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Cellular Signaling Pathways in Alcoholic Liver Disease

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1. Introduction

The pathogenesis of acute and chronic alcohol consumption is complex with diverse consequences in different tissues. Alcohol abuse is associated with a continuum of liver abnormalities ranging from steatosis or fat deposition, steatohepatitis or fat plus inflammation to cirrhosis and hepatocellular carcinoma. The progression of alcohol-induced liver damage involves both parenchymal and non-parenchymal cells of the liver. The signaling pathways affected by direct or indirect alcohol exposure range from oxidative stress mechanisms, metabolism related effects, inflammation, and apoptosis. Understanding the interactions of inter- and intra-cellular signaling pathways in the liver during alcohol exposure will aid in identification of new integrative approaches as it relates to alcoholic liver disease and provide potential new directions to develop therapeutic target intervention. The goal of this chapter is to review signaling pathways related to oxidative stress and inflammatory responses modulated by alcohol in parenchymal and non-parenchymal cells of the liver important to ALD. Here, we will first review liver cell types involved in alcohol-induced oxidative stress and inflammation resulting in hepatic injury and then discuss the signaling pathways identified in ALD.

2. Cell types involved in ALD

Research done, so far, on the effects of cellular stress pathways and immune cell activation during ALD indicates involvement of different liver cell types. Liver cells such as hepatocytes, Kupffer cells, endothelial cells, etc., are directly or indirectly affected by alcohol. Alcohol-induced oxidative stress in the liver microenvironment affects not only the resident liver cells but also circulating immune cells such as dendritic cells, neutrophils, T cells and bone-marrow derived stem cells that migrate to the liver, contributing to inflammatory responses and thus propagating alcoholic liver injury.

2.1 Hepatocytes

Hepatocytes make up 70-80% of the total mass of the liver and are involved in protein synthesis, protein storage and transformation of carbohydrates, synthesis of cholesterol, bile salts and phospholipids, and detoxification, modification and excretion of exogenous and

endogenous substances. Chronic alcohol consumption has long been associated with progressive liver disease towards the development of hepatic cirrhosis and subsequent increased risk for developing hepatocellular carcinomas. Many of the deleterious effects of alcohol can be attributed to its metabolism primarily occurring in hepatocytes (Lu & Cederbaum, 2008).

Acute and chronic alcohol exposure increases the production of reactive oxygen species (ROS), lowers cellular antioxidant levels, and enhances oxidative stress in the liver (Cederbaum et al., 2009). Ethanol-induced oxidative stress plays a major role in the mechanisms by which ethanol sensitizes to liver injury (Cederbaum et al., 2009). In isolated hepatocytes, this damaging effect of chronic ethanol is evident in that a greater sensitivity to proapoptotic challenges is observed, more specifically, to the cytotoxic actions of tumor necrosis factor α (TNF α) (Hoek & Pastorino, 2004). The presence of alcohol results in an oxidative environment and TNF α mediated hepatocyte death (Pastorino & Hoek, 2000). Ethanol administration also facilitates apoptosis by increasing the amount of Fas protein expression on hepatocytes (McVicker et al., 2006). Besides ROS, reactive nitrogen species (RNS) generated in response to inducible nitric oxide synthase (iNOS) activation in hepatocytes during chronic alcohol exposure also contributes to liver injury (McKim et al., 2003). iNOS knock-out mice were protected from ALD (McKim et al., 2003). Ethanol promotes oxidative stress, not only by increased formation of ROS but also depletion of anti-oxidative defenses in hepatocytes. For instance, depletion of glutathione from mitochondria leads to increased accumulation of ROS (Fernandez-Checa et al., 1997).

The induction of mitochondrial dysfunction is also linked to the metabolism of alcohol by cytochrome P4502E1 (CYP2E1) and increased oxidative stress (Cederbaum et al., 2009). Primary hepatocytes and rat hepatoma cells when treated with ethanol led to an increase in ROS/RNS and loss of mitochondrial function due to damaged mitochondrial DNA and ribosomes and subsequent inhibition of mitochondrial protein synthesis (Mantena et al., 2007). These studies suggest that alcohol induced oxidative stress pathways in hepatocytes set the stage for proinflammatory cytokine induced cell death and alcoholic liver injury.

2.2 Kupffer cells or liver resident macrophages

Kupffer cells, non-parenchymal cells of the liver, are specialized macrophages located in the liver and their activation plays a central role in early ethanol-induced liver injury. In the universally accepted “two-hit” model of alcoholic liver injury, recognition of gut-derived endotoxin by the Kupffer cells is the first step leading to induction of pro-inflammatory responses (Thurman et al., 1999). Engagement of endotoxin with the Toll-like receptor 4 (TLR4) and CD14 receptor on Kupffer cells activates the down-stream kinases, interleukin-1 receptor associated kinase (IRAK) and I-kappa-B kinase (IKK) and transcription factor nuclear factor- κ B (NF κ B) and induction of pro-inflammatory cytokines such as TNF α (Takeda & Akira, 2005). Kupffer cells produce reactive oxygen species (ROS) in response to chronic alcohol exposure as well as endotoxin (Kono et al., 2000). Alcohol-induced sensitization to lipopolysaccharide (LPS) has been attributed to ROS production (Thakur et al., 2006a). Previous studies from Nagy and colleagues (Nagy, 2003) show that chronic ethanol feeding increases the sensitivity of Kupffer cells to LPS, leading to increased TNF α expression. This sensitization can be reversed by treatment of primary cultures of alcohol-exposed Kupffer cells with adiponectin, an anti-inflammatory adipokine (Thakur et al.,

2006b). Globular adiponectin prevents LPS-stimulated TNF α expression in Kupffer cells through the activation of the interleukin (IL)-10/STAT3/HO-1 (heme oxygenase-1) pathway (Mandal et al., 2010). In vivo pretreatment with diphenyliodonium (DPI), an inhibitor of NADPH oxidase, in alcohol-fed rats, normalized ROS production, decreased LPS-induced extracellular signal-regulated kinase (ERK1/2) phosphorylation and inhibited TNF α production in Kupffer cells (Kono et al., 2000; Thakur et al., 2006b). The importance of toll-like receptors (TLR) particularly TLR4 expressed on Kupffer cells plays a major part in ALD. Based on studies so far, it is perceivable that increased sensitization of Kupffer cells to endotoxin/LPS resulting in enhanced inflammatory responses contributes to alcoholic liver disease.

2.3 Dendritic cells

Dendritic cells (DCs) are central mediators of immune regulation, yet little is known about liver DCs. Myeloid DCs (mDCs), one of the most potent antigen-presenting cells (APC) in vivo, represent a terminally differentiated stage of monocytes (Palucka et al., 1998). Myeloid dendritic cells (mDCs) capture antigens in the periphery and then migrate to the lymphoid organs to initiate immunity (Steinman & Inaba, 1999). Alcohol-treated mDCs show reduced IL-12, increased IL-10 production, and a decrease in expression of the costimulatory molecules CD80 and CD86 (Mandrekar et al., 2004). Cytokine profiles of mDCs isolated from ethanol-fed mice indicate enhanced interleukin (IL)-1 β and IL-10 and decreased TNF α , IL-12, interferon gamma (IFN γ), and IL-6 secretion (Aloman et al., 2007; Eken et al., 2011). Altered DC function is one of the major changes induced by long-term alcohol consumption, which subsequently impairs the cellular immune response. Chronic alcoholism in the absence of liver disease in patients is associated with an increased secretion of inflammatory cytokines by peripheral blood dendritic cells (Laso et al., 2007). Hepatic DCs from chronic alcohol-fed mice are less affected than splenic DCs, which exhibit impaired functional maturation following CpG stimulation (Lau et al., 2006). Thus, alcohol exerts a negative influence on innate and adaptive immunity leading to severe immunosuppression (Lau et al., 2009). Inflammatory responses mediated by increased TNF α in liver fibrosis were associated with altered dendritic cell function (Connolly et al., 2009). Future studies are needed to identify signaling mechanisms contributing to DC dysfunction during chronic alcohol exposure.

2.4 Neutrophils

Neutrophils, the most abundant phagocyte constitutes 50% to 60% of the total circulating white blood cells and can secrete products that stimulate monocytes and macrophages. Neutrophil secretions increase phagocytosis and the formation of reactive oxygen compounds involved in intracellular killing (Soehnlein et al., 2008). In the alcoholic liver, damage by neutrophils can contribute to injury in response to the release of endotoxins produced by bacteria (Ricevuti, 1997). Neutrophil dysfunction in alcoholic hepatitis is associated with endotoxemia, increased expression of TLR2, 4, and 9 as well as energy depletion leading to increased incidence of infection (Stadlbauer et al., 2009). Augmentation of TLR 2, 4, and 9 did not improve phagocytic function of neutrophils, indicating that TLR overexpression may be the result and not the cause of neutrophil activation (Stadlbauer et al., 2009). Neutrophil contact with hepatocytes mediates oxidative killing of hepatocytes by

initiation of oxidative-stress mediated respiratory burst and neutrophil degranulation leading to hepatocellular necrosis (Ramaiah & Jaeschke, 2007). Induction of osteopontin (OPN), an important mediator of inflammation regulated by oxidative stress pathways (Maziere et al., 2010) is the likely contributing factor for higher neutrophil recruitment to the liver in female rats during alcoholic steatohepatitis (Banerjee et al., 2006). Hepatic neutrophil infiltration can be largely inhibited *in vivo* by a neutralizing OPN antibody (Banerjee et al., 2006).

2.5 T cells

In alcoholic liver disease, the number of lymphocytes in the liver increases and the type and distribution of these infiltrating cells determines the nature of inflammation. Steatohepatitis is associated with a T helper (Th)1 cytokine response characterized by IFN γ and TNF α elevation, that reflects involvement of T lymphocytes, in particular CD4⁺ T cells (Tiegs, 2007). In the liver, IL-17 secreting cells contribute to inflammatory infiltrates in alcoholic cirrhosis, and alcoholic hepatitis foci show many Th17 cells, including T lymphocytes and neutrophils (Lemmers et al., 2009). Chronic alcohol consumption significantly induces peripheral T cell lymphopenia in female C57BL/6 mice, up-regulates expression of CD43 on CD8⁺ T cells, increases the percentage of interferon- γ -producing T cells; decreases the percentage of CD8⁺CD28⁺ T cells; and down-regulates the expression of CD28 on CD4⁺ T cells (Gurung et al., 2009; Laso et al., 2000). *In vivo* bromodeoxyuridine incorporation in the same experiments demonstrated that chronic alcohol consumption increases proliferation of memory T cells, and accelerates peripheral T cell turnover (Zhang & Meadows, 2005). Patients with advanced ALD show a high prevalence of circulating IgG and T-lymphocytes towards epitopes derived from protein modification by hydroxyethyl free radicals (HER) and end-products of lipid peroxidation. In both chronic alcohol-fed rats and heavy drinkers the elevation of IgG against lipid peroxidation-derived antigens is associated with an increased production of pro-inflammatory cytokines/chemokines and severity of histological signs of liver inflammation (Albano & Vidali, 2009).

2.6 Natural killer (NK) and natural killer T (NKT) cells

Although a variety of cell populations infiltrate the liver during inflammation, it is generally assumed that CD8⁺ T lymphocytes promote while natural killer (NK) cells inhibit liver fibrosis (Park et al., 2009). NK cells inhibited liver fibrosis by directly killing activated hepatic stellate cells and production of gamma-interferon (IFN γ) (Jeong & Gao, 2008). In a chronic alcohol exposure model, poly I:C activation of NK cell cytotoxicity against hepatic stellate cells was attenuated in ethanol-fed mice compared with pair-fed mice, which was due to reduced natural killer group 2 member D (NKG2D), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and IFN γ expression on NK cells from ethanol-fed mice (Jeong et al., 2008).

On the other hand, natural killer T cells (NKT) are an important subset of T lymphocytes and are unique in their ability to produce both Th1 and Th2 associated cytokines, thus being capable of steering the immune system into either inflammation or tolerance. Disruption of NKT cell numbers or function results in severe deficits in immune surveillance against pathogens and tumor cells. Experimental evidence suggests that hepatosteatosis may

increase resident hepatic as well as peripheral NKT cells. The change in NKT cell numbers in animal models of alcohol-related hepatosteatosis are associated with a disruption of cytokine homeostasis, resulting in a more pronounced release of proinflammatory cytokines which renders the steatotic liver highly susceptible to secondary insults (Minagawa et al., 2004). In alcohol-fed animals, liver NKT cells increase, and further activation by alpha-galactosylceramide causes lethal liver injury (Minagawa et al., 2004). This can be explained by alcohol-induced hepatocyte sensitization to cell-mediated lysis, which develops concomitant to increased cytolytic activity of natural killer T cells. Alcohol-fed natural killer T cell-deficient mice exhibit a delay in alcohol-induced liver injury (Minagawa et al., 2004). In general, based on the tissue microenvironment, NK and NKT cells can accelerate early liver injury by producing proinflammatory cytokines and killing hepatocytes in an oxidative milieu.

2.7 Bone-marrow derived stem cells (BMSCs)

While maturation, activation, and proliferation of lymphoid cells occurs in secondary lymphoid organs (spleen, thymus, and lymph nodes), generation of these cells occurs from progenitor cells termed as bone marrow derived stem cells. Bone marrow derived stem cells were originally thought to contribute to liver repair based on the environmental insult but recent evidence suggests these cells may contribute to liver injury and fibrosis (Dalakas et al., 2010). Alcoholic hepatitis patients show increased CD34+ cell counts in liver tissue and in blood as compared with matched controls. Alcohol induced liver injury mobilizes CD34+ stem cells into circulation and recruits them into the liver. These bone marrow derived stem cells contribute to the hepatic myofibroblast population but not to parenchymal lineages and do not promote hepatocyte repair (Dalakas et al., 2010). Bone marrow stem cells generally reside in a hypoxic environment and increased reactive oxygen species (ROS) modulates their cell cycle allowing them to escape the bone marrow and affecting their self-renewal (Iwasaki & Suda, 2009). Recent studies show that acute alcohol exposure affects the hematopoietic stem cell response to bacterial infections by inhibiting differentiation and impairing host defense in alcohol abusers (Raasch et al., 2010). Further Inokuchi et al. (Inokuchi et al., 2011) indicate the importance of bone marrow derived cells in alcohol induced liver injury. Whether the effect of alcohol on stem cells links to alteration in immune and hepatocyte injury during ALD is unclear.

3. Signaling pathways and inflammation

3.1 Toll like receptors in ALD

Toll-like receptors (TLRs) are membrane-associated or endosomal and recognize distinct microbial components activating different signaling pathways by selective utilization of adaptor molecules (Takeda & Akira, 2005). TLRs mediate responses to a number of danger signals including extracellular pathogens and intracellular mediators such as ROS, high mobility group protein (HMGB)1, fibrinogen and heat shock proteins (hsps) (Lotze et al., 2007). The role of toll-like receptors (TLRs) and particularly TLR4 has been investigated in alcoholic tissue injury (Hritz et al., 2008; Uesugi et al., 2001; Inokuchi et al., 2011). Increasing evidence suggests that various TLRs, signaling components activated by TLRs play an important role in the pathogenesis of ALD. Figure 1 shows signaling adapters and kinases

down-stream of TLRs, some of which have been directly or indirectly altered by alcohol exposure and implicated in liver injury. The cross-talk of stress regulated intracellular molecules with TLRs, intracellular kinases and transcription factors resulting in alterations in cytokines/chemokines in ALD are of great importance and need further investigation.

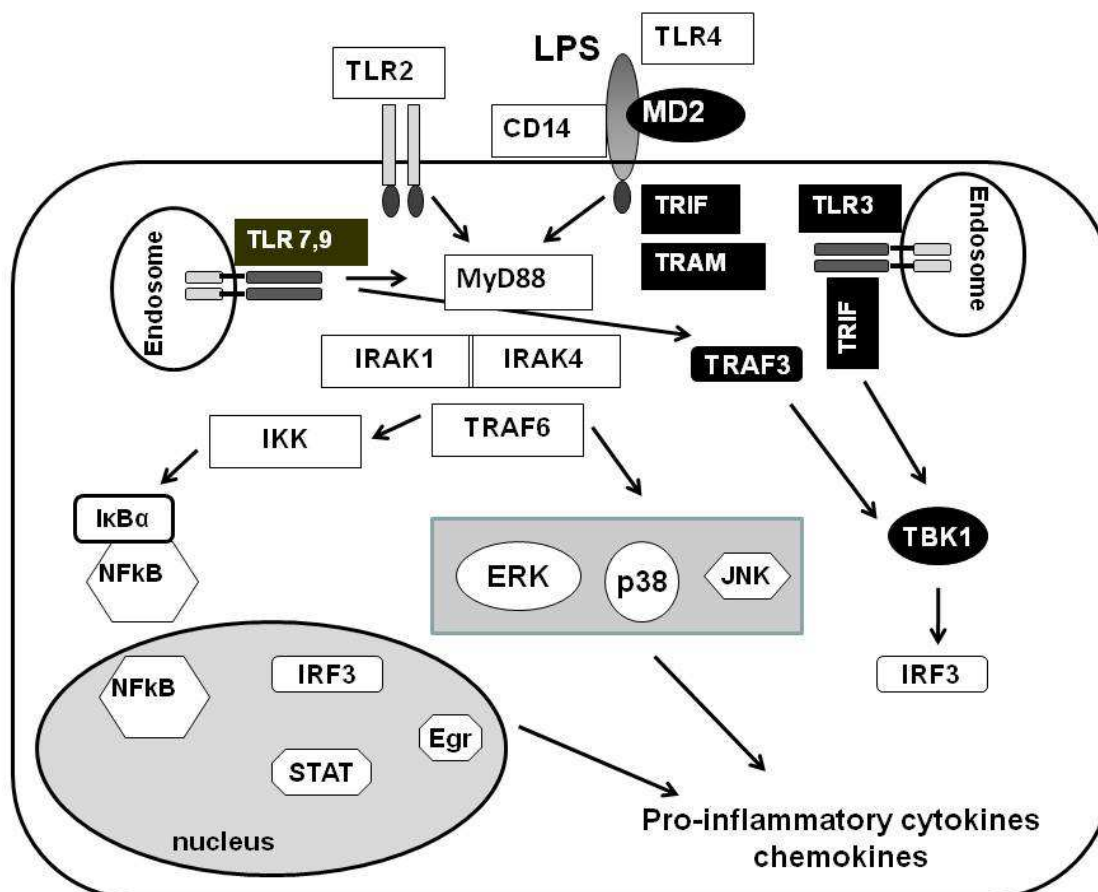


Fig. 1. Innate immune signaling in ALD. Toll like receptors particularly TLR4, in ALD, activate down-stream signaling adaptors, kinases and transcription factors to induce pro-inflammatory cytokines and chemokines. All signaling molecules that have been studied in ALD are identified by black color font whereas molecules not studied in ALD yet are seen in white color font.

Pattern recognition receptors (PRRs) are expressed on liver non-parenchymal and parenchymal cells and function as sensors of microbial danger signals enabling the vertebrate host to initiate an immune response. The complexity of cellular expression of PRRs in the liver provides unique aspects to pathogen recognition and tissue damage in the liver (Szabo et al., 2006). It is now well accepted that the innate immune system recognizes both damage (or danger)- and pathogen-associated molecular patterns (DAMPs and PAMPs, respectively) through pattern recognition receptors, such as Toll-like receptors (TLRs) and/or Nod-like receptors (NLRs). TLRs such as TLR4 and TLR2 that detect PAMPs for instance LPS and lipoproteins are located on the cell surface whereas TLRs such as TLR3, TLR7 and TLR9 that detect viral RNA and DNA are located in the endosome (Takeda & Akira, 2005). Engagement of LPS and activation of the CD14/TLR4 complex activates down-stream signaling molecules such as IRAK1/4, TRAF6 leading to activation of MAP kinases

and NF κ B in the liver (Mandrekar & Szabo, 2009). Recent studies by (Hritz et al., 2008; Inokuchi et al., 2011) indicate the requirement for TLR4 in alcohol induced steatosis. Oxidative stress also contributes to TLR4 signaling in macrophages and various other cell types in the liver via NADPH oxidase (Park et al., 2004). A pivotal role for NADPH oxidase in TLR4 mediated alcoholic liver injury has been recently shown (Hritz et al., 2008; Thakur et al., 2006a). Gustot et. al. (Gustot et al., 2006) also showed that oxidative stress regulates TLR 2, 4, 6 and 9 mRNA induction in alcoholic liver injury. In vivo alcohol exposure activates oxidative stress pathways and increases sensitization to TLR ligands, particularly TLR4, in alcoholic liver disease (Hritz et al., 2008; Gustot et al., 2006). TLR2 deficiency did not seem to have a significant effect on alcoholic liver injury (Hritz et. al., 2008).

The role of DAMPs in chronic liver diseases has been reported previously. Amongst the well characterized DAMPs, HMGB1, S100 proteins, hyaluronan and heat shock protein 60 (hsp60) are known to be recognized by TLR2 and TLR4 (Lotze et al., 2007). In addition, necrotic or apoptotic cells are also recognized as DAMPs by TLRs (Sloane et al., 2010). In alcoholic liver injury, apoptotic bodies generated due to alcohol-induced oxidative stress could be recognized by DAMPs (McVicker et al., 2007) and thus play an important role in inflammatory responses in the liver.

3.2 IKK and MAPK signaling

Activation of TLR4 recruits IRAK-1 to the TLR4 complex via interaction with MyD88 and IRAK-4 (Takeda & Akira, 2005). The role of MyD88, the common TLR4 adaptor molecule was recently evaluated in a mouse model of alcoholic liver injury (Hritz et al., 2008). These studies showed that MyD88 knock-out mice were highly susceptible to alcohol-induced fatty liver (Hritz et al., 2008). While alcohol feeding in TLR4 deficient mice prevented liver injury, alcohol-fed MyD88 deficient mice showed increased oxidative stress and liver injury (Hritz et al., 2008). TLR4-induced MyD88-dependent and independent pathways lead to IKK kinase activation resulting in pro-inflammatory cytokine production (Takeda & Akira, 2005). Chronic alcohol exposure induces LPS-mediated IRAK-1 kinase activation in murine macrophages (Mandrekar et al., 2009).

Members of the mitogen-activated protein kinase (MAPK) family including extracellular receptor activated kinases 1/2 (ERK1/2), p38 and c-jun-N-terminal kinase (JNK) are activated down-stream of TLRs resulting in pro-inflammatory cytokine TNF α production (Weinstein et al., 1992). Chronic alcohol increases LPS-induced ERK1/2 activation and subsequent transcription of Egr-1, an immediate early gene transcription factor, contributing to expression of TNF α in murine hepatic macrophages (Kishore et al., 2002; Shi et al., 2002). LPS stimulation of Kupffer cells in vitro exposed to chronic alcohol in vivo exhibited increased p38 activity and decreased JNK activity (Kishore et al., 2001). Inhibition of p38 activation completely abrogated alcohol-mediated stabilization of TNF α mRNA likely via interaction with tristetraprolin (TTP) (Mahtani et al., 2001). Conversely, ERK1/2 inhibition did not alter TNF α mRNA stability but affected mRNA transcription in chronic alcohol exposed macrophages (Kishore et al., 2002).

3.3 Transcription factors and alcohol

TLR4-induced MyD88-independent signaling leads to activation of NF κ B and/or interferon regulatory factor 3 (IRF3) resulting in induction of pro-inflammatory cytokines or Type I

IFN (Fig 1) (Kawai et al., 2001; Fitzgerald et al., 2003). Studies so far have shown that chronic alcohol exposure induces LPS/TLR4 mediated NF κ B activation in human monocytes and macrophages contributing to production of pro-inflammatory cytokine, TNF α (Mandrekar et al., 2009). Other investigators found that activated IRF3 binds to the TNF α promoter in macrophages after chronic alcohol administration (Zhao et al., 2008) and induces TNF α production. While IRF3 in myeloid cells contributes to alcoholic liver injury, IRF3 and Type I interferons in parenchymal cells appears to be protective (Petrasek et al., 2010). Whether NF κ B and IRF3 in myeloid cells act in concert with each other to increase pro-inflammatory cytokines and liver injury is not yet clear. LPS stimulation of JNK leads to phosphorylation of c-jun and subsequent binding of c-jun to CRE/activator protein (AP)-1 site in the TNF α promoter (Diaz & Lopez-Berestein, 2000). Although chronic alcohol feeding decreased JNK activity without any effect on TNF α mRNA, short-term alcohol exposure increased JNK phosphorylation as well as AP-1 binding in the presence of combined TLR4 plus TLR2 stimulation (Oak et al., 2006) in human monocytes. Recent studies indicate a role for AP-1 in RANTES expression during alcohol mediated inflammation (Yeligar et al., 2009).

Alcoholic steatosis is associated with increased expression of genes regulating fatty acid synthesis and suppression of genes involved in fatty acid oxidation (Crabb & Liangpunsakul, 2006). Transcription factors like sterol regulatory element binding protein (SREBP) and peroxisome proliferator activated receptor (PPAR) α play a pivotal role in early alcoholic liver injury and rodent models as well as in vitro treatment with alcohol show downregulation of PPAR α mRNA (Wan et al., 1995). Further, DNA binding activity of PPAR α is significantly reduced resulting in decreased target gene expression after alcohol exposure (Galli et al., 2001). Decreased PPAR α activity was accompanied by increased oxidative stress in the liver resulting in increased sensitization of TNF α induced liver injury (Crabb & Liangpunsakul, 2006). Further studies are needed to establish a direct relationship between oxidative stress, cytokines and hepatic fatty acid metabolism in alcoholic liver disease.

The role of STAT3, another transcription factor in alcoholic liver injury has been investigated (Gao, 2005). Compared with wild-type mice, Kupffer cells from alcohol-fed hepatocyte-specific STAT3KO mice produced similar amounts of ROS and hepatic proinflammatory cytokines compared to control mice. On the other hand, Kupffer cells from M/N-STAT3KO mice produced higher ROS and TNF α compared with wild-type controls. These results suggest that STAT3 in hepatocytes promotes ROS production and inflammation whereas myeloid cell STAT3 reduces ROS and hepatic inflammation during alcoholic liver injury (Horiguchi et al., 2008). Endothelial STAT3 seems to play an important dual role of attenuating hepatic inflammation and sinusoidal endothelial cell death during alcoholic liver injury (Miller et al., 2010). Thus, STAT3 may regulate liver injury during alcohol exposure in a cell-type dependent manner.

3.4 Anti-inflammatory pathways in ALD

Diminution of inflammatory gene expression to curb the inflammatory response during ALD is pivotal to development of injury. Various anti-inflammatory mediators such as IL-10, prostaglandins, transforming growth factor (TGF)- β (Schmidt-Weber & Blaser, 2004; Asadullah et al., 2003) have been identified to control the inflammatory response. In addition, intracellular signaling molecules such as IRAK-M, ST2, phosphoinositide (PI)3-

kinase (K), suppressor of cytokine signaling (SOCS) 1, A20 and single immunoglobulin IL-1R-related molecule (SIGIRR) (Han & Ulevitch, 2005) also contribute to the anti-inflammatory pathway. While chronic alcohol did not significantly affect IL-10 during alcohol exposure in wild-type mice (Hill et al., 2002), IL-10 deficient mice showed greater susceptibility to alcoholic liver injury due to increase in pro-inflammatory cytokines (Hill et al., 2002). These results suggest that anti-inflammatory cytokine IL-10 is unable to counter-regulate the sustained pro-inflammatory activation in the chronic alcoholic liver. Recent studies show that IL-10 was decreased in alcohol exposed Type-I IFN receptor deficient mice, indicating a role for Type I IFNs in induction of anti-inflammatory responses during ALD (Petrasek et al., 2011). Other immunoinhibitory molecules such as SOCS1 and SOCS3 and adiponectin appear to induce anti-inflammatory responses during ALD. Adiponectin is decreased after chronic alcohol feeding and treatment of mice with adiponectin (Thakur et al., 2006b) prevents alcohol-induced liver injury. This protective effect of adiponectin has been attributed to decreased LPS-induced ERK1/2 signaling resulting in normalization of TNF α production by Kupffer cells after chronic alcohol exposure (Thakur et al., 2006b). Additional studies to understand anti-inflammatory mechanisms will provide a better understanding of the contribution of these molecules in alcohol-induced liver injury.

4. Signaling pathways and hepatocyte injury

Alcohol-induced liver disease is linked to a state of “oxidative stress” and induction of cell death. Alcohol exposure, whether acute or chronic increases production of ROS, lowers the anti-oxidant systems, and results in enhancement of oxidative stress. The consequences of ROS generation in the alcoholic liver are widespread. Some ROS related effects of alcohol include oxidative stress induced by metabolizing enzymes such as CYP2E1, formation of adducts, stress at the level of the endoplasmic reticulum, stress-induced heat shock proteins, regulation of nuclear receptors, all leading to sensitization of hepatocytes to cellular injury and death.

4.1 Alcohol metabolism and oxidative stress

The classical pathway of alcohol metabolism involves enzymatic breakdown of alcohol by the enzyme, alcohol dehydrogenase and its subsequent conversion to acetaldehyde and formation of free radicals. In addition, the microsomal electron transport system also oxidizes ethanol via catalysis by the cytochrome P450 enzymes. The 2E1 isoform of the cytochrome P450 system is induced during chronic alcohol consumption and results in formation of ROS and increased generation of hydroxyl radicals (Cederbaum, 2001). The role of CYP2E1 in hepatocyte injury has been elucidated using HEPG2 cells expressing CYP2E1 (Wu & Cederbaum, 1996). Increased oxidative stress from induction of CYP2E1 in vivo sensitizes hepatocytes to LPS and TNF toxicity (Wu & Cederbaum, 1996). Oxidants, such as peroxynitrite, activation of p38 and JNK MAP kinases and mitochondrial dysfunction are downstream mediators of the CYP2E1-LPS/TNF potentiated hepatotoxicity (Lu & Cederbaum, 2009). Further, studies indicate that oral alcohol feeding of CYP2E1 knock-out mice prevents alcoholic liver injury and this may be due to inhibition of oxidative stress and up-regulation of PPAR α (Lu et al., 2008). Oxidation of ethanol by alcohol dehydrogenase and subsequent metabolism of acetaldehyde results in increased NADH/NAD $^{+}$ ratio in the cytoplasm and mitochondria. The increase in NADH results in

inhibition of mitochondrial β -oxidation and accumulation of intracellular lipids leading to steatosis (Polavarapu et al., 1998; Wu & Cederbaum, 2003). Future studies on pathways activated by alcohol metabolism in various cell types of the liver would provide additional information to identify strategies to alleviate alcoholic liver injury.

4.2 Alcohol and protein adducts

Alcohol metabolism and oxidative stress results in the formation of reactive aldehydes such as acetaldehyde, malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) that can bind to proteins to form adducts. In vivo models of chronic alcohol consumption have shown that acetaldehyde, MDA and HNE adduct formation is increased in various organs including the liver. Acetaldehyde and MDA react with proteins synergistically to form hybrid protein adducts called malondialdehyde-acetaldehyde (MAA) adducts (Niemela et al., 1994). Recognition of MAA-adducts by Kupffer cells, endothelial and stellate cells via the scavenger receptor leads to upregulation of cytokine and chemokine production, and increased expression of adhesion molecules (Thiele et al., 2004; Duryee et al., 2005). Circulating antibodies to MAA-adducts were detected in patients with alcoholic hepatitis and cirrhosis and correlated with the severity of liver injury (Rolla, 2000). Although evidence suggests the existence of protein adducts during chronic alcohol consumption, their identification in animal models has been challenging and limits their role in pathogenesis of ALD.

4.3 ER stress and ALD

The unfolded protein response (UPR) that is a protective response of the cell is referred to as the ER stress response during pathological conditions. In alcoholic liver disease increased expression of GRP78, GRP94, CHOP and caspase-12 indicated a UPR/ER stress response (Kaplowitz & Ji, 2006). Up-regulation of ER-localized transcription factors and activation such as SREBP-1c and SREBP-2 was associated with increased lipid accumulation and induction of fatty liver during chronic alcohol (Ji et al., 2006). Another important inducer of ER stress, homocysteine, was increased in alcoholic human subjects leading to hyperhomocystenemia, also observed in alcohol feeding models (Ji & Kaplowitz, 2003). The role of ER stress in triglyceride accumulation and fatty liver comes from studies showing that betaine increases an enzyme, betaine homocysteine methyltransferase (BHMT) and reduces homocysteine levels to inhibit lipid accumulation (Ji & Kaplowitz, 2003). Although several studies suggest a pivotal role for ER stress in alcoholic liver disease, the alcohol-mediated mechanisms that trigger ER stress are not fully understood.

4.4 Alcohol and heat shock proteins

Stress or heat shock proteins (hsps) are ubiquitous, highly conserved proteins and originally identified for their cytoprotective function and assistance in the correct folding of nascent and stress-accumulated misfolded proteins. Oxidative stress induces heat shock proteins via activation of the heat shock transcription factor (HSF) (Finkel & Holbrook, 2000). Earlier studies on the effects of ethanol on the heat shock proteins in neuronal cells (Miles et al., 1991) showed that chronic alcohol increases Hsc 70 mRNA transcription and this may be important in neuronal adaptation and development of tolerance and

dependence in alcoholics. Male Wistar rats fed with acute as well as chronic ethanol feeding (for 12 weeks) showed induction of hsp70 in the various regions of the brain and the liver (Calabrese et al., 1996; Calabrese et al., 1998). Hsp90 levels were also increased in cultured rat hepatocytes exposed to acute alcohol (Ikeyama et al., 2001). Studies have also shown that acute and chronic alcohol induces HSF activation and differentially induces hsp70 and hsp90 to affect inflammatory cytokine production in macrophages (Mandrekar et al., 2008). Comprehensive studies on the role of heat shock proteins and their chaperone function in the liver will provide further information to develop therapeutic strategies in ALD.

4.5 Alcohol and nuclear receptors

Nuclear receptors are a class of unique intracellular transcription factors that are activated by their ligands and can directly bind to DNA to regulate transcription of target genes that play key roles in development and cellular homeostasis (Wang & Wan, 2008). Three groups of nuclear receptors exist: the first is the classic steroid or thyroid hormone receptors such as glucocorticoid receptor (GR) and thyroid receptor (TR), the second is the nuclear orphan receptors such as the nuclear receptor related-1 (Nurr-1) and neuron derived orphan receptor-1 (NOR1), the third class receptors that include the retinoid X receptor (RXR), peroxisome proliferators activated receptors (PPARs) and liver X receptor (LXR). It is the third class of nuclear receptors, particularly PPARs that are implicated in hepatic lipid metabolism and inflammatory processes and have been the main area of interest in alcohol-induced steatosis. Among various PPARs, the importance of PPAR α in lipid metabolism and PPAR γ in inflammatory processes is being investigated in alcoholic liver disease (Crabb & Liangpunsakul, 2006). PPAR α dimerizes with another nuclear receptor, RXR to control transcription of target genes involved in free fatty acid transport and oxidation (Issemann & Green, 1990; Bocos et al., 1995). Whereas PPAR γ is an essential regulator for adipocyte differentiation and lipid storage in mature adipocytes (Rosen & Spiegelman, 2001; Tsai & Maeda, 2005), both PPAR α and PPAR γ exert anti-inflammatory effects (Wang & Wan, 2008). Ethanol feeding of mice induced fatty liver injury and was accompanied by inhibition of transcriptional and DNA binding activity of PPAR α , resulting in decreased expression of target genes such as carnitine palmitoyl transferase-1 (CPT-1) (Galli et al., 2001; Nakajima et al., 2004). Ethanol seemed to down-regulate RXR expression and PPAR α levels to influence PPRE binding (Wan et al., 1995; Beigneux et al., 2000). Like hepatocyte-specific RXR α deficient mice, PPAR α -null mice are more susceptible to alcohol-induced liver injury (Nakajima et al., 2004; Gyamfi et al., 2008). Treatment with PPAR α agonists WY14643 resulted in increased expression of genes related to fatty acid oxidation and hence amelioration of alcoholic liver disease (Fischer et al., 2003). Thus, it appears that impaired activation of PPAR α during ethanol consumption contributes to alcoholic fatty liver induction. Recent studies show that PPAR α and γ agonists can reduce severity of chronic alcohol induced liver injury even in the context of continued alcohol consumption (de la Monte et al., 2011). Thus, nuclear localization of PPARs and their DNA binding partners, RXRs seem to play an important role in alcohol induced fatty liver injury.

4.6 Death receptor pathways: intrinsic and extrinsic

Chronic alcohol-induced hepatocyte apoptosis is a multifactorial process and involves interactions of oxidative stress and cytokines that activate death receptors and

mitochondrial death pathways (Fig 2). Studies show that chronic alcohol-induced hepatocyte apoptosis occurs via the receptor-mediated pathway: TNF α and Fas receptors, and the intrinsic pathway: mitochondrial apoptotic pathway (Hoek & Pastorino, 2002). Activation of the death receptor pathways, Fas/FasL and TNF α /TNFR1 is strongly implicated in alcoholic liver disease (Hoek & Pastorino, 2002). Increased TNF α and TNF-R1 levels in animal models and humans with alcohol steatohepatitis have suggested an involvement of the TNF α /TNF-R1 pathway in hepatocyte killing (Pastorino et al., 2003; Pianko et al., 2000). Increased oxidative stress in chronic alcohol exposed rats promotes hepatocyte apoptosis and necrosis and is implicated in the alcohol-induced sensitization to the pro-apoptotic action of TNF α (Pastorino et al., 2003; Pastorino & Hoek, 2000). Additionally, TNFR1 knock-out mice, but not TNFR2 knock-out mice, were resistant to alcoholic liver injury (Yin et al., 2008) further strengthening a role for the TNF α /TNFR1

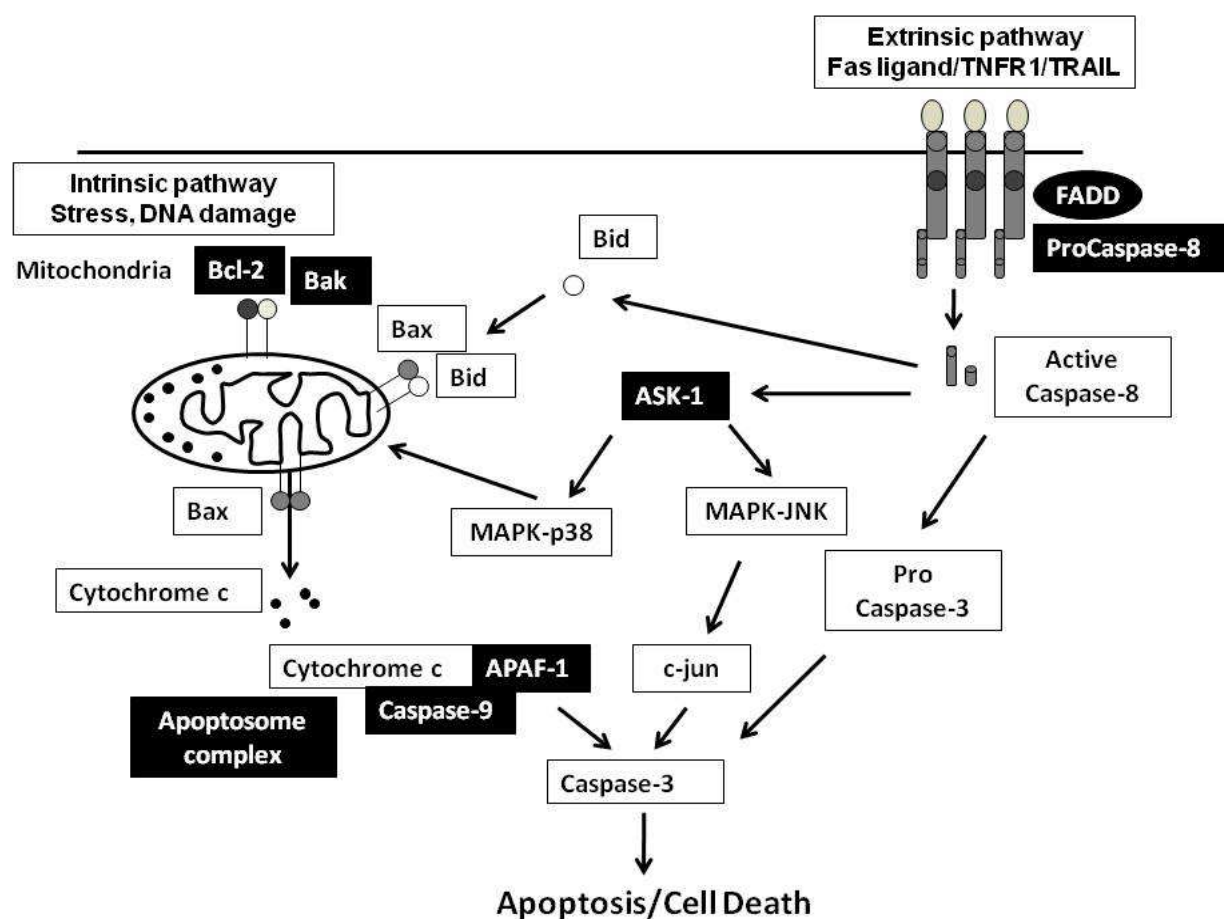


Fig. 2. Apoptotic signaling pathways in ALD. Two major apoptotic pathways are illustrated: one activated via death receptor activation ('extrinsic') and the other by stress-inducing stimuli ('intrinsic'). Triggering of cell surface death receptors of the tumour necrosis factor (TNF) receptor superfamily, including CD95 (Fas) and TNF-related apoptosis-inducing ligand (TRAIL)-R results in rapid activation of the initiator caspase 8 through the adaptor molecule Fas-associated death domain protein (FADD). In the intrinsic pathway, stress-induced apoptosis results in perturbation of mitochondria, release of cytochrome *c* and cell death. All signaling molecules that have been studied in ALD are identified by black color font whereas molecules not studied in ALD yet are seen in white color font.

pathway in alcoholic liver disease. Besides TNF α , FasL and Fas receptor expression were increased in livers of alcohol-fed mice (Deaciuc et al., 1999) leading to Fas-mediated cell killing, suggesting a significant role for the Fas/FasL pathway. Expression of Fas receptor also increased in human hepatocytes during alcoholic liver disease (Taieb et al., 1998).

Studies have shown that alcohol induced ROS generation leads to alteration in mitochondrial membrane permeability and membrane potential that in turn initiates the release of proapoptotic factors such as cytochrome c (Hoek & Pastorino, 2002; Hoek, 2002). Transition of mitochondrial permeability then results in increased caspase-3 activation in hepatocytes and this depends on p38 MAPK activation but is independent of caspase-8 (Pastorino et al., 2003; Pastorino & Hoek, 2000). Studies also implicate a role for MAP kinase, JNK2, independent of caspase-8, in TNF-induced mitochondrial death pathways (Schattenberg et al., 2006). The exposure of hepatocytes to ethanol induces ROS-mediated JNK activation, c-jun phosphorylation, Bid fragmentation, cytochrome c release and pro-caspase 3 cleavage (Cabrales-Romero Mdel et al., 2006). Whether alcohol affects JNK2 activation is not clear. But recent studies indicate a role for JNK1, but not JNK2, in CYP2E1 and TNF α mediated hepatotoxicity (Wang et al., 2011). Chronic ethanol feeding also decreases ATP concentration associated with decreased viability in hepatocytes isolated from rats fed either high- or low-fat, ethanol-containing diets (Bailey & Cunningham, 1999). Various studies now show that decreased ATP synthesis accompanied by reduced mitochondrial protein synthesis, inhibition of the oxidative phosphorylation system (OxPhos) and damage to mitochondrial DNA leads to dysfunctional mitochondria in alcoholic liver disease (Bailey & Cunningham, 2002). Detailed studies of death receptors and mitochondrial sensitization mechanisms leading to hepatocyte death by alcohol will improve our understanding of ALD.

5. Therapeutic targets in ALD

While mechanistic studies have pointed to various therapeutic targets, abstinence from alcohol appears to be most effective in resolution of ALD. However, motivating patients to maintain sobriety, follow their compliance and prevent relapse are major obstacles in treatment of ALD. Pharmacotherapy using naltrexone and disulfuram assist in reducing or eliminating alcohol intake (Bouza et al., 2004; Williams, 2005). Nutritional therapy with supplementation of minerals like Zn (Kang & Zhou, 2005) and vitamins have been used to improve and attenuate alcoholic hepatitis. While multiple clinical trials have supported the use of glucocorticosteroids in patients with alcoholic hepatitis (McCullogh & O'Connor, 1998), their benefit still remains in question (Christensen, 2002). Considering the dysregulated inflammatory response in alcoholic hepatitis, various studies used specific anti-TNF α antibody therapy (Tilg et al., 2003) with little or no success. Complete neutralization of TNF α led to increased complications such as tuberculosis infections limiting its clinical utility. Future therapeutic interventions will thus have to be focused on partial attenuation of TNF α with lower infectious complications. Recent studies show that treatment with IL-22 ameliorates alcoholic liver injury in a mouse model of ALD (Ki et al., 2010). Based on induction of oxidative stress by alcohol, a combined regimen of anti-oxidant therapies including N-acetylsysteine and vitamins has been tested without significant differences in improvement rates of ALD (Stewart et al., 2007). Other alternative therapies using silymarin, S-adenosylmethionine and betaine have been suggested for future clinical

trials (Frazier et al., 2011). While liver transplantation offers the most effective treatment, limited organ availability and post-transplant drinking dampen long-term outcomes. Future research combining biologics and anti-oxidant therapies may offer lasting therapeutic efficacies in ALD patients.

6. Conclusions and future directions

Alcoholic liver disease is a very complex and multifactorial disorder. Alcohol exerts its effects at many levels; individual signaling molecules, cells and finally the entire organ. Integrative approaches providing a comprehensive picture of how alcohol affects intracellular signaling pathways in tissues at different levels (Guo & Zhakari, 2008) is needed. A multidimensional analysis of inflammation and death signaling pathways in immune and non-immune cells of the liver to identify molecular targets in the host leading to systemic and organ inflammation will enhance our understanding of the pathogenesis of alcoholic liver disease. Until now various key signaling cascades triggered in the innate immune response such as toll-like receptor, interferon, NFkB and stress pathways such as ROS mediated activation of transcription factors, heat shock proteins or chaperones, mitochondrial damage and ER stress, have been viewed as separate entities rather than an integrated network of molecular interactions in alcoholic liver injury. A pathway diagram map which attempts to integrate these pathways will present a powerful aid for interpreting pathway interactions and highlight the valuable contributions of molecular interactions contributing to initiation and perpetuation of ALD. Future approaches to enable comprehensive analysis of these interactions could offer a powerful tool to understand diagnosis, prognosis, and treatment of ALD.

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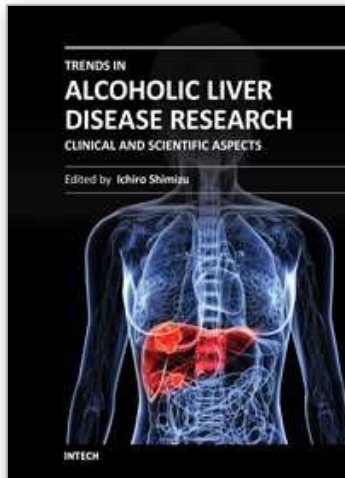
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Alcoholic liver disease occurs after prolonged heavy drinking. Not everyone who drinks alcohol in excess develops serious forms of alcoholic liver disease. It is likely that genetic factors determine this individual susceptibility, and a family history of chronic liver disease may indicate a higher risk. Other factors include being overweight and iron overload. This book presents state-of-the-art information summarizing the current understanding of a range of alcoholic liver diseases. It is hoped that the target readers - hepatologists, clinicians, researchers and academicians - will be afforded new ideas and exposed to subjects well beyond their own scientific disciplines. Additionally, students and those who wish to increase their knowledge will find this book a valuable source of information.

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