ROLE OF TUMOR NECROSIS FACTOR AND IL-18 IN ALCOHOLIC HEPATITIS

BACKGROUND

Alcoholic liver disease (ALD) is a major cause of illness and death in many countries. It is the fourth leading cause of death among adult men of 24-65 years residing in urban areas of USA. This disease is characterized by fatty liver, hepatitis, fibrosis, and cirrhosis. Up to 35 percent of heavy drinkers develop alcoholic hepatitis, though the condition is often poorly diagnosed. The clinical features of alcoholic hepatitis may include abdominal pain, fever, jaundice, and liver failure. The disease can progress to cirrhosis and even hepatocellular carcinoma. Histopathologically, it is characterized by liver cell death and infiltration of leukocytes into the hepatic parenchyma. Although many treatments are being used for the amelioration of alcoholic hepatitis, none of them are actually effective. To develop an effective treatment for this disease, it is important to understand the underlying mechanisms by which chronic alcohol ingestion triggers the development of the inflammatory disease process.

Alcohol is thought to render the intestinal wall more permeable to endotoxin. This results in increased amount of bacterial endotoxin in hepatic portal system, which activates Kupffer cells of the liver via the CD14 surface receptor ([1]). This activation initiates a cascade of events leading to generation of free radicals, activation of nuclear transcription factor-kB (NF-kB), increased transcription of inflammatory cytokines and chemokines, enhanced expression of adhesion molecules, and massive infiltration of inflammatory cells into the liver ([2],[3],[4],[5]). These changes are associated with the histopathological findings of fatty liver, necrosis, and inflammation of the liver. Despite this progress in our understanding of ALD, the mechanisms by which chronic ethanol consumption results in alcoholic hepatitis (AH) in humans are not clear.

Tumor necrosis factor (TNFα or TNF), a cytokine induced by endotoxins, bacteria and many other stimuli, covers an enormous range of actions as a mediator of inflammation, tissue damage, immunopathological reactions and host defense ([6]). Historically, TNF was considered to be a major pro-inflammatory cytokine inducing a wide range of other mediators of inflammation such as chemokines. However, studies on TNF deficient mice suggest an anti-inflammatory role involving its capacity to regulate macrophage IL-12 production ([7], [8]).

Although TNF is expressed as a cell membrane protein, it exerts preferentially its biological functions as a soluble protein. Thereby, TNF is cleaved from the transmembrane 26kd precursor into 17kd secreted monomers that subsequently form biological active trimers. The proteolitic cleavage of TNF is mediated by a cell membrane bound metalloprotease(s), the TNF converting enzyme (TACE or ADAM-17) ([9], [10], [11], [12], [13]). The activity of TACE can be efficiently blocked by specific inhibitors and treated mice were completely protected from endotoxic shock ([14], [15]). Hence, administration of TACE inhibitors has been proposed as a novel therapeutic treatment to modulate the deleterious effects of excessive TNF secretion in inflammatory disorders.

ities of the TNF molecule are transduced by two cell surface re expressed on the majority of cell types and tissues, 55 kDa Da TNFR2, which may have distinct roles ([16]). Lymphotoxin alpha TNF-β), a protein structurally and functionally related to TNF, NFR1 and TNFR2 and causes cytotoxicity and inflammation in a TNF ([17],[18]). These receptors also exist in a soluble form as the from the membranes, probably in acute inflammatory reactions, a believed to represent a form of transient protection against TNF re injury by neutralization of TNF.

FR1 is very effective at binding mouse TNF, and this property has te chimeric molecules (human TNFR-human FcIgG) which, when , prevent fatal liver injury induced by lipopolysaccharide (LPS)- D-galactosamine-(D-GalN)-sensitized animals ([19]). Furthermore, NF by soluble receptors (blocking both TNF and LTα) or anti-TNF oven to be the most efficacious treatment for several human ng rheumatoid arthritis, Crohn's disease, and ulcerative colitis ([20]). ment of septic shock patients with TNF inhibitors has yielded s ([21]): for example, while the sTNFR2 did not reduce mortality and oses actually appeared to be associated with increased mortality have shown reduced mortality rate, and decreased incidence and ailure with sTNFR1 ([23], [24], [25]). This suggests that TNF inhibition is ult in unexpected outcome depending on human pathologies.

hepatotoxity induced by different compounds including endotoxin -GalN-sensitized mice ([26]). TNF is also involved in AH by causing esions ([27]). In animal models of AH such as Tsukamoto and eatment of rats with anti-TNF antibodies significantly reduced ory hepatic lesions caused by ethanol administration ([28]). deficient in TNFR1 are protected from hepatotoxicity induced by e data suggest that the control of TNF expression in AH can be a utic approach.

a cytokine mediating liver toxicity in certain conditions and a r therapeutic strategies. In the LPS-D-GalN mouse liver injury n shown that administration of antibodies to IL-18 prevented liver evels of IL-18 in patients with acute hepatitis and fulminant hepatitis