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Complements are involved in alcoholic fatty liver disease, hepatitis and fibrosis

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Abstract

The complement system is a key component of the body's immune system. When abnormally activated, this system can induce inflammation and damage to normal tissues and participate in the development and progression of a variety of diseases. In the past, many scholars believed that alcoholic liver disease (ALD) is induced by the stress of ethanol on liver cells, including oxidative stress and dysfunction of mitochondria and protease bodies, causing hepatocyte injury and apoptosis. Recent studies have shown that complement activation is also involved in the genesis and development of ALD. This review focuses on the roles of complement activation in ALD and of therapeutic intervention in complement-activation pathways. We intend to provide new ideas on the diagnosis and treatment of ALD.

Key words: Alcoholic liver disease; Complement system proteins; Complement regulator; Liver cells; Hepatocyte injury

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Core tip: In this review, we cited evidence that the complement system is involved in the pathogenesis of each stage of alcoholic liver disease (ALD) that include fatty liver, alcoholic hepatitis, and fibrosis/cirrhosis, and we also summarized the complement regulation in ALD. We intend to provide new ideas on the treatment of ALD.

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INTRODUCTION

Liver disease caused by long-term excessive ethanol drinking is a major cause of chronic liver disease. As the global incidence of alcoholic liver disease (ALD) increases year by year, it has become a serious threat to human health. Almost all heavy drinkers have fatty liver, 10%-20% of which develop into alcoholic hepatitis, cirrhosis, and even hepatocellular carcinoma^[1]. Exploration of the mechanisms of alcohol-induced liver injury and repair is extremely important in developing methods for preventing and treating ALD.

The complement system plays an important beneficial role in the immune system: Complement activation promotes target-cell lysis, with the associated elimination of exogenous pathogens. Yet, the complement system is a "double-edged sword", as the excessive activation of complement can induce inflammation and lead to autoimmune diseases, such as autoimmune kidney disease, glomerular nephritis, acute lung injury, and others^[2-5]. Most plasma complement components are synthesized in liver cells. Thus, the liver becomes the main target of damage by complement activation^[6-8]. This connection is likely due to the direct effects of alcohol that activate complement, but not because the liver is a major producer of complement proteins. Several studies have illustrated that complement activation is involved in the development of ALD^[8-14] (Table 1).

METABOLIC PATHWAYS OF ETHANOL

Most ingested ethanol is absorbed into the blood circulation, and soon reaches each organ of the body. About 90% of the ingested ethanol is metabolized in the liver^[15], and most is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase to form acetic acid, which can be used as substrate in the tricarboxylic acid cycle to produce energy. With excessive drinking, the body can activate another metabolic pathway, *i.e.*, the microsomal ethanol oxidation system (MEOS), which catalyzes ethanol mainly by cytochrome P450 2E1 in Kupffer cells. The MEOS can over produce reactive oxygen species and reactive nitrogen species, which may exceed the body's antioxidant capacity. Free radicals produced *via* the MEOS pathway exert a series of toxic effects: Membrane-lipid peroxidation, intracellular protease degeneration, oxidative modification of DNA, and others, which eventually lead to necrosis or apoptosis of hepatocytes^[14,16-18]. A small percentage of ethanol is metabolized by fatty acid ethyl ester synthase to produce fatty acid ethyl ester through the non-oxidative pathway.

Fatty acid ethyl ester has cytotoxicity, which can further injure the liver and pancreas^[19]. Thus the liver becomes the main organ damaged by ethanol. Chronic ethanol exposure results in decreased protease activity in liver cells, imbalance of the liver's detoxification function, and overproduction of acetaldehyde, thus inducing hepatic oxidative stress and complement activation; all these activities can injure hepatocytes^[20].

COMPLEMENT ACTIVATION PATHWAY

The complement system consists of more than 30 kinds of proteins with enzyme-like activities which are inherent components, regulatory proteins, and complement receptors. Complement regulatory proteins include plasma soluble factors, membrane binding proteins, homologous restriction factor, and membrane inhibitors of reactive lysis. Because the complement system is involved in inflammation and immune regulation, it plays an important role in regulation of pathophysiological functions^[21].

Complement is activated by three pathways: The classical, mannan-binding lectin (MBL), and alternative pathways. The three pathways start with different mechanisms, but they end with a common terminal pathway, as shown in Figure 1. The classical pathway is the main mechanism of immune responses. In it, C1q identifies immune complexes, followed by the activation of C1r and C1s. Activated C1s cleaves C2 and C4 to form C3 convertase (C4bC2a), which cleaves C3 to form C5 convertase (C4bC2aC3b). In contrast to activation of the classical pathway, activation of the lectin pathway does not depend on immune complexes. In this pathway, the cascade of enzymatic reactions proceeds in this sequence: MBL identifies the pathogens to form MBL-associated serine proteases (MASP1, MASP2); MASP1 directly cleaves C3 to form C3 convertase (C3bBb), MASP2 cleaves C4 and C2 in a manner similar to that of C1s, forming C3 convertase (C4bC2a), which continues to cleave C5 to form C5 convertase (C4bC2aC3b). Thus, this pathway can cross-promote the classical and alternative pathways. The alternative pathway is activated with hydrolysis of C3 into C3(H₂O), factor B and factor D, the activation of which is also independent of immune complexes, and participates in the defense mechanisms of the early stage of inflammation^[13,22-24]. The above three pathways merge into the terminal pathway, in which C5 convertase cleaves C5 to form C5a and C5b, and C5b combines with C6, C7, C8 and C9 to form the membrane attack complex (MAC). Formation of the MAC leads to cell lysis and induces cells to release inflammatory cytokines.

COMPLEMENT ACTIVATION IN ALD

ALD progresses in three distinct stages: Fatty liver, alcoholic hepatitis, and fibrosis/cirrhosis. In this review, we cite evidence that the complement system is involved

Table 1 Important publications on complement in alcoholic liver disease

Study	Complement component	Alcoholic liver disease	Species
Järveläinen <i>et al</i> ^[10]	C1, Crry, CD59	Alcohol-induced injury	Rat
Bykov <i>et al</i> ^[11]	C3	Liver steatosis	Mouse
Pritchard <i>et al</i> ^[8]	C3, C5, DAF	Fatty liver	Mouse
He <i>et al</i> ^[7]	C3	Liver steatosis	Mouse
Cohen <i>et al</i> ^[13]	C1q	Alcohol-induced injury	Mouse
Wlazlo <i>et al</i> ^[27]	C3	Liver steatosis	Human
Shen <i>et al</i> ^[6]	C3	Alcoholic hepatitis	Mouse
Maslowska <i>et al</i> ^[30]	Factor D	Alcoholic hepatitis	Mouse

Crry: Complement receptor 1-related protein y; DAF: Decay accelerating factor.

in the pathogenesis of each of these stages.

Complement activation in alcoholic fatty liver disease

The liver is the main site of fat metabolism. Disorders of fat metabolism, caused by various factors, can lead to excessive fat accumulation in the liver cells, *i.e.*, fatty liver. Long-term heavy drinking is the main independent risk factor of fatty liver disease^[25], but its pathogenesis is not clearly defined. Liu *et al*^[26] found that gut microbiota played a synergistic role in the liver response, and the complement system was suppressed in fatty liver which was partially due to increased blood lactic acid from enriched *Lactobacillus*. Abnormal complement activation reportedly enhances the sensitivity of steatotic livers to ischemia and reperfusion injury, which leads to the development of fatty liver^[27,28]. Järveläinen *et al*^[10] found that deposition of complement C1, C3, and C8 was increased, and the expression of membrane-binding proteins, complement receptor 1-related protein y (Crry), and CD59 was decreased in the liver cells of a mouse ALD model. These findings proved that alcohol-induced complement activation can result in ALD, at least in an experimental model. In a study in mice chronically exposed to ethanol, Cohen *et al*^[13] found that lipid deposition in liver cells as well as values of liver-related serum enzymes (alanine aminotransferase and aspartate amino transferase) increased significantly; various degrees of liver cell apoptosis were also found. Moreover, with knock out of the C1q gene, hepatic steatosis in the mice was significantly decreased^[13]. This study illustrated that complement activation could be associated with ethanol-induced hepatic steatosis.

Bykov *et al*^[11] fed C3+/+ and C3-/- mice a high fat and high alcohol diet, respectively, and found that hepatic steatosis and significant increases in triglyceride values occurred in the C3+/+mice, whereas C3-/-mice were protected from ethanol-induced liver injury; research by Stewart *et al*^[9] yielded similar results.

At the complement activation pathways, C3a converted to C3adesAg, C3adesArg which known as acylation stimulating protein had been shown to have lipogenic activity *via* its receptor C5L2, and promoted

triglyceride storage in adipocytes^[29,30] It was also found that C3adesArg was involved in the triglyceride metabolism^[31].

Thus, activation of complement C1 and C3 appears to play a significant role in promoting fatty accumulation in the liver. Further definition of the relationship between activated complement C1, C3 and lipid metabolism in the liver may aid in the development of methods for intervention and treatment of alcoholic fatty liver disease. Besides C1 and C3, complement C5 also is involved in lipid metabolism. Bavia *et al*^[32,33] found that the activation of complement C5 by high-dose ethanol exposure can affect the distribution of lipid in liver cells and serum. Less lipid and cholesterol is deposited in hepatocytes of C5- mice than in hepatocytes of C5+mice, and values of IL-17, which are involved in the synthesis and metabolism of lipid and cholesterol, are higher in C5-mice than in C5+mice^[34,35]. The above-cited reports indicate that activation of C5 may play a role in the development of alcoholic fatty liver.

Complement activation in alcoholic hepatitis

ALD has many potential pathogenic factors, such as endotoxin, which may lead to complement activation and deposition in the liver cells. Shen *et al*^[6] found that complement activation was involved in humans with ALD. Cohen *et al*^[13] found that long-term alcohol exposure can lead to apoptosis of liver cells, and the degree of apoptosis is positively correlated with liver injury. However, whether short-term alcohol exposure can cause hepatocyte apoptosis was not known. Further research found that short-term alcohol exposure did not cause hepatocyte apoptosis, but it did promote the deposition of complement C3b and the expression of inflammatory cytokines (tumor necrosis factor and IL6). After the Cq gene was knocked out, the expression of inflammatory cytokines was significantly reduced compared to that in wild-type animals^[12,13]. Experiments by Païdassi *et al*^[36] and Lu *et al*^[37] supported these observations.

Complement C5, a core component of the complement activation pathway, is involved in the occurrence and development of alcoholic hepatitis, in addition to fatty liver^[6,8,38]. Bavia *et al*^[38] documented this in a hepatitis model induced by alcohol; they found that values of pro-inflammatory cytokines (IL-6, IFN- γ , IL-1 β , and others) in B6C5+ mice were significantly higher than those in B6C5- mice, and anti-inflammatory factors (IL10 and IL17) were secreted significantly more in B6C5- mice. These findings illustrated that activated C5 induced the expression of proinflammatory cytokines after alcohol exposure. Up-regulated expression of pro-inflammatory cytokines (IL-6, IFN- γ , IL-1 β , and others) aids the body's defense against pathogenic microorganisms, but it also participates in the pathogenesis of alcoholic fatty liver and alcoholic hepatitis^[8,39-41].

Complement activation in alcoholic hepatic fibrosis

Intrahepatic inflammatory reaction and a decrease

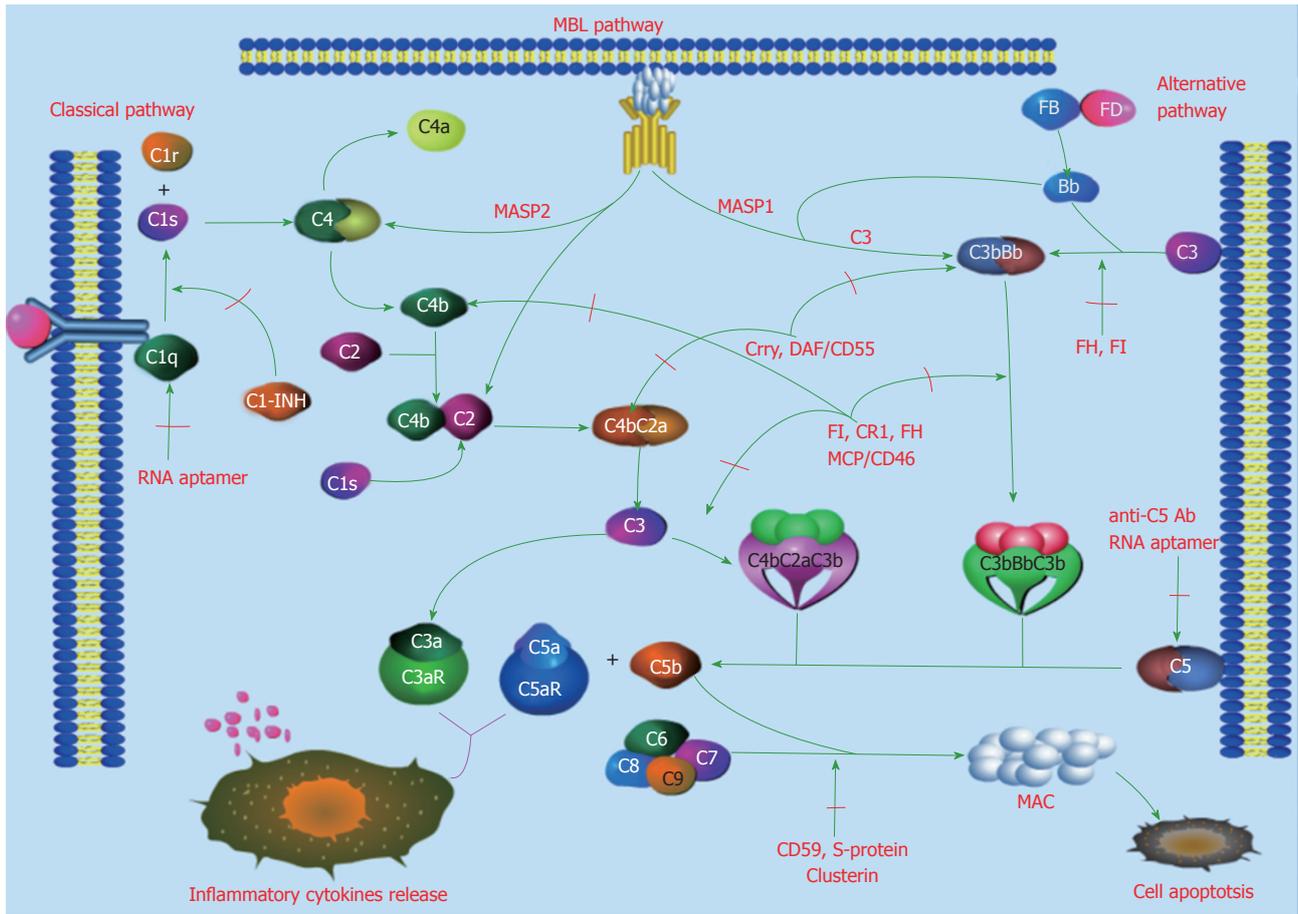


Figure 1 Complement activation pathway and regulation. Three pathways (classical, pathway, mannan-binding lectin, and alternative) are involved in complement activation. Green arrows without a red line indicate the process of complement activation. Green arrows with red line indicate the the process of inhibiting complement activation. MBL: Mannan-binding lectin; MASP: MBL-associated proteases; FB: Factor B; FH: Factor H; FI: Factor I.

in structural integrity of hepatic sinusoidal endothelial cells after long-term alcohol exposure are important inducements to liver injury. Sinusoidal endothelial cells express C5R1, which is the foundation of C5 activation-induced alcoholic hepatic fibrosis^[42]. In recent years, the pathogenesis of alcoholic hepatic fibrosis has attracted worldwide attention, but the cause of the fibrosis is still not fully defined^[43-45]. According to published reports^[46,47], complement C3, C4 and activation of the MBL pathway are involved in the development of fibrosis. Bavia *et al*^[38] using the mouse model of ALD, found that values of TGF-β, which promotes hepatic fibrosis, were significantly higher in B6C5+ mice than in B6C5- mice^[38,48]. Hillebradt *et al*^[49] found that the C5 gene was involved in the regulation of hepatic fibrosis on human chromosome, and further study found that C5- mice had decreased hepatic fibrosis. Thus, the evidence indicates that activation of complement C5 may promote hepatic fibrosis. Exploration of the relationship between complement activation and alcoholic hepatic fibrosis, and of possible intervention in ALD by reversing the progression of hepatic fibrosis in its early stage, seems worthwhile goals.

Complement-induced Kupffer cells activation in ALD
Kupffer cells, located in liver sinusoids, are an important

part of the mononuclear phagocyte system. Alcohol exposure in the early stage can promote apoptosis of Kupffer cells, but longer exposure usually is needed^[13,50,51]. Ethanol-induced activation of complement component C1q at the early stage of ALD promotes the release of inflammatory cytokines from Kupffer cells, which further promote alcoholic liver injury^[51-56]. Furthermore, Kupffer cells can express C3R and C5R, then induce prostaglandin release and synthesis of pro-inflammatory cytokines^[57-60]. However, in certain pathological conditions, activated C5 combines with C5R, inducing the upregulation of fibrinogen on Kupffer cells, an interaction that is believed to lead to hepatic fibrosis^[22,61]. In addition, alcohol-induced upregulation of CD14 leads to Kupffer cells combining with lipopolysaccharide, which induces liver damage through the activation of TLR4 in Kupffer cells and inflammatory signaling pathways; these events can further aid in the development of hepatic fibrosis or cirrhosis^[62]. Thus, Kupffer cells seem to be extensively involved in the development of ALD^[63-66].

COMPLEMENT REGULATION IN ALD

Reducing inflammatory reactions by inhibiting amplification of the complement cascade and blocking the

Table 2 Complement regulators

Type of regulators	Regulators	Functions
Complement regulatory protein	DAF/CD55, Crry, FH, FI CD59, protein S, clusterin	Inhibit C3, C5 convertase Inhibit MAC
Complement inhibitor	C1-INH	Inhibit C1r, C1s
Targeted inhibitor	h5G1, 1-ScFv	Inhibit C5 activation
RNA aptamer		Specifically bind C1q, C5

DAF: Decay accelerating factor; Crry: Complement receptor 1-related protein y; FH: Factor H; FI: Factor I; MAC: Membrane attack complex.

combination of complement with the corresponding complement receptors are being pursued worldwide. Excessive activation of complement can be inhibited by self-regulation of the body (Table 2). For example, the complement regulatory protein decay accelerating factor (DAF) can inhibit C3, C5 convertase, thereby inhibiting amplification of the complement cascade. The complement regulatory protein Crry can cooperate with DAF and factor H to accelerate dissociation of C3 and C5 convertase and to cleave C3b and C4b, so that the cells avoid being attacked by autologous complement^[67-69]. Deficiency of CD55/DAF and complement regulatory factors aggravate liver injury^[8,11], whereas factor H can control the activity and stability of C3 convertase *via* binding with C3b^[70,71]. Also, defects in the factor H gene can cause persistent activation of complement pathways and trigger various diseases^[72-75]. By contrast, factor H-related proteins (FHRs), including FHR1-5, can either promote or inhibit complement activation. The degree of complement activation depends on the homeostasis between factor H and FHR^[71]. However, the relationship between factor H and ALD has not been clarified and needs further research. McCullough *et al.*^[76] found FD-dependent amplification of complement is an adaptive response that promotes hepatic healing and recovery in response to chronic ethanol. In other complement regulatory activities, CD59, protein S and clusterin inhibit the formation of the MAC through limiting the binding of complement C9^[77-81]. Membrane cofactor protein (MCP) and factor I can inhibit cells from binding with C3b and C4b^[82,83].

Specific epitope structures of complement, such as anti-complement antibody, complement antisense strand, and complement mutants^[84-91] have been invented, with the intent of inhibiting complement activation. In addition, complement inhibitors and RNA aptamer are being used to inhibit progression of complement-related diseases^[92,93], and C1-INH and CR1 have been used in the treatment of ALD and other diseases^[10].

CONCLUSION

Mounting evidence indicates that complement activation is involved in the development of ALD at all its stages - fatty liver, alcoholic hepatitis, and fibrosis/cirrhosis. Moreover, all three pathways of complement activation (classical, MBL, and alternative) promote

the development of ALD. Therapeutic strategies, using various measures to inhibit complement activation, might prevent the development of ALD. Thorough understanding of the relationships between complement activation and ALD may aid in developing new approaches for the treatment of ALD.

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