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Review

Signalling pathways in alcohol-induced liver inflammation☆

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The pathogenesis of alcoholic liver injury involves interactions of several intracellular signalling pathways in different cell types of the liver. Alcohol-induced sensitization of liver macrophages to portal endotoxin/lipopolysaccharide (LPS) is considered a hallmark of alcoholic liver disease (ALD). Intracellular mechanisms associated with LPS-induced signalling play a crucial role in the initiation and progression of alcoholic liver injury, and are being extensively explored. LPS recognition by Toll-like receptor 4 (TLR4) on macrophages and other cell types in the liver, activation of downstream signalling pathways culminating in activation of transcription factors such as NFκB, AP-1 leads to increased inflammatory cytokine production in ALD. In addition, LPS-induced MAPK such as ERK and p38 also contribute to liver injury. The importance of alcohol-induced reactive oxygen species and interactions with TLR pathways in macrophages leading to inflammation is becoming increasingly evident. Collectively, these signalling pathways induce pro- and anti-inflammatory cytokines that play an important role in ALD. In this review we describe the key signalling intermediates leading to alcohol-induced inflammation in alcoholic liver disease.

***Keywords*: Macrophages; Kupffer cells; TLRs; MAP kinases; Transcription factors**

1. Introduction

Alcohol consumption is associated with a spectrum of diseases in the liver ranging from steatosis, steatohepatitis to cirrhosis and hepatocellular carcinoma. The pathogenesis of acute and chronic alcohol consumption is multi-factorial with diverse consequences in different cell types. Alcohol-induced injury occurs at multiple levels ranging from the innate immune cells to the liver parenchymal cells, hepatocytes. The innate immune cells including hepatic macrophages (Kupffer cells) play a pivotal role in early alcohol-induced liver injury via recognition of endotoxin/lipopolysaccharide in the portal circulation. The progression of alcohol-induced liver damage involves parenchymal cells and macrophages through the direct effects of alcohol as well as indirect effects of metabolites, oxidative stress, immunologic and inflammatory events. In macrophages, alcohol directly induces oxidative stress and sensitizes to LPS-induced inflammatory cytokine production. Inflammatory cytokines particularly TNFα, contributes to the development of alcoholic liver disease (ALD). Alcohol sensitizes hepatocytes to TNFα-induced apoptosis. A complete understanding of alcohol-mediated intracellular signalling mechanisms leading to inflammatory cytokine induction in macrophages will provide new insights into the development of new potential targets for therapeutic intervention.

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Abbreviations: ALD, alcoholic liver disease; Egr-1, early growth response factor-1; HSF, heat shock transcription factor; IRF, interferon-responsive factor; NFkB, nuclear factor kappa B; MAPK, mitogen activated protein kinase; MyD88, myeloid differentiation primary response gene (88); STAT, signal transducers and activators of transcription; SOCS, suppressor of cytokine signalling; TLR, Toll-like receptor.

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The goal of this concise article is to review the alcohol-mediated signalling pathways, particularly Toll-like receptors and their adaptors in macrophages. The importance of transcription factors such as NFκB, AP-1, Egr-1 and STATs, intracellular kinases such as MAP kinases and pro- and anti-inflammatory cytokines in ALD will also be reviewed.

2. Interactions of immune and parenchymal cells of the liver in ALD

Innate immune responses activated in the resident liver macrophages, Kupffer cells play a key role in the early pathogenesis of alcohol-induced liver injury [1]. Increased levels of circulating LPS in alcoholic patients have been shown [2]. The currently accepted model of alcoholic liver injury elucidates that LPS promotes hepatic injury via induction of Kupffer cell activation resulting in production of TNFα and other inflammatory mediators. The Kupffer cells respond to stimulation by gut-derived endotoxins and apoptotic dead cells in the tissue resulting in increased inflammatory responses. Circulating TNFα is increased in chronic alcoholics as well as in mouse chronic alcohol feeding models [3,4]. In addition to hepatocytes, abnormal stellate cell activity and induction of fibrosis is also dependent on Kupffer cells via production of reactive oxygen species and pro-inflammatory cytokines [5]. Liver natural killer (NK) cells exposed to alcohol contribute to fibrosis and inflammation via inhibition of NK cell accumulation and reduced NK cell killing of hepatic stellate cells [6]. Thus, modulation of the innate immune system is an important mechanism contributing to liver inflammation, hepatocyte death and liver fibrosis (Fig. 1).

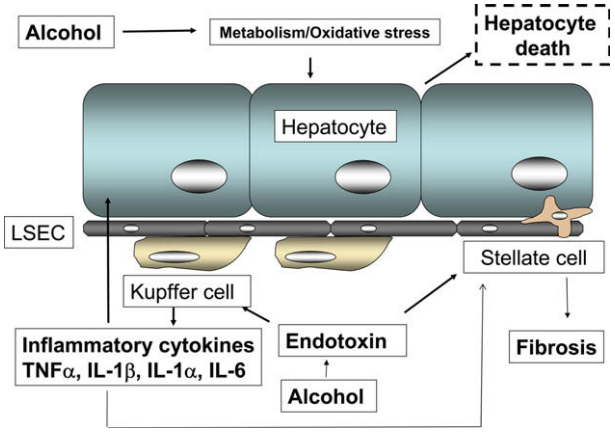

Fig. 1. Cells involved in alcoholic liver injury. Alcohol-mediated increase in gut-derived endotoxin with oxidative stress mechanisms sensitizes hepatic macrophages to release inflammatory cytokines such as TNFα, IL-1β, IL-1α and IL-6 that affects stellate cells and hepatocyte functions. Endotoxin also affects stellate cell and endothelial cell activation and contributes to liver injury.

3. Receptor-mediated signalling pathways affected by alcohol in liver inflammatory cells

3.1. Toll-like receptors, adapters and signalling

Recent discoveries of pattern recognition receptors focused attention on Toll-like receptors (TLRs) that sense pathogen-derived molecules as well as host-derived damage signals [7,8]. Among 10 different TLRs described in humans, the functional significance of TLR4 and its downstream signalling in alcoholic liver disease is extensively elucidated (Fig. 2). TLR4 recognizes the lipid A motif of the lipopolysaccharide (LPS), a suggested cofactor in the pathogenesis of ALD [9]. TLR4 is a major component of the LPS recognition receptor complex, which also involves the co-receptors CD14 and MD-2, and LPS binding protein (LBP) [10,11]. LBP is a soluble shuttle protein that directly binds LPS and facilitates the association between LPS and CD14 [12,13].

CD14 is a glycosylphosphatidylinositol-anchored protein, which also exists in a soluble form. CD14 facilitates the transfer of LPS to the TLR4/MD2 receptor complex and modulates LPS recognition [14]. CD14 facilitates TLR4 induced responses [7,15] and appears to be required for MyD88-independent signalling [16].

MD2 is a soluble protein that non-covalently associates with TLR4 and binds LPS directly to form a complex with LPS in the absence of TLRs [17–19]. Although no evidence suggests that TLR4 can bind LPS directly, TLR4 can enhance the binding of LPS to MD2 [20].

In the liver, TLR4 is expressed not only on innate immune cells such as Kupffer cells and recruited macrophages, but also on hepatocytes, sinusoidal endothelial cells, biliary epithelial cells and stellate cells. Indeed, LPS activation was shown to result in functional changes in all of these cell types in different liver diseases [21,22].

A major role for LPS-induced, TLR4 mediated signalling via its ligand, endotoxin, in alcoholic liver disease (ALD) was established by studies of Thurman and colleagues [23,24]. Studies in knockout mouse models have shown that chronic alcohol feeding in mice deficient of CD14, TLR4 and LPS-binding protein (LBP) results in alleviation of alcohol-induced liver injury indicating an important role for the TLR4 pathway [24–27]. Recent studies suggested that LPS recognition by TLR4 expressed on hepatic stellate cells and sinusoidal epithelial cells may further contribute to the progression of ALD [28,29].

Alcohol sensitizes Kupffer cells and monocytes/macrophages to produce increased TNFα in response to endotoxin [30]. Studies investigating mechanisms of alcohol-induced sensitization of Kupffer cells to endotoxin focused on intermediates of the TLR4 induced signalling pathway. Reports on the effects of alcohol on