2023 World Journal of Innovation and Modern Technology, Vol.6, Issue 6, (Dec)
ISSN 2682-5910
DOI: 10.53469/wjimt.2023.06(06).09

Recent Advances in the Study of Mechanisms of Alcoholic Liver Disease

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Abstract: ***Alcohol liver disease (ALD) is one of the major diseases caused by chronic alcohol consumption and a major global health problem, but the specific pathogenesis of ALD remains elusive and many obstacles remain to the prevention and treatment of ALD. This paper reviews recent international advances in studying ALD pathogenesis, such as alcohol metabolism, autophagy, immune response and hepatic stellate cell activation, aiming to explore new directions for ALD prevention and treatment.***

Keywords: ALD; The pathway of alcohol metabolism; Autophagy; Immune response; HSCs activation; Enterohepatic circulation.

1. INTRODUCTION

According to the World Health Organization, alcohol consumption is responsible for 3.3 million deaths annually, accounting for approximately 5.9% of all global deaths[1].The liver is the primary organ responsible for metabolising alcohol, and long-term heavy drinking can lead to alcoholic liver disease (ALD), which is a major contributor to liver-related morbidity and mortality, and has been identified as a significant risk factor for the development of hepatocellular carcinoma[2]. Approximately 3 million liver-related deaths are caused by ALD each year.ALD worsens over time and with increasing alcohol consumption, progressing from asymptomatic hepatic steatosis to fibrosis, cirrhosis and, in some cases, hepatocellular carcinoma. It is important to note that this disease is not caused by a single episode of heavy drinking, but by prolonged and excessive alcohol consumption[3].However, it is of great importance to study the mechanistic aspects of ALD because the mechanisms responsible for the pathogenesis of ALD and its complications remain unclear. This review summarises the newly discovered key mechanisms that cause the pathogenesis of ALD, aiming to provide meaningful insights for preventing and treating ALD and its complications.

2. PATHOGENESIS OF ALD

2.1 The pathway of alcohol metabolism

Hepatic mitochondrial metabolism is essential for the maintenance of normal liver function and is responsible for various metabolic processes such as glucose, fatty acid and amino acid metabolism[4].Liver mitochondrial dysfunction can lead to metabolic disorders and diseases, including hypoglycaemia, non-alcoholic fatty liver disease, alcoholic fatty liver disease and hyperammonemia[5].During the metabolism of alcohol, lactate dehydrogenase (ADH) produces significant amounts of reactive oxygen species (ROS) and acetaldehyde, both of which are by-products that are not only toxic to liver tissue, but also interfere with mitochondrial function[6,7].ROS can directly damage mitochondrial DNA, proteins and lipids, causing structural damage and increased oxidative stress, which can lead to release of mitochondrial proteins into the cytoplasm, triggering inflammation through damage-related molecular patterns[8]， Acetaldehyde can also interfere with mitochondrial function and metabolism and has been shown to induce phosphorylation of mitochondrial fission-associated proteins, which promotes mitochondrial fragmentation[9].Research has shown that acetaldehyde can have a significant effect on electron transport and oxidative phosphorylation in the respiratory chain by inhibiting the activity of mitochondrial complexes I and IV[10].

Ethanol oxidation still consumes NAD+ and produces NADH, but elevated NADH/NAD+ ratios inhibit fatty acid β-oxidation, with the unwanted consequence of hepatic triglyceride accumulation[11].Ethanol catabolism depletes choline, which impairs the synthesis of phosphatidylcholine, an essential nutrient and synthetic building block. This leads to a reduction in the level of phosphatidylcholine, which in turn leads to an accumulation of triglycerides in the liver.Previous studies have shown that ethanol exposure leads to acetylation and activation of

SREBP-1c and ChREBP, two potent transcriptional inducers that regulate adipogenesis, thus explaining how ethanol modifies adipogenesis at the transcriptional level[12,13].

Chronic alcohol consumption increases the expression and activity of certain cytochrome enzyme families, in particular CYP2E1, which plays a crucial role in the oxidation of ethanol to acetaldehyde and in the metabolism of ethanol. This process generates excess reactive oxygen species (ROS), even in the absence of a substrate, leading to cellular damage, particularly in hepatocytes.

2.2 Autophagy

Liver autophagy plays a complex and important role in ALD. Autophagy and membrane trafficking share common components and interact with each other to repair cell damage and promote cell survival[14].Progression of ALD is associated with cell damage and death caused by dysregulation or overactivation of autophagy and membrane trafficking[14,15]. Acute and chronic ethanol exposure models impair transcription factor EB (TFEB)-mediated lysosomal biogenesis by activating mTORC1, resulting in defective autophagy[15].In addition, it has been shown that the production of exosomes in ALD is associated with autophagy and lysosomal dysfunction[16].

2.3 Immune response

Kupffer cells, which are liver macrophages, play a crucial role in initiating and resolving innate immune responses and inflammation against infections. Alcohol has complex and bidirectional effects on macrophage function. Alcohol impairs the ability of macrophages to engulf and destroy pathogens by directly reducing phagocytosis[17]. In addition, alcohol reduces the production of cytokines such as IL-17 and TNF-α, which are essential for macrophage activation and function[18].Furthermore, extracellular vesicles containing CD40L extracted from ethanol-injured hepatocytes in a caspase-dependent manner have been reported to induce macrophage activation, thereby exacerbating inflammation in situ[19].

Natural killer (NK) cells are responsible for the killing of cells infected by pathogens and the surveillance of malignant cells that are proliferating out of control. Alcohol and its major metabolites have been shown to directly inhibit the cytotoxicity of NK cells. This impairs their ability to kill infected or transformed cells. Furthermore, ethanol exposure induces transcriptional perturbations leading to decreased transcription and secretion of pro-NK cytokines, as well as inhibiting signalling pathways associated with NK cell activation and proliferation. As a result, the overall NK cell response is impaired40,41.Alcohol has been reported to stimulate the production of prostaglandin E2 (PGE2) by hepatic stellate cells (HSCs), which is an inhibitor of natural killer (NK) cell cytotoxicity and cytokine production[20].

T lymphocytes, consisting of multiple subpopulations with complex functions under pathological conditions in the liver, are the fundamental cell type of the adaptive immune system. Alcohol can interfere with T-cell function through a variety of mechanisms, with the result being immune dysfunction and impaired hepatic immune surveillance. In addition to direct toxicity, it affects T cell receptor signalling and cytokine production. Alcohol has been reported to inhibit the phosphorylation of key signalling molecules for TCR activation, ZAP-70 and LAT, and to interfere with T cell-mediated immune responses44.In addition, after alcohol consumption, increased acetaldehyde and glucocorticoids regulate glucose metabolism. This promotes the development of hepatitis by inhibiting T cell glucose metabolism.

2.4 HSCs activation

HSCs are the primary extracellular matrix (ECM) producing cells during fibre formation[21].Hepatic stellate cells secrete laminin, proteoglycans and IV collagen to form basement membranes and remain quiescent until activated. The activation of hepatic stellate cells is a key component in the development of hepatic fibrosis and cirrhosis. When activated, they play a crucial role in the reconstitution of the hepatic lobules by producing large amounts of extracellular matrix proteins, such as collagen. Alcohol metabolism disrupts the balance between hepatic extracellular matrix synthesis and degradation, leading to liver injury and stellate cell activation, resulting in the excessive accumulation of extracellular matrix proteins that characterise hepatic fibrosis, a severe condition that distorts liver structure and impairs liver function. Studies have shown that alcohol metabolism induces miR-155 expression. This promotes stellate cell activation and liver fibrosis[22].Prolonged fibrosis of the liver results in the accumulation of extracellular matrix (ECM) proteins and leads to the replacement of functional liver parenchyma with non-functional scar tissue. Hepatic stellate cells, when activated and proliferating, increase the amount of

alpha-smooth actin and up-regulate the synthesis of type I and type III collagen and ECM proteins such as fibronectin[23].

2.5 Enterohepatic circulation

The gut-liver axis is central to the understanding of the pathogenesis of ALD. Alcohol consumption affects several aspects of intestinal physiology. These include increased intestinal permeability and changes in microbial composition and metabolism[24].The epithelial barrier has additional defences, including a thick mucus layer composed mainly of mucin (Muc) produced by cup cells 2 and secreting various antimicrobial peptides (AMPs). In ALD, the intestinal barrier is severely compromised and the liver is the first organ exposed to microbial constituents and metabolites of intestinal origin.As ethanol is consumed, intestinal permeability increases[25], allowing PAMPs (such as LPS) to enter the liver through the portal vein. This is a prerequisite for the development of ALD in mouse models[26].Increased permeability facilitates migration of microorganisms and microbial components into circulation. For example, ethanol increases the level of Muc2 in patients with ALD, and Muc2 deficiency protects mice from chronic ethanol-induced injury. Conversely, chronic ethanol reduces the expression of the c-type lectin AMPs Reg3β and Reg3γ, and overexpression of Reg3γ protects cells from injury[27].

Current evidence suggests that altered gut physiology contributes to the progression of ALD, in addition to the direct effects of alcohol on the liver[28].The progression of ALD may be influenced by changes in the flora of the gut61.Research has demonstrated that alcohol consumption leads to an increase in the production of bacterial LPS and is associated with liver damage.The severity of alcoholic hepatitis correlated with increased abundance of potentially pathogenic families, including Enterobacteriaceae and Streptococcaceae, in a translational analysis of patients with alcoholic hepatitis.Alcohol consumption is associated with a significant reduction in fungal and bacterial diversity, with commensal fungi reduced when Candida species become overgrown[29].Similarly, the abundance of beneficial bacteria, such as Ruminococcaceae, Faecalibacterium, and Prevotella, decreased, while the abundance of Gram-negative bacteria, such as Aspergillus, Enterobacteriaceae, and E. coli, increased. The beneficial bacteria produce short-chain fatty acids, which are known to maintain and improve intestinal health[24].Dysbiotic stress can cause certain bacteria to produce virulence factors. For instance, Enterococcus faecalis produces lysins that directly affect hepatocyte survival. In patients with ALD, there was no overall increase in E. faecalis. However, the presence of lysins was highly correlated with disease severity[30].

3. SUMMARY AND FUTURE PERSPECTIVES

The pathology of alcohol-related liver disease (ALD) is multifaceted. It involves the direct effects of ethanol and its metabolites on the liver, as well as alterations in metabolic homeostasis, oxidative stress and inflammation. Our understanding of the pathogenesis of ALD has been greatly enhanced by current research. Future studies are needed in appropriate cell and animal models and in humans to find new targets to prevent and treat ALDs.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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