X. Ding, X.-M. Yin (eds.), *Cellular Injury in Liver Diseases*, Cell Death
in Biology and Diseases, DOI 10.1007/978-3-319-53774-0_2

X.-M. Yin and Z. Dong (Series eds.), *Cell Death in Biology and Diseases*

MRP2	Multidrug resistance-associated protein 2
PERK	Protein kinase RNA-like endoplasmic reticulum kinase
S1P	Serine protease site-1 protease
S2P	Metalloprotease site-2 protease
SCAP	SREBP cleavage-activating protein
SREBP	Sterol regulatory element-binding proteins
TLR4	Toll-like receptor 4
UPR	Unfolded protein response
XBP1	X-box-binding protein 1
XBP1s	Spliced XBP1
XBP1u	Unspliced XBP1

2.1 Introduction

Drug-induced liver injury (DILI) is a serious public health concern and represents one of the leading causes of liver transplantation and the most frequent single cause for withdrawal of an approved drug from the market or termination of clinical trials of potential drug candidates in the past five decades (Devarbhavi 2012; Giordano et al. 2014; Lee et al. 2016). In the United States, more than 1000 drugs, toxins, and over-the-counter herbal medicines have been reported to cause liver injury (Rangnekar and Fontana 2011; Devarbhavi 2012; Giordano et al. 2014). The number of annual cases of acute liver failure is approximately 2000 and more than half of them are drug-induced (Rangnekar and Fontana 2011; Devarbhavi 2012; Giordano et al. 2014). In addition, drug-induced hepatitis accounts for 10% of all cases of acute hepatitis. The global data of DILI is currently unavailable due to the difficulty in discerning the true incidence of DILI. There is no simple objective test currently available for the diagnosis of DILI and patients are often on multiple medications and dietary supplements (Kim and Naisbitt 2016; Giordano et al. 2014; Devarbhavi 2012).

Most of the hepatic toxins predominantly cause hepatocellular injury (Kim and Naisbitt 2016). Although many drugs also cause cholestasis, this condition is generally reversible after drug discontinuation and rarely leads to liver failure or death. DILI is associated with a variety of risk factors such as race, age, sex, alcohol consumption, preexisting liver disease, genetic factors, virus infection, metabolic syndrome, etc. Multiple pathological mechanisms of DILI have been identified, including apoptosis of hepatocytes, disruption of the hepatic transporters, activation of the immune response, disruption of mitochondrial function, and injury of the bile duct, etc (Gu and Manautou 2012; Lee et al. 2016). Most recently, activation of ER stress has been identified as an important contributor to various liver diseases including DILI (Yao et al. 2016b; Lou et al. 2009; Kaplowitz et al. 2007; Ji and Kaplowitz 2004; Wu et al. 2016; Sharkey et al. 2016; Ashraf and Sheikh 2015; Zhang et al. 2014; Pagliassotti 2012; Kaplowitz and Ji 2006; Mahdi et al. 2016). In this chapter, the current understanding of ER stress and its role in DILI are reviewed with a primary focus on HIV protease inhibitor (PI)-induced hepatic injury.

2.2 ER Stress and the Unfolded Protein Response (UPR)

The ER is an important organelle that plays a critical role in maintaining intracellular homeostasis via regulating intracellular calcium levels, protein synthesis, protein folding and assembly, and lipid and cholesterol synthesis (Jung and Choi 2016). Although the ER has significant adaptive capacity to manage the metabolic demands during feeding and fasting, the duration is limited. It has less flexibility to manage chronic and other escalating challenges. The accumulation of misfolded or unfolded proteins in the ER under a variety of pathological conditions or exposure to certain pharmacological compounds leads to ER stress and activation of an intracellular stress signaling cascade termed the unfolded protein response (UPR) (Schonthal 2012; Dandekar et al. 2015).

The activation of the UPR is a protective mechanism in response to a harmful challenge. The canonical UPR signaling pathways have been well described in eukaryotic cells (Ron and Walter 2007; Todd et al. 2008; Hotamisligil 2010). Three ER-transmembrane proteins (PERK: PKR-like eukaryotic initiation factor 2 α kinase; IRE1 α : inositol requiring enzyme 1 α ; and ATF6: activating transcription factor-6) and one chaperone protein (BiP/GRP78: binding immunoglobulin protein/78 kDa glucose-regulated protein) have been identified as crucial regulators of the UPR. As shown in Fig. 2.1, under stress-free conditions, BiP/GRP78 is bound to the intraluminal domains (amino-terminals of IRE1 α and PERK and carboxyl-terminal of ATF6) of three UPR transducers to maintain them in an inactivated state (Bertolotti et al. 2000). When ER stress occurs due to accumulation of misfolded or unfolded proteins, BiP/GRP78 is dissociated from these UPR sensors, which results in oligomerization and auto-phosphorylation of PERK and IRE1 α . Activation of PERK results in the phosphorylation of eukaryotic initiation factor 2 alpha (eIF2 α) and attenuation of global mRNA translation. Activation of PERK also selectively increases the translation of certain mRNAs such as ATF4 (a member of the basic leucine-zipper family of transcription factors) and its downstream targets such as CCAAT enhancer-binding protein homologous protein (CHOP) (Fig. 2.1a). CHOP is a proapoptotic transcription factor that plays a critical role in ER stress-mediated apoptosis (Zhou and Liu 2014). Activated IRE1 α has intrinsic endoribonuclease activity, which processes the unspliced X-box-binding protein (XBP1u) mRNA by removing 26-nucleotides to produce the active transcription factor XBP1s. XBP1s is able to promote the expression of genes involved in restoring the ER protein folding capacity or degrading misfolded or unfolded proteins (Fig. 2.1b). Activation of the third UPR pathway requires translocation of ATF6 to the Golgi apparatus where its C-terminal region is cleaved by the serine protease site-1 protease (S1P) and the metalloprotease site-2 protease (S2P) to produce an active soluble transcription factor, ATF6N (Fig. 2.1c) (Hotamisligil 2010). Activation of the canonical UPR response mitigates ER stress by reducing protein synthesis, increasing production of chaperones, and facilitating protein degradation. Sustained ER stress as a result of accumulation of misfolded or unfolded proteins can also activate the ER-associated protein degradation (ERAD) (Schwartz and Ciechanover 2009). If the initial UPR

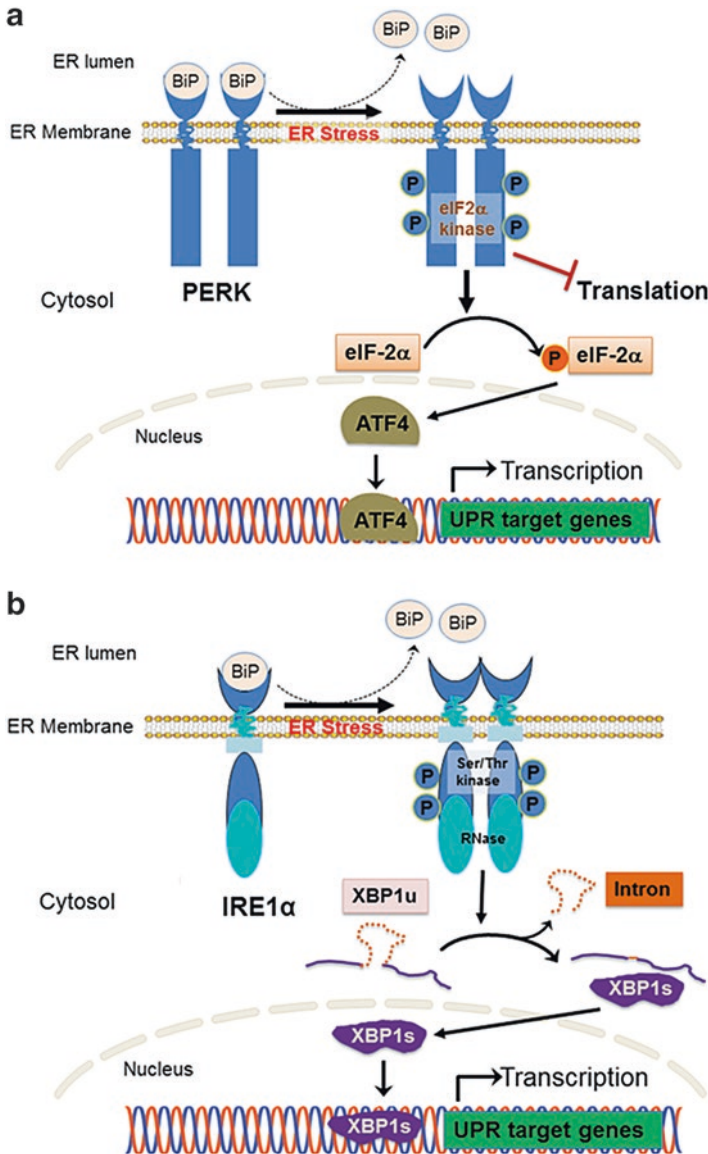


Fig. 2.1 The unfolded protein response (UPR). Three UPR sensors, protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring protein 1 α (IRE1 α) and activating transcription factor 6 (ATF6), and one master regulator Bip/GRP78 have been identified. Under non-stress condition, GRP78 binds to three UPR sensors and prevents their activation. Accumulation of misfolded or unfolded proteins in the ER lumen results in dissociation of GRP78 from the UPR sensors and subsequent activation of PERK, IRE1 α , and ATF6. **(a)** The activated PERK phosphorylates the eukaryotic initiation factor 2 α (eIF2 α), which attenuates the global protein translation and selectively activates ATF4, a key transcription factor regulating the transcription of genes involved in apoptosis, lipid and energy metabolism, autophagy, and stress response. **(b)** The activation of IRE1 α results in splicing of the transcription factor X box-binding 1 (XBP1u) and expression of an

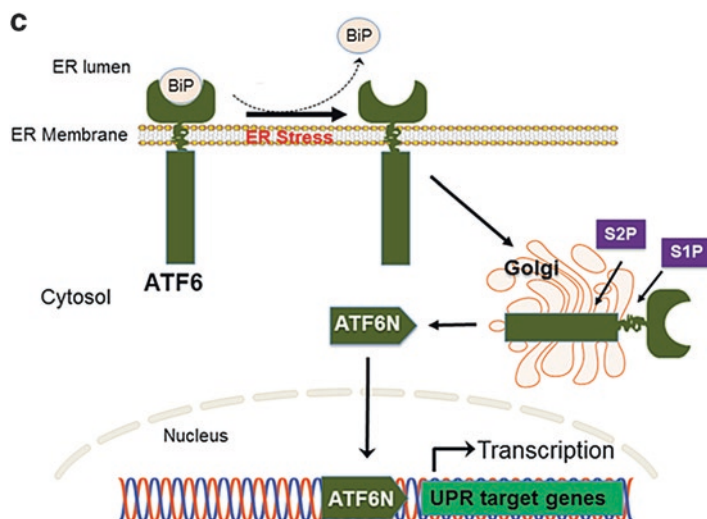


Fig. 2.1 (continued) active transcription factor, spliced XBP1 (XBP1s) by excising a 26-nucleotide intron. XBP1s is involved in regulation of ER-associated degradation (ERAD) and the entry of proteins into the ER and modulation of phospholipid synthesis to accommodate ER membrane expansion under ER stress. (c) ATF6 is a member of basic Leu zipper transcription factors. Under ER stress, ATF6 is translocated into Golgi and processed by site 1 protease (S1P) and S2P to generate active ATF6N. ATF6N controls the expression of key genes involved in ERAD and XBP-1. The UPR activation controls multiple physiological processes such as apoptosis, ERAD, protein folding, lipid synthesis, protein secretion, autophagy, etc

fails to resolve ER stress, further activation of the UPR will trigger death responses (Todd et al. 2008; Liu et al. 2016; Schonthal 2012; Jager et al. 2012).

Activation of ER stress by pharmacologic agents or pathophysiologic stimuli results in perturbation of normal cellular function that has been associated with the initiation and progression of numerous human diseases such as cardiovascular diseases, metabolic diseases, inflammatory diseases, immune diseases, neurodegenerative diseases, and various liver diseases including DILI (Chen et al. 2014; Chan et al. 2016; Malhi and Kaufman 2011; Rayavarapu et al. 2012; Back et al. 2012; Cao et al. 2016; Volchuk and Ron 2010; Cui et al. 2016; Cnop et al. 2012; Liu et al. 2016; Go et al. 2016).

2.3 Drug-Induced Liver Injury (DILI)

Most of the drugs that have adverse effects can affect many different organs such as the liver, heart, kidney, lung, skeletal muscle, or central nerve system (Hohenegger 2012; Miltenburg and Boogerd 2014; Marrer and Dieterle 2010; Begriche et al. 2011; Tocchetti et al. 2013; Fofelle and Fromenty 2016). DILI represents the most

common indication of adverse drug reaction for the drug withdrawal (Lee et al. 2016). Most of DILIs are unrecognized and underreported. The true incidence is difficult to estimate and varies significantly depending on the setting (Devarbhavi 2012). DILI can be idiosyncratic or intrinsic. Acetaminophen is the leading cause of DILI in the western countries and it is well known to be dose-related or intrinsic in nature. The intrinsic DILI results from drug-induced direct hepatotoxicity over the course of a few days or longer time period. Idiosyncratic DILI is a rare and unpredictable event and occurs in a minority of susceptible individuals with a prolonged latency (Ghabril et al. 2010; Devarbhavi 2012).

The most common drugs leading to liver injury in the United States are antibiotics, nonsteroidal anti-inflammatory drugs, central nervous system drugs, antiviral agents, immunomodulatory agents, and herbal/dietary supplements (Ghabril et al. 2010; Giordano et al. 2014; Kim and Naisbitt 2016). The risk factors associated with DILI are multifactorial, which includes age, sex, race, genetic factors, preexisting liver diseases, hepatitis infection, human immunodeficiency virus-1 (HIV-1) infection, diabetes mellitus, alcohol use, environmental toxins, etc. (Giordano et al. 2014; Kim and Naisbitt 2016). In the United States, DILI has been associated with more than 1000 medications and is the leading cause of acute liver failure in patients referred for liver transplantation (Kim and Naisbitt 2016; Giordano et al. 2014; Rangnekar and Fontana 2011; Devarbhavi 2012). Since the introduction of anti-HIV drugs in the late 1980s, hepatotoxicity has become a major clinical concern for anti-HIV therapy, especially for HIV protease inhibitors (HIV PIs). The incidence of DILI continues to increase with the increasing number of new drugs that have been introduced into clinical use over the past several decades. It has become a significant threat to the public health for an over-medicated society.

2.4 HIV/AIDS and HIV PIs

The acquired human immunodeficiency syndrome (AIDS) epidemic has rapidly expanded since the discovery of HIV as the cause of this disease in 1983. By the end of 2014, the estimated number of people living with HIV reached 36.9 million worldwide and the mortality rate for AIDS reached 1.2 million that year (Bhatti et al. 2016). As HIV biology and events critical to viral replication in the host cell are elucidated, a number of specific pharmacological agents targeting the key steps of HIV life cycle have been developed (Ghosh et al. 2016). The current available anti-HIV medicines include HIV reverse transcriptase inhibitors, HIV PIs, fusion inhibitors, and integrase inhibitors.

The highly active anti-retroviral therapy (HAART) is the most effective treatment currently available for HIV/AIDS, which includes two or three different classes of anti-HIV drugs. HIV PI is the core component of HAART, which specifically inhibits HIV protease activity and prevents the formation of mature HIV virions. The Food and Drug Administration (FDA) approved the first HIV PI, saquinavir, in 1995. Incorporation of saquinavir in HIV therapy greatly improved

patient outcomes by reducing viral loads, improving CD4 cell counts, and halting the progression to AIDS (Ghosh et al. 2016). Since then, a total of nine HIV PIs with several different dosages and combinations have been licensed by the FDA: amprenavir (Agenerase), atazanavir (Reyataz), darunavir (Prezista, TMC114), indinavir (Crixivan), fosamprenavir (Lexiva), lopinavir/ritonavir (Kaletra, Aluvia), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (fortovase, soft gel cap), and tipranavir (Aptivus). The incorporation of HIV PIs in HAART has successfully suppressed viral replication in HIV patients, significantly reduced morbidity and mortality, and changed HIV infection from an acute disease with a high morbidity and mortality to a manageable chronic disease (Poorolajal et al. 2016; Krentz et al. 2005). Unfortunately, current anti-HIV drugs are very toxic, especially HIV PIs. The benefits of HAART are compromised by serious side effects (Bhatti et al. 2016). Antiretroviral hepatotoxicity occurs in approximately 10% of patients and is higher in those with underlying liver disease (Lana et al. 2001; Nunez et al. 2001; Merwat and Vierling 2011). Although HIV-infected patients under HAART have a similar lifespan as non HIV-infected population, the quality of life of HIV-infected patients is compromised by the hepatic and metabolic toxicities of anti-HIV drugs, especially with HIV PIs (Guira et al. 2016; Hurwitz et al. 2004; Jain et al. 2001; Parakh et al. 2009). As of June 2015, the United Nations Program on HIV/AIDS (UNAIDS) approximates 15.8 million people living with HIV have access to anti-retroviral therapy. Hepatic toxicity and lipodystrophy specifically associated with HIV PIs have become a matter of particular concern in the clinical realm (McGovern 2004; Surgers and Lacombe 2013).

2.5 ER Stress and HIV PI-Induced Hepatotoxicity

Hepatotoxicity is characterized by an abnormal liver function test, which monitors the changes in key liver enzymes, such as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (AP) levels. Preclinical and clinical studies have shown elevated serum ALT and/or AST with HIV PI treatment, particularly with ritonavir administration (Sulkowski 2004; Brunet et al. 2012; Macias et al. 2012). HIV PI-induced liver injury results in the disruption of the normal cellular function of hepatocytes, which are the cells responsible for lipid homeostasis, bile acid synthesis, and gluconeogenesis. Long-term HAART treatment has been associated with metabolic side effects including dyslipidemia, insulin resistance, and cardiovascular complications including atherosclerosis (Sulkowski 2004; Dieterich 2003; Djedaini et al. 2009; Ioannou et al. 2015; Gleason et al. 2016; Parakh et al. 2009). Although the mechanism underlying HIV PI-induced hepatotoxicity remains to be fully identified, an increasing body of evidence suggests that multiple mechanisms may be involved and individual PIs may have different effects on hepatic liver injury (Wu et al. 2014). Studies from our group and others' suggest that activation of the ER stress could be a critical cellular event involved in HIV PI-induced hepatic toxicity and metabolic syndrome, in

addition to other key mechanisms such as inflammation, oxidative stress, and mitochondrial dysfunction (Bruning 2011; Taura et al. 2013; Zha et al. 2013a; Zhang et al. 2009; Zhou 2011; Zha and Zhou 2012; Fougelle and Fromenty 2016).

2.5.1 HIV PI-Induced Lipogenesis

The liver plays a central role in regulating nutrient absorption, cholesterol metabolism, lipogenesis, and gluconeogenesis (Bechmann et al. 2012; Lee et al. 2012). In addition, it is also important for hormone production, xenobiotic metabolism, and detoxification. Hepatic lipid homeostasis is maintained by numerous nuclear receptors and transcription factors (Zhou and Liu 2014). The sterol regulatory element-binding proteins (SREBPs) are a family of membrane-bound transcription factors responsible for regulating more than two dozen genes involved in the synthesis and uptake of cholesterol, fatty acids, triglycerides, and phospholipids and lipid metabolism (Horton et al. 2002; Fougelle et al. 2007). There are three isoforms of SREBPs including SREBP-1a, SREBP-1c, and SREBP-2. With alternative splicing both SREBP-1a and SREBP-1c are obtained from a single gene. SREBP-1a has the general effect of activating all SREBP-responsive genes, while SREBP-1c and SREBP-2 are specific for enhancing the transcription of genes required for fatty acid and cholesterol synthesis (Horton et al. 2002; Fougelle et al. 2007). The functionality of SREBPs depends on association with the SREBP cleavage-activating protein (SCAP) and the insulin-induced gene (Insig) complex. SREBPs are processed into active forms by the same proteases (S1P and S2P) that process ATF6 in the Golgi. ER stress-mediated activation of PERK and IRE1 α -XBP-1 signaling pathways results in the attenuation of protein translation and promotion of protein degradation, which are responsible for the depletion of insig-1 and subsequently the proteolytic activation of SREBPs leading to lipogenesis (Lee and Ye 2004; Kammoun et al. 2009b). Overexpression of GRP78 or insig-1 inhibits SREBP-1c activation and hepatic steatosis (Chen et al. 2011; Kammoun et al. 2008, 2009a; Zhang et al. 2012). The disruption of hepatic cholesterol, bile acid, and lipid homeostasis from an imbalance of biosynthesis and metabolism leads to hepatic lipid accumulation, inflammation, and eventually hepatic injury (Sanyal 2005, 2013, 2015; Puri et al. 2009).

Regulation of hepatic lipogenesis has been linked to ER stress and the activity of the UPR (Zhang and Wang 2016; Lee et al. 2012; Zhou and Liu 2014). Our previous studies have shown that individual HIV PIs had different effects on the activation of ER stress in hepatocytes and macrophages, which correlated to the incidence of dyslipidemia associated with different HIV PIs in the clinic (Zhou et al. 2005, 2006). Initial studies done by Williams, K et al. with indinavir in primary rodent hepatocytes indicated that indinavir specifically upregulated the expression and activation of SREBPs (Williams et al. 2004). The mRNA levels of cholesterol 7 α -hydroxylase (CYP7A1) were markedly decreased, while fatty acid synthase mRNA levels were up-regulated (Williams et al. 2004). The ability of HIV PI to

activate the UPR is linked to its effect on hepatic lipid accumulation and lipotoxicity (Zhou et al. 2007). Our previous studies also found that ritonavir had the most significant effect on the UPR activation, while amprenavir did not activate the UPR in primary hepatocytes (Zhou et al. 2006). This may explain why ritonavir induces hepatic lipid accumulation and cell apoptosis, but not amprenavir. In addition, ritonavir has the most adverse metabolic effects, including insulin resistance, lipodystrophy, and hyperlipidemia in HIV patients and currently used only as a pharmacoenhancer of other HIV PIs (Mateo et al. 2014; Pere et al. 2008; Putcharoen et al. 2015). HIV PIs are extensively metabolized by cytochrome P450 3A4 (CYP3A) in the liver. The plasma half-life is remarkably short when used alone (Putcharoen et al. 2015). Ritonavir is a strong inhibitor of CYP3A and in combination with other HIV PIs significantly increases their half-life. In addition, ritonavir also inhibits the drug transporters ABCB1 (ATP-binding cassette subfamily B member 1, also called P-glycoprotein) and ABCC2 (ATP-binding cassette subfamily C member 2; also called MRP2: Multidrug resistance-associated protein), which have been shown to pump out the HIV PIs from the intestinal cells and macrophages (Holmstock et al. 2012; Zha et al. 2013b).

Activation of the ER stress and extended upregulation of CHOP have been shown to be involved in various liver injuries, including DILI, lipotoxicity, and cholestasis (Pffaffenbach et al. 2010; Tamaki et al. 2008; Uzi et al. 2013; Willy et al. 2015). Our studies demonstrated that HIV PI-induced hepatic lipotoxicity is closely linked to the upregulation of CHOP in hepatocytes and in liver (Wang et al. 2013; Zhou et al. 2007). Lopinavir and ritonavir significantly induced lipogenesis, hepatic lipid accumulation, and apoptosis in wild-type mice, but not in CHOP knockout mice (Wang et al. 2013). These studies suggest that CHOP is an important molecular link to ER stress and hepatic lipotoxicity and that increased expression of CHOP represents a critical factor underlying events leading to HIV PI-induced hepatic injury (Wang et al. 2013).

2.5.2 HIV PI-Induced Inflammation

Inflammation and ER stress are important adaptive defense responses that help promote cell survival under various stress conditions (Dandekar et al. 2015). However, chronic inflammation and prolonged activation of the ER stress have been identified as important contributors to various liver injuries and metabolic diseases (Adolph et al. 2012; Ashraf and Sheikh 2015; Cao et al. 2016; Dandekar et al. 2015; Duwaerts and Maher 2014; Hasnain et al. 2012; Hotamisligil 2010). Our previous studies showed that HIV PIs induced inflammatory cytokines, TNF- α , and IL-6 in macrophages via ER stress/CHOP-mediated ERK1/2 activation, and as a result, increased the cytosolic translocation of RNA-binding protein HuR and subsequent binding to the 3'UTR (3'-untranslated region) of TNF- α and IL-6 mRNAs in macrophages (Chen et al. 2009). The activation of the innate immune response has recently been shown to play an important role in promoting DILI (Goto et al. 2015). Hepatic

macrophages play critical roles in maintaining homeostasis in the liver and in the pathogenesis of various hepatic injuries (Ju and Tacke 2016). However, the heterogeneity of macrophages in the liver is very complex. Macrophages derived from different origins can have distinct effects on hepatic metabolic homeostasis and liver injury. In addition, macrophages can be polarized to different subpopulations, including classically activated and inflammatory M1 and alternatively activated/anti-inflammatory M2, in response to various external signals and insults (Ju and Tacke 2016; Harvey et al. 2015; Zhou et al. 2014).

The Kupffer cell (hepatic resident macrophages)-mediated inflammation is of critical importance to hepatic injuries induced by drugs, toxins, and lipids via secreting various pro- and anti-inflammatory mediators (Goto et al. 2015; Arguello et al. 2015; Ju and Tacke 2016; Li and Diehl 2003; Meli et al. 2014; Ni et al. 2016; Wan et al. 2014; Wenfeng et al. 2014). Recently, it has been reported that ER stress-mediated signaling pathways are involved in regulation of macrophage polarization (Xiu et al. 2015). CHOP and ER stress are implicated in the induction and differentiation of M2 macrophages (Yao et al. 2016a). Moreover, the gut-derived endotoxin lipopolysaccharide (LPS) activates the toll-like receptor 4 (TLR4) and triggers hepatocyte apoptosis (Wenfeng et al. 2014). Our previous studies also reported that HIV PIs induce ER stress in intestinal epithelial cells. HIV PI-mediated upregulation of CHOP in intestine is responsible for dysfunction of intestinal barrier function, microbial translocation, and induction of systemic inflammation (Wu et al. 2010). ER stress and inflammation have also been linked to inhibition of E-cadherin and zonula occludens-1 expression, the key components of intestinal epithelia, and result in a defective epithelial barrier (Fan et al. 2014). Gut-derived microbial products and inflammatory mediators significantly promote the progression of various liver diseases including DILI, fatty liver diseases, and alcoholic liver disease (Bieghs and Trautwein 2014; Chen and Schnabl 2014; Duwaerts and Maher 2014; Schnabl and Brenner 2014).

2.6 Summary

The liver is the largest internal organ of the human body and plays a critical role in metabolizing nutrients, drugs, and environmental toxicants. It is the most frequent site of drug-induced toxicity. Although severe DILI is relatively rare, drug-induced hepatic injury is the most common indication for drug withdrawal and the most frequent cause of acute liver failure. The clinical impact of DILI is substantial because of the number of drugs used and the number of patients treated. The diagnosis and treatment of DILI remain significant challenges due to the complexities of disease pathogenesis and a lack of understanding of the underlying cellular/molecular mechanisms. During the last decade, numerous studies have shown that the activation of ER stress represents a key step in the development of DILI even at therapeutic doses, especially for HIV PIs. HIV-1 infection continues to be a serious global health problem. As the key component of HAART, a life-long treatment for HIV infection, reduction of HIV PI-induced hepatic injury remains a difficult task. Identification of the ER stress as a critical player in HIV PI-induced inflammation,

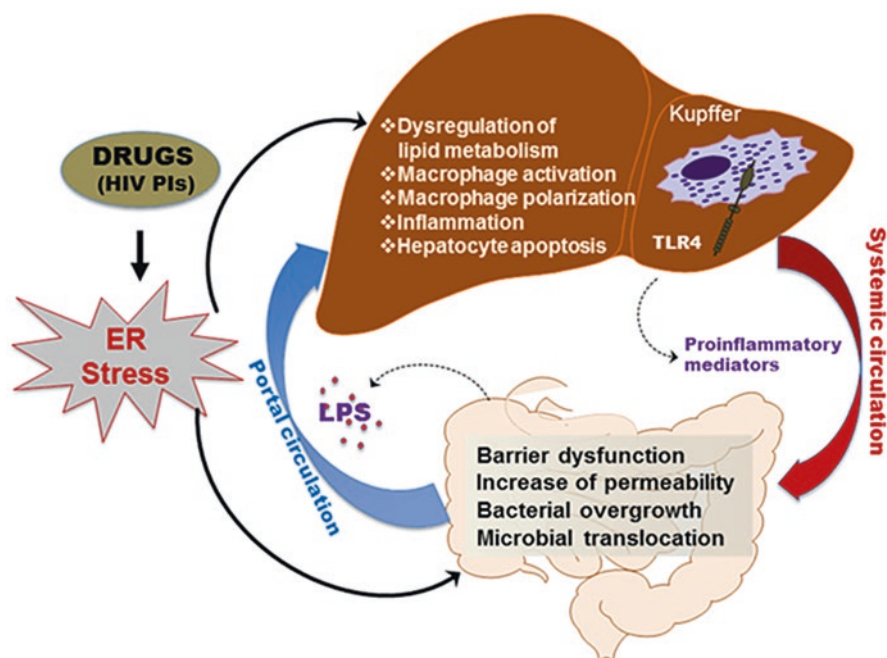


Fig. 2.2 Mechanisms of HIV PI-mediated liver injury. Activation of ER stress in hepatic cells results in dysfunction of hepatocytes, dysregulation of lipid metabolism, activation of Kupffer cells, and production of proinflammatory mediators. Liver-derived inflammatory mediators reach intestine via system circulation. Drug-induced activation of the ER stress in intestinal epithelial cells and systemic inflammatory mediators disrupt intestinal barrier integrity and increase of bacterial overgrowth. Increase of gut permeability results in high circulating endotoxin that reaches the liver via portal circulation. Endotoxin (lipopolysaccharide or LPS) is recognized by the Toll-like receptor (TLR)-4 complex on resident macrophages or Kupffer cells in the liver, leading to production of proinflammatory cytokines and resulting in injury to hepatocytes

disruption of intestinal barrier integrity, and dysregulation of hepatic lipid metabolism opened new direction for the development of preventive and therapeutic strategies for HIV PI-induced liver injury, as well as for other DILIs (Fig. 2.2). In addition, elucidating of the underlying mechanism of DILI not only has high scientific values but also has significant economic impact on improving new drug development by developing new reliable screening systems to eliminate the candidates with hepatotoxicity at an early stage.

Taken together, the rapid progress in understanding ER stress in DILI and other liver diseases gives rise to the expectation that ER stress may be used as a biomarker and therapeutic target for DILI as well as other liver diseases.

Acknowledgment This study was supported by National Natural Science Foundation of China Grants (81070245 and 81270489 to HZ); National Institutes of Health Grants (R21AI068432; R01AT004148; 1R01DK104893; DK-057543), VA Merit Awards (I01BX001390); NIAAA 1F31AA024713; VCU Massey Cancer Pilot grant (A35362 to HZ). We would like to thank Elaine Studer Kennedy for English editing and proof-reading.

References

- Adolph TE, Niederreiter L, Blumberg RS, Kaser A (2012) Endoplasmic reticulum stress and inflammation. *Dig Dis* 30(4):341–346. doi:[10.1159/000338121](https://doi.org/10.1159/000338121)
- Arguello G, Balboa E, Arrese M, Zanlungo S (2015) Recent insights on the role of cholesterol in non-alcoholic fatty liver disease. *Biochim Biophys Acta* 1852(9):1765–1778. doi:[10.1016/j.bbadis.2015.05.015](https://doi.org/10.1016/j.bbadis.2015.05.015)
- Ashraf NU, Sheikh TA (2015) Endoplasmic reticulum stress and oxidative stress in the pathogenesis of non-alcoholic fatty liver disease. *Free Radic Res* 49(12):1405–1418. doi:[10.3109/10715762.2015.1078461](https://doi.org/10.3109/10715762.2015.1078461)
- Back SH, Kang SW, Han J, Chung HT (2012) Endoplasmic reticulum stress in the beta-cell pathogenesis of type 2 diabetes. *Exp Diabetes Res* 2012:618396. doi:[10.1155/2012/618396](https://doi.org/10.1155/2012/618396)
- Bechmann LP, Hannivoort RA, Gerken G, Hotamisligil GS, Trauner M, Canbay A (2012) The interaction of hepatic lipid and glucose metabolism in liver diseases. *J Hepatol* 56(4):952–964. doi:[10.1016/j.jhep.2011.08.025](https://doi.org/10.1016/j.jhep.2011.08.025)
- Begriffe K, Massart J, Robin MA, Borgne-Sanchez A, Fromenty B (2011) Drug-induced toxicity on mitochondria and lipid metabolism: mechanistic diversity and deleterious consequences for the liver. *J Hepatol* 54(4):773–794. doi:[10.1016/j.jhep.2010.11.006](https://doi.org/10.1016/j.jhep.2010.11.006)
- Bertolotti A, Zhang Y, Hendershot LM, Harding HP, Ron D (2000) Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. *Nat Cell Biol* 2(6):326–332. doi:[10.1038/35014014](https://doi.org/10.1038/35014014)
- Bhatti AB, Usman M, Kandi V (2016) Current scenario of HIV/AIDS, treatment options, and major challenges with compliance to antiretroviral therapy. *Cureus* 8(3):e515. doi:[10.7759/cureus.515](https://doi.org/10.7759/cureus.515)
- Bieghs V, Trautwein C (2014) Innate immune signaling and gut-liver interactions in non-alcoholic fatty liver disease. *Hepatobiliary Surg Nutr* 3(6):377–385. doi:[10.3978/j.issn.2304-3881.2014.12.04](https://doi.org/10.3978/j.issn.2304-3881.2014.12.04)
- Brunet C, Reliquet V, Jovelin T, Venisse N, Winer N, Bui E et al (2012) Effectiveness and safety of saquinavir/ritonavir in HIV-infected pregnant women: INEMA cohort. *Med Mal Infect* 42(9):421–428. doi:[10.1016/j.medmal.2012.07.010](https://doi.org/10.1016/j.medmal.2012.07.010)
- Bruning A (2011) Analysis of nelfinavir-induced endoplasmic reticulum stress. *Methods Enzymol* 491:127–142. doi:[10.1016/b978-0-12-385928-0.00008-0](https://doi.org/10.1016/b978-0-12-385928-0.00008-0)
- Cao SS, Luo KL, Shi L (2016) Endoplasmic reticulum stress interacts with inflammation in human diseases. *J Cell Physiol* 231(2):288–294. doi:[10.1002/jcp.25098](https://doi.org/10.1002/jcp.25098)
- Chan P, Stolz J, Kohl S, Chiang WC, Lin JH (2016) Endoplasmic reticulum stress in human photoreceptor diseases. *Brain Res* 1648(Pt B):538–541. doi:[10.1016/j.brainres.2016.04.021](https://doi.org/10.1016/j.brainres.2016.04.021)
- Chen P, Schnabl B (2014) Host-microbiome interactions in alcoholic liver disease. *Gut Liver* 8(3):237–241. doi:[10.5009/gnl.2014.8.3.237](https://doi.org/10.5009/gnl.2014.8.3.237)
- Chen L, Jarujaron S, Wu X, Sun L, Zha W, Liang G et al (2009) HIV protease inhibitor lopinavir-induced TNF-alpha and IL-6 expression is coupled to the unfolded protein response and ERK signaling pathways in macrophages. *Biochem Pharmacol* 78(1):70–77. doi:[10.1016/j.bcp.2009.03.022](https://doi.org/10.1016/j.bcp.2009.03.022)
- Chen K, Jin P, He HH, Xie YH, Xie XY, Mo ZH (2011) Overexpression of Insig-1 protects beta cell against glucolipotoxicity via SREBP-1c. *J Biomed Sci* 18:57. doi:[10.1186/1423-0127-18-57](https://doi.org/10.1186/1423-0127-18-57)
- Chen S, Melchior WB Jr, Guo L (2014) Endoplasmic reticulum stress in drug- and environmental toxicant-induced liver toxicity. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 32(1):83–104. doi:[10.1080/10590501.2014.881648](https://doi.org/10.1080/10590501.2014.881648)
- Cnop M, Foulfelle F, Velloso LA (2012) Endoplasmic reticulum stress, obesity and diabetes. *Trends Mol Med* 18(1):59–68. doi:[10.1016/j.molmed.2011.07.010](https://doi.org/10.1016/j.molmed.2011.07.010)
- Cui Y, Zhao D, Barrow PA, Zhou X (2016) The endoplasmic reticulum stress response: a link with tuberculosis? *Tuberculosis (Edinb)* 97:52–56. doi:[10.1016/j.tube.2015.12.009](https://doi.org/10.1016/j.tube.2015.12.009)
- Dandekar A, Mendez R, Zhang K (2015) Cross talk between ER stress, oxidative stress, and inflammation in health and disease. *Methods Mol Biol* 1292:205–214. doi:[10.1007/978-1-4939-2522-3_15](https://doi.org/10.1007/978-1-4939-2522-3_15)

- Devarbhavi H (2012) An update on drug-induced liver injury. *J Clin Exp Hepatol* 2(3):247–259. doi:[10.1016/j.jceh.2012.05.002](https://doi.org/10.1016/j.jceh.2012.05.002)
- Dieterich D (2003) Managing antiretroviral-associated liver disease. *J Acquir Immune Defic Syndr* 34(Suppl 1):S34–S39
- Djedaini M, Peraldi P, Drici MD, Darini C, Saint-Marc P, Dani C et al (2009) Lopinavir co-induces insulin resistance and ER stress in human adipocytes. *Biochem Biophys Res Commun* 386(1):96–100. doi:[10.1016/j.bbrc.2009.05.148](https://doi.org/10.1016/j.bbrc.2009.05.148)
- Duwaerts CC, Maher JJ (2014) Mechanisms of liver injury in non-alcoholic steatohepatitis. *Curr Hepatol Rep* 13(2):119–129. doi:[10.1007/s11901-014-0224-8](https://doi.org/10.1007/s11901-014-0224-8)
- Fan L, Hu L, Yang B, Fang X, Gao Z, Li W et al (2014) Erlotinib promotes endoplasmic reticulum stress-mediated injury in the intestinal epithelium. *Toxicol Appl Pharmacol* 278(1):45–52. doi:[10.1016/j.taap.2014.04.015](https://doi.org/10.1016/j.taap.2014.04.015)
- Foufelle F, Fromenty B (2016) Role of endoplasmic reticulum stress in drug-induced toxicity. *Pharmacol Res Perspect* 4(1):e00211. doi:[10.1002/prp.2.211](https://doi.org/10.1002/prp.2.211)
- Foufelle F, Hainault I, Kammoun H, Chabanon H, Ferre P (2007) SREBP-1c and the transcriptional control of lipogenesis. *Int J Obes (Lond)* 31:S3–S3
- Ghabril M, Chalasani N, Bjornsson E (2010) Drug-induced liver injury: a clinical update. *Curr Opin Gastroenterol* 26(3):222–226. doi:[10.1097/MOG.0b013e3283383c7c](https://doi.org/10.1097/MOG.0b013e3283383c7c)
- Ghosh AK, Osswald HL, Prato G (2016) Recent progress in the development of HIV-1 protease inhibitors for the treatment of HIV/AIDS. *J Med Chem* 59(11):5172–5208. doi:[10.1021/acs.jmedchem.5b01697](https://doi.org/10.1021/acs.jmedchem.5b01697)
- Giordano C, Rivas J, Zervos X (2014) An update on treatment of drug-induced liver injury. *J Clin Transl Hepatol* 2(2):74–79. doi:[10.14218/JCTH.2014.00005](https://doi.org/10.14218/JCTH.2014.00005)
- Gleason RL Jr, Caulk AW, Seifu D, Rosebush JC, Shapiro AM, Schwartz MH et al (2016) Efavirenz and ritonavir-boosted lopinavir use exhibited elevated markers of atherosclerosis across age groups in people living with HIV in Ethiopia. *J Biomech* 49(13):2584–2592. doi:[10.1016/j.jbiomech.2016.05.018](https://doi.org/10.1016/j.jbiomech.2016.05.018)
- Go BS, Kim J, Yang JH, Choe ES (2016) Psychostimulant-induced endoplasmic reticulum stress and neurodegeneration. *Mol Neurobiol*. doi:[10.1007/s12035-016-9969-0](https://doi.org/10.1007/s12035-016-9969-0)
- Goto S, Deguchi J, Nishio N, Nomura N, Funabashi H (2015) Hepatotoxins induce cytokine imbalance in response to innate immune system. *J Toxicol Sci* 40(3):389–404. doi:[10.2131/jts.40.389](https://doi.org/10.2131/jts.40.389)
- Gu X, Manautou JE (2012) Molecular mechanisms underlying chemical liver injury. *Expert Rev Mol Med* 14:e4. doi:[10.1017/s1462399411002110](https://doi.org/10.1017/s1462399411002110)
- Guira O, Tieno H, Diender AE, Sagna Y, Diallo I, Yameogo B et al (2016) Features of metabolic syndrome and its associated factors during highly active antiretroviral therapy in Ouagadougou (Burkina Faso). *J Int Assoc Provid AIDS Care* 15(2):159–163. doi:[10.1177/2325957415601503](https://doi.org/10.1177/2325957415601503)
- Harvey LD, Yin Y, Attarwala IY, Begum G, Deng J, Yan HQ et al (2015) Administration of DHA reduces endoplasmic reticulum stress-associated inflammation and alters microglial or macrophage activation in traumatic brain injury. *ASN Neuro* 7(6). doi:[10.1177/1759091415618969](https://doi.org/10.1177/1759091415618969)
- Hasnain SZ, Lourie R, Das I, Chen AC, McGuckin MA (2012) The interplay between endoplasmic reticulum stress and inflammation. *Immunol Cell Biol* 90(3):260–270. doi:[10.1038/icb.2011.112](https://doi.org/10.1038/icb.2011.112)
- Hohenegger M (2012) Drug induced rhabdomyolysis. *Curr Opin Pharmacol* 12(3):335–339. doi:[10.1016/j.coph.2012.04.002](https://doi.org/10.1016/j.coph.2012.04.002)
- Holmstock N, Annaert P, Augustijns P (2012) Boosting of HIV protease inhibitors by ritonavir in the intestine: the relative role of cytochrome P450 and P-glycoprotein inhibition based on Caco-2 monolayers versus in situ intestinal perfusion in mice. *Drug Metab Dispos* 40(8):1473–1477. doi:[10.1124/dmd.112.044677](https://doi.org/10.1124/dmd.112.044677)
- Horton JD, Goldstein JL, Brown MS (2002) SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest* 109(9):1125–1131. doi:[10.1172/JCI15593](https://doi.org/10.1172/JCI15593)
- Hotamisligil GS (2010) Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 140(6):900–917. doi:[10.1016/j.cell.2010.02.034](https://doi.org/10.1016/j.cell.2010.02.034)

- Hurwitz BE, Klimas NG, Llabre MM, Maher KJ, Skyler JS, Bilsker MS et al (2004) HIV, metabolic syndrome X, inflammation, oxidative stress, and coronary heart disease risk : role of protease inhibitor exposure. *Cardiovasc Toxicol* 4(3):303–316
- Ioannou GN, Bryson CL, Weiss NS, Boyko EJ (2015) Associations between lipodystrophy or antiretroviral medications and cirrhosis in patients with HIV infection or HIV/HCV coinfection. *Eur J Gastroenterol Hepatol* 27(5):577–584. doi:[10.1097/meg.0000000000000290](https://doi.org/10.1097/meg.0000000000000290)
- Jager R, Bertrand MJ, Gorman AM, Vandenabeele P, Samali A (2012) The unfolded protein response at the crossroads of cellular life and death during endoplasmic reticulum stress. *Biol Cell* 104(5):259–270. doi:[10.1111/boc.201100055](https://doi.org/10.1111/boc.201100055)
- Jain RG, Furfine ES, Pedneault L, White AJ, Lenhard JM (2001) Metabolic complications associated with antiretroviral therapy. *Antiviral Res* 51(3):151–177
- Ji C, Kaplowitz N (2004) Hyperhomocysteinemia, endoplasmic reticulum stress, and alcoholic liver injury. *World J Gastroenterol* 10(12):1699–1708
- Ju C, Tacke F (2016) Hepatic macrophages in homeostasis and liver diseases: from pathogenesis to novel therapeutic strategies. *Cell Mol Immunol* 13(3):316–327. doi:[10.1038/cmi.2015.104](https://doi.org/10.1038/cmi.2015.104)
- Jung TW, Choi KM (2016) Pharmacological modulators of endoplasmic reticulum stress in metabolic diseases. *Int J Mol Sci* 17(2). doi:[10.3390/ijms17020192](https://doi.org/10.3390/ijms17020192)
- Kammoun H, Chabanon H, Hainault I, Ferre P, Foufelle F (2008) Endoplasmic reticulum stress prevention improves hepatic steatosis of ob/ob mice through an inhibition of SREBP-1c proteolytic cleavage. *Diabetologia* 51:S315–S316
- Kammoun HL, Chabanon H, Hainault I, Luquet S, Magnan C, Koike T et al (2009a) GRP78 expression inhibits insulin and ER stress-induced SREBP-1c activation and reduces hepatic steatosis in mice. *J Clin Invest* 119(5):1201–1215. doi:[10.1172/JCI37007](https://doi.org/10.1172/JCI37007)
- Kammoun HL, Hainault I, Ferre P, Foufelle F (2009b) Nutritional related liver disease: targeting the endoplasmic reticulum stress. *Curr Opin Clin Nutr Metab Care* 12(6):575–582. doi:[10.1097/MCO.0b013e32833189db](https://doi.org/10.1097/MCO.0b013e32833189db)
- Kaplowitz N, Ji C (2006) Unfolding new mechanisms of alcoholic liver disease in the endoplasmic reticulum. *J Gastroenterol Hepatol* 21(Suppl 3):S7–S9. doi:[10.1111/j.1440-1746.2006.04581.x](https://doi.org/10.1111/j.1440-1746.2006.04581.x)
- Kaplowitz N, Than TA, Shinohara M, Ji C (2007) Endoplasmic reticulum stress and liver injury. *Semin Liver Dis* 27(4):367–377. doi:[10.1055/s-2007-991513](https://doi.org/10.1055/s-2007-991513)
- Kim SH, Naisbitt DJ (2016) Update on advances in research on idiosyncratic drug-induced liver injury. *Allergy Asthma Immunol Res* 8(1):3–11. doi:[10.4168/aa.2016.8.1.3](https://doi.org/10.4168/aa.2016.8.1.3)
- Krentz HB, Kliwer G, Gill MJ (2005) Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. *HIV Med* 6(2):99–106. doi:[10.1111/j.1468-1293.2005.00271.x](https://doi.org/10.1111/j.1468-1293.2005.00271.x)
- Lana R, Nunez M, Mendoza JL, Soriano V (2001) Rate and risk factors of liver toxicity in patients receiving antiretroviral therapy. *Med Clin (Barc)* 117(16):607–610
- Lee JN, Ye J (2004) Proteolytic activation of sterol regulatory element-binding protein induced by cellular stress through depletion of Insig-1. *J Biol Chem* 279(43):45257–45265. doi:[10.1074/jbc.M408235200](https://doi.org/10.1074/jbc.M408235200)
- Lee JS, Mendez R, Heng HH, Yang ZQ, Zhang K (2012) Pharmacological ER stress promotes hepatic lipogenesis and lipid droplet formation. *Am J Transl Res* 4(1):102–113
- Lee SJ, Lee YJ, Park KK (2016) The pathogenesis of drug-induced liver injury. *Expert Rev Gastroenterol Hepatol*:1–11. doi:[10.1080/17474124.2016.1196133](https://doi.org/10.1080/17474124.2016.1196133)
- Li Z, Diehl AM (2003) Innate immunity in the liver. *Curr Opin Gastroenterol* 19(6):565–571
- Liu MQ, Chen Z, Chen LX (2016) Endoplasmic reticulum stress: a novel mechanism and therapeutic target for cardiovascular diseases. *Acta Pharmacol Sin* 37(4):425–443. doi:[10.1038/aps.2015.145](https://doi.org/10.1038/aps.2015.145)
- Lou LX, Geng B, Chen Y, Yu F, Zhao J, Tang CS (2009) Endoplasmic reticulum stress involved in heart and liver injury in iron-loaded rats. *Clin Exp Pharmacol Physiol* 36(7):612–618. doi:[10.1111/j.1440-1681.2008.05114.x](https://doi.org/10.1111/j.1440-1681.2008.05114.x)
- Macias J, Neukam K, Mallolas J, Lopez-Cortes LF, Carton JA, Domingo P et al (2012) Liver toxicity of initial antiretroviral drug regimens including two nucleoside analogs plus one non-nucleoside analog or one ritonavir-boosted protease inhibitor in HIV/HCV-coinfected patients. *HIV Clin Trials* 13(2):61–69. doi:[10.1310/hct1302-61](https://doi.org/10.1310/hct1302-61)

- Mahdi AA, Rizvi SH, Parveen A (2016) Role of endoplasmic reticulum stress and unfolded protein responses in health and diseases. *Indian J Clin Biochem* 31(2):127–137. doi:[10.1007/s12291-015-0502-4](https://doi.org/10.1007/s12291-015-0502-4)
- Malhi H, Kaufman RJ (2011) Endoplasmic reticulum stress in liver disease. *J Hepatol* 54(4):795–809. doi:[10.1016/j.jhep.2010.11.005](https://doi.org/10.1016/j.jhep.2010.11.005)
- Marrer E, Dieterle F (2010) Impact of biomarker development on drug safety assessment. *Toxicol Appl Pharmacol* 243(2):167–179. doi:[10.1016/j.taap.2009.12.015](https://doi.org/10.1016/j.taap.2009.12.015)
- Mateo MG, Gutierrez Mdel M, Vidal F, Domingo P (2014) An update on the pharmacological strategies in the treatment of HIV-1-associated adipose redistribution syndromes. *Expert Opin Pharmacother* 15(12):1749–1760. doi:[10.1517/14656566.2014.928694](https://doi.org/10.1517/14656566.2014.928694)
- McGovern B (2004) Hepatic safety and HAART. *J Int Assoc Physicians AIDS Care (Chic)* 3(Suppl 2):S24–S40
- Meli R, Mattace Raso G, Calignano A (2014) Role of innate immune response in non-alcoholic fatty liver disease: metabolic complications and therapeutic tools. *Front Immunol* 5:177. doi:[10.3389/fimmu.2014.00177](https://doi.org/10.3389/fimmu.2014.00177)
- Merwat SN, Vierling JM (2011) HIV infection and the liver: the importance of HCV-HIV coinfection and drug-induced liver injury. *Clin Liver Dis* 15(1):131–152. doi:[10.1016/j.cld.2010.09.012](https://doi.org/10.1016/j.cld.2010.09.012)
- Miltenburg NC, Boogerd W (2014) Chemotherapy-induced neuropathy: a comprehensive survey. *Cancer Treat Rev* 40(7):872–882. doi:[10.1016/j.ctrv.2014.04.004](https://doi.org/10.1016/j.ctrv.2014.04.004)
- Ni Y, Zhuge F, Nagashimada M, Ota T (2016) Novel action of carotenoids on non-alcoholic fatty liver disease: macrophage polarization and liver homeostasis. *Nutrients* 8(7). doi:[10.3390/nu8070391](https://doi.org/10.3390/nu8070391)
- Nunez M, Lana R, Mendoza JL, Martin-Carbonero L, Soriano V (2001) Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 27(5):426–431
- Pagliassotti MJ (2012) Endoplasmic reticulum stress in nonalcoholic fatty liver disease. *Annu Rev Nutr* 32:17–33. doi:[10.1146/annurev-nutr-071811-150644](https://doi.org/10.1146/annurev-nutr-071811-150644)
- Parakh A, Dubey AP, Kumar A, Maheshwari A (2009) Lipodystrophy and metabolic complications of highly active antiretroviral therapy. *Indian J Pediatr* 76(10):1017–1021. doi:[10.1007/s12098-009-0216-9](https://doi.org/10.1007/s12098-009-0216-9)
- Pere D, Ignacio SL, Ramon T, Fernando L, Alberto T, Pompeyo V et al (2008) Dyslipidemia and cardiovascular disease risk factor management in HIV-1-infected subjects treated with HAART in the Spanish VACH cohort. *Open AIDS J* 2:26–38. doi:[10.2174/1874613600802010026](https://doi.org/10.2174/1874613600802010026)
- Pfaffenbach KT, Gentile CL, Nivala AM, Wang D, Wei Y, Pagliassotti MJ (2010) Linking endoplasmic reticulum stress to cell death in hepatocytes: roles of C/EBP homologous protein and chemical chaperones in palmitate-mediated cell death. *Am J Physiol Endocrinol Metab* 298(5):E1027–E1035. doi:[10.1152/ajpendo.00642.2009](https://doi.org/10.1152/ajpendo.00642.2009)
- Poorolajal J, Hooshmand E, Mahjub H, Esmailnasab N, Jenabi E (2016) Survival rate of AIDS disease and mortality in HIV-infected patients: a meta-analysis. *Public Health*. doi:[10.1016/j.puhe.2016.05.004](https://doi.org/10.1016/j.puhe.2016.05.004)
- Puri P, Wiest MM, Cheung O, Mirshahi F, Sargeant C, Min HK et al (2009) The plasma lipidomic signature of nonalcoholic steatohepatitis. *Hepatology* 50(6):1827–1838. doi:[10.1002/hep.23229](https://doi.org/10.1002/hep.23229)
- Putcharoen O, Do T, Avihingsanon A, Ruxrungtham K (2015) Rationale and clinical utility of the darunavir-cobicistat combination in the treatment of HIV/AIDS. *Drug Des Devel Ther* 9:5763–5769. doi:[10.2147/dddt.s63989](https://doi.org/10.2147/dddt.s63989)
- Rangnekar AS, Fontana RJ (2011) An update on drug induced liver injury. *Minerva Gastroenterol Dietol* 57(2):213–229
- Rayavarapu S, Coley W, Nagaraju K (2012) Endoplasmic reticulum stress in skeletal muscle homeostasis and disease. *Curr Rheumatol Rep* 14(3):238–243. doi:[10.1007/s11926-012-0247-5](https://doi.org/10.1007/s11926-012-0247-5)
- Ron D, Walter P (2007) Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Rev Mol Cell Biol* 8(7):519–529. doi:[10.1038/nrm2199](https://doi.org/10.1038/nrm2199)
- Sanyal AJ (2005) Mechanisms of disease: pathogenesis of nonalcoholic fatty liver disease. *Nat Clin Pract Gastroenterol Hepatol* 2(1):46–53. doi:[10.1038/ncpgasthep0084](https://doi.org/10.1038/ncpgasthep0084)

- Sanyal AJ (2013) An integrated view of liver injury and disease progression in nonalcoholic steatohepatitis. *Hepato Int* 7(Suppl 2):800–805. doi:[10.1007/s12072-013-9479-3](https://doi.org/10.1007/s12072-013-9479-3)
- Sanyal AJ (2015) Novel therapeutic targets for steatohepatitis. *Clin Res Hepatol Gastroenterol* 39(Suppl 1):S46–S50. doi:[10.1016/j.clinre.2015.05.012](https://doi.org/10.1016/j.clinre.2015.05.012)
- Schnabl B, Brenner DA (2014) Interactions between the intestinal microbiome and liver diseases. *Gastroenterology* 146(6):1513–1524. doi:[10.1053/j.gastro.2014.01.020](https://doi.org/10.1053/j.gastro.2014.01.020)
- Schonthal AH (2012) Endoplasmic reticulum stress: its role in disease and novel prospects for therapy. *Scientifica (Cairo)* 2012:857516. doi:[10.6064/2012/857516](https://doi.org/10.6064/2012/857516)
- Schwartz AL, Ciechanover A (2009) Targeting proteins for destruction by the ubiquitin system: implications for human pathobiology. *Annu Rev Pharmacol Toxicol* 49:73–96. doi:[10.1146/annurev.pharmtox.051208.165340](https://doi.org/10.1146/annurev.pharmtox.051208.165340)
- Sharkey LM, Davies SE, Kaser A, Woodward JM (2016) Endoplasmic reticulum stress is implicated in intestinal failure-associated liver disease. *JPEN J Parenter Enteral Nutr* 40(3):431–436. doi:[10.1177/0148607115571014](https://doi.org/10.1177/0148607115571014)
- Sulkowski MS (2004) Drug-induced liver injury associated with antiretroviral therapy that includes HIV-1 protease inhibitors. *Clin Infect Dis* 38(Suppl 2):S90–S97. doi:[10.1086/381444](https://doi.org/10.1086/381444)
- Surgers L, Lacombe K (2013) Hepatotoxicity of new antiretrovirals: a systematic review. *Clin Res Hepatol Gastroenterol* 37(2):126–133. doi:[10.1016/j.clinre.2013.02.008](https://doi.org/10.1016/j.clinre.2013.02.008)
- Tamaki N, Hatano E, Taura K, Tada M, Kodama Y, Nitta T et al (2008) CHOP deficiency attenuates cholestasis-induced liver fibrosis by reduction of hepatocyte injury. *Am J Physiol Gastrointest Liver Physiol* 294(2):G498–G505. doi:[10.1152/ajpgi.00482.2007](https://doi.org/10.1152/ajpgi.00482.2007)
- Taura M, Kariya R, Kudo E, Goto H, Iwawaki T, Amano M et al (2013) Comparative analysis of ER stress response into HIV protease inhibitors: lopinavir but not darunavir induces potent ER stress response via ROS/JNK pathway. *Free Radic Biol Med* 65:778–788. doi:[10.1016/j.freeradbiomed.2013.08.161](https://doi.org/10.1016/j.freeradbiomed.2013.08.161)
- Tocchetti CG, Gallucci G, Coppola C, Piscopo G, Cipresso C, Maurea C et al (2013) The emerging issue of cardiac dysfunction induced by antineoplastic angiogenesis inhibitors. *Eur J Heart Fail* 15(5):482–489. doi:[10.1093/eurjhf/hft008](https://doi.org/10.1093/eurjhf/hft008)
- Todd DJ, Lee AH, Glimcher LH (2008) The endoplasmic reticulum stress response in immunity and autoimmunity. *Nat Rev Immunol* 8(9):663–674. doi:[10.1038/nri2359](https://doi.org/10.1038/nri2359)
- Uzi D, Barda L, Scaiewicz V, Mills M, Mueller T, Gonzalez-Rodriguez A et al (2013) CHOP is a critical regulator of acetaminophen-induced hepatotoxicity. *J Hepatol* 59(3):495–503. doi:[10.1016/j.jhep.2013.04.024](https://doi.org/10.1016/j.jhep.2013.04.024)
- Volchuk A, Ron D (2010) The endoplasmic reticulum stress response in the pancreatic beta-cell. *Diabetes Obes Metab* 12(Suppl 2):48–57. doi:[10.1111/j.1463-1326.2010.01271.x](https://doi.org/10.1111/j.1463-1326.2010.01271.x)
- Wan J, Benkdane M, Alons E, Lotersztajn S, Pavoine C (2014) M2 kupffer cells promote hepatocyte senescence: an IL-6-dependent protective mechanism against alcoholic liver disease. *Am J Pathol* 184(6):1763–1772. doi:[10.1016/j.ajpath.2014.02.014](https://doi.org/10.1016/j.ajpath.2014.02.014)
- Wang Y, Zhang L, Wu X, Gurley EC, Kennedy E, Hylemon PB et al (2013) The role of CCAAT enhancer-binding protein homologous protein in human immunodeficiency virus protease-inhibitor-induced hepatic lipotoxicity in mice. *Hepatology* 57(3):1005–1016. doi:[10.1002/hep.26107](https://doi.org/10.1002/hep.26107)
- Wenfeng Z, Yakun W, Di M, Jianping G, Chuanxin W, Chun H (2014) Kupffer cells: increasingly significant role in nonalcoholic fatty liver disease. *Ann Hepatol* 13(5):489–495
- Williams K, Rao YP, Natarajan R, Pandak WM, Hylemon PB (2004) Indinavir alters sterol and fatty acid homeostatic mechanisms in primary rat hepatocytes by increasing levels of activated sterol regulatory element-binding proteins and decreasing cholesterol 7 α -hydroxylase mRNA levels. *Biochem Pharmacol* 67(2):255–267
- Willy JA, Young SK, Stevens JL, Masuoka HC, Wek RC (2015) CHOP links endoplasmic reticulum stress to NF-kappaB activation in the pathogenesis of nonalcoholic steatohepatitis. *Mol Biol Cell* 26(12):2190–2204. doi:[10.1091/mbc.E15-01-0036](https://doi.org/10.1091/mbc.E15-01-0036)
- Wu X, Sun L, Zha W, Studer E, Gurley E, Chen L et al (2010) HIV protease inhibitors induce endoplasmic reticulum stress and disrupt barrier integrity in intestinal epithelial cells. *Gastroenterology* 138(1):197–209. doi:[10.1053/j.gastro.2009.08.054](https://doi.org/10.1053/j.gastro.2009.08.054)

- Wu X, Li Y, Peng K, Zhou H (2014) HIV protease inhibitors in gut barrier dysfunction and liver injury. *Curr Opin Pharmacol* 19:61–66. doi:[10.1016/j.coph.2014.07.008](https://doi.org/10.1016/j.coph.2014.07.008)
- Wu FL, Liu WY, Van Poucke S, Braddock M, Jin WM, Xiao J et al (2016) Targeting endoplasmic reticulum stress in liver disease. *Expert Rev Gastroenterol Hepatol*:1–12. doi:[10.1080/17474124.2016.1179575](https://doi.org/10.1080/17474124.2016.1179575)
- Xiu F, Catapano M, Diao L, Stanojic M, Jeschke MG (2015) Prolonged endoplasmic reticulum-stressed hepatocytes drive an alternative macrophage polarization. *Shock* 44(1):44–51. doi:[10.1097/shk.0000000000000373](https://doi.org/10.1097/shk.0000000000000373)
- Yao Y, Wang Y, Zhang Z, He L, Zhu J, Zhang M et al (2016a) Chop deficiency protects mice against Bleomycin-induced pulmonary fibrosis by attenuating M2 macrophage production. *Mol Ther* 24(5):915–925. doi:[10.1038/mt.2016.36](https://doi.org/10.1038/mt.2016.36)
- Yao X, Li Y, Cheng X, Li H (2016b) ER stress contributes to alpha-naphthyl isothiocyanate-induced liver injury with cholestasis in mice. *Pathol Res Pract* 212(6):560–567. doi:[10.1016/j.prp.2016.05.001](https://doi.org/10.1016/j.prp.2016.05.001)
- Zha BS, Zhou H (2012) ER stress and lipid metabolism in adipocytes. *Biochem Res Int* 2012:312943. doi:[10.1155/2012/312943](https://doi.org/10.1155/2012/312943)
- Zha BS, Wan X, Zhang X, Zha W, Zhou J, Wabitsch M et al (2013a) HIV protease inhibitors disrupt lipid metabolism by activating endoplasmic reticulum stress and inhibiting autophagy activity in adipocytes. *PLoS One* 8(3):e59514. doi:[10.1371/journal.pone.0059514](https://doi.org/10.1371/journal.pone.0059514)
- Zha W, Wang G, Xu W, Liu X, Wang Y, Zha BS et al (2013b) Inhibition of P-glycoprotein by HIV protease inhibitors increases intracellular accumulation of berberine in murine and human macrophages. *PLoS One* 8(1):e54349. doi:[10.1371/journal.pone.0054349](https://doi.org/10.1371/journal.pone.0054349)
- Zhang L, Wang HH (2016) The essential functions of endoplasmic reticulum chaperones in hepatic lipid metabolism. *Dig Liver Dis*. doi:[10.1016/j.dld.2016.03.016](https://doi.org/10.1016/j.dld.2016.03.016)
- Zhang S, Carper MJ, Lei X, Cade WT, Yarasheski KE, Ramanadham S (2009) Protease inhibitors used in the treatment of HIV+ induce beta-cell apoptosis via the mitochondrial pathway and compromise insulin secretion. *Am J Physiol Endocrinol Metab* 296(4):E925–E935. doi:[10.1152/ajpendo.90445.2008](https://doi.org/10.1152/ajpendo.90445.2008)
- Zhang C, Chen X, Zhu RM, Zhang Y, Yu T, Wang H et al (2012) Endoplasmic reticulum stress is involved in hepatic SREBP-1c activation and lipid accumulation in fructose-fed mice. *Toxicol Lett* 212(3):229–240. doi:[10.1016/j.toxlet.2012.06.002](https://doi.org/10.1016/j.toxlet.2012.06.002)
- Zhang XQ, Xu CF, Yu CH, Chen WX, Li YM (2014) Role of endoplasmic reticulum stress in the pathogenesis of nonalcoholic fatty liver disease. *World J Gastroenterol* 20(7):1768–1776. doi:[10.3748/wjg.v20.i7.1768](https://doi.org/10.3748/wjg.v20.i7.1768)
- Zhou H (2011) HIV protease inhibitors induce endoplasmic reticulum stress and disrupt barrier integrity in intestinal epithelial cells. *Methods Enzymol* 490:107–119. doi:[10.1016/b978-0-12-385114-7.00006-4](https://doi.org/10.1016/b978-0-12-385114-7.00006-4)
- Zhou H, Liu R (2014) ER stress and hepatic lipid metabolism. *Front Genet* 5:112. doi:[10.3389/fgene.2014.00112](https://doi.org/10.3389/fgene.2014.00112)
- Zhou H, Pandak WM Jr, Lyall V, Natarajan R, Hylemon PB (2005) HIV protease inhibitors activate the unfolded protein response in macrophages: implication for atherosclerosis and cardiovascular disease. *Mol Pharmacol* 68(3):690–700. doi:[10.1124/mol.105.012898](https://doi.org/10.1124/mol.105.012898)
- Zhou H, Gurley EC, Jarujaron S, Ding H, Fang Y, Xu Z et al (2006) HIV protease inhibitors activate the unfolded protein response and disrupt lipid metabolism in primary hepatocytes. *Am J Physiol Gastrointest Liver Physiol* 291(6):G1071–G1080. doi:[10.1152/ajpgi.00182.2006](https://doi.org/10.1152/ajpgi.00182.2006)
- Zhou H, Jarujaron S, Gurley EC, Chen L, Ding H, Studer E et al (2007) HIV protease inhibitors increase TNF-alpha and IL-6 expression in macrophages: involvement of the RNA-binding protein HuR. *Atherosclerosis* 195(1):e134–e143. doi:[10.1016/j.atherosclerosis.2007.04.008](https://doi.org/10.1016/j.atherosclerosis.2007.04.008)
- Zhou D, Huang C, Lin Z, Zhan S, Kong L, Fang C et al (2014) Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways. *Cell Signal* 26(2):192–197. doi:[10.1016/j.cellsig.2013.11.004](https://doi.org/10.1016/j.cellsig.2013.11.004)

Cellular Injury in Liver Diseases

Ding, W.-X.; Yin, X.-M. (Eds.)

2017, XIII, 263 p. 26 illus., 22 illus. in color., Hardcover

ISBN: 978-3-319-53773-3