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Roles of and Interventions for the Complement System in Liver Regeneration

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ABSTRACT

Complement system, consisting of more than 50 proteins present in blood or anchored on the surfaces of cells, is activated by classical, lectin, or alternative pathways. All three pathways finally lead to the formation of a membrane attack complex (MAC), resulting in cell lysis. Current studies suggest that complement is involved in liver regeneration, and targeting the complement cascade modulates liver regeneration. In this mini-review, we discuss the role of complement system and the therapeutic potential of its interventions in liver regeneration.

Keywords: Complement, liver regeneration, complements inhibitor.

Abbreviations: MBL: Mannose Binding Lectin; MAC: Membrane Attack Complex; MCP: Membrane Cofactor Protein; DAF: Decay Acceleration Factor; CR1: Complement Receptor 1; HDL: High-Density Lipoprotein; LXR: Liver X Receptor; LPS: Lipopolysaccharides; TLR: Toll-Like Receptor; IRI: Ischemia/Reperfusion Injury; C1-INH: C1-Esterase Inhibitor; CR2: Complement Receptor 2; Crry: Complement Receptor 1-Related Protein Y.

INTRODUCTION

Complement (C) system consists of more than 50 proteins present in blood or anchored on the surfaces of cells. The primary functions of the complementary system are to participate in host defense machinery to regulate immunological and inflammatory processes [1,2]. In addition, complement is now known to be involved in lipid metabolism, tumorigenesis, stem cell biology, tissue regeneration and homeostasis [3-5].

The liver, aside from its role in digestion, is critical to protein synthesis, detoxification of metabolites, and processing of nutrients. Hepatic blood supply is unique, having hepatic arteries and portal veins, which increases the liver's vulnerability to toxins, toxicants, metabolic products, and circulatory insults. Fortunately, the liver can regenerate without interventions, and viral or toxic injuries or partial hepatectomy can stimulate liver regeneration [6]. Data show that complement is involved in hepatic regeneration, and in this mini-review, we describe the action and intervention of complement in the process of liver regeneration.

The Components and Regulation of Complement System

The complement system is a network of interacting cell surface-bound and circulating proteins and as many as 50 molecules are involved in the complement cascade [7]. Signaling from the classical, lectin, or alternative pathways can activate the complement system [8-10], but each of these three complement pathways differs with respect to the initial target recognition even though they all activate component C3. The activated surface binding of the C1 complex (C1q, C1r, C1s) to antibody or to C-reactive protein initiates the

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classical pathway to form C4bC2a (the classical C3 convertase) from C4 and C2, which subsequently cleaves C3. Similar to the classical pathway, the lectin pathway is activated by collagen-containing C-type lectins (collectins) such as mannose binding lectin (MBL). The alternative pathway is different: after C3 is hydrolyzed spontaneously or C3b is deposited by the above-mentioned two pathways, C3b directly binds to microbial surfaces and begins activating the alternative pathway. Once factor B is cleaved, C3b can bind it to form C3bBb, the alternative C3 convertase. Enzyme complexes C4bC2a or C3bBb must be formed in all three complement pathways, and they cleave C3 to form C3a and C3b. Subsequently C5 is cleaved to produce C5a and C5b. Finally, the terminal pathway is initiated by C5b to form MAC, creating a pore in the cell membrane and causing cell lysis [11,12].

Complement activation generates many potent pro-inflammatory mediators like C3a, C4a and C5a or anaphylatoxins such as C3a and C5a [13]. When responding to anaphylatoxins, phagocytic cells can increase C3b, iC3b and C3d, which are recognized by cell surface receptors [14]. To prevent autologous complement-mediated injury *in vivo*, the complement system is precisely controlled by regulating factors that target convertase which is critical to the complement activating cascade. For example, factor H is a serum protein regulating the alternative pathway; the C4b binding protein regulates the classical and lectin pathways; and some proteins can bind to the membrane, such as decay acceleration factor (DAF), membrane cofactor protein (MCP), and complement receptor 1 (CR1), which also predominately affects convertase [15,16]. In addition, when C5b678 deposition induced by complement activation appeared on host cells, cell-bound CD59 could bind C9 and inhibit MAC formation [17].

Complement is Required for Liver Regeneration

Hepatic regeneration is initiated after liver damage or resection [6] and this is governed by hormones, growth factors, and immune mediators. During acute liver injury, the innate immune system coordinates regeneration [18] and complement is essential for these early events. After the initiation of regeneration, C3 is activated and C3-cleaved products appear in the blood just 2h after carbon tetrachloride (CCL_4) injection. Deposition of C3a peaks within 3h [19]. Poor hepatic regeneration was observed in C3-deficient or C3aR-deficient mice treated with CCL_4. For C3-/- mice, C3a reconstitution restored liver regeneration, but C3aR-/- mice did not receive this benefit. The authors postulated a priming effect of C3a via C3aR in liver regeneration [19].

A recent study proposed a mechanistic relationship between the activation of C3, acute-phase proteins and cholesterol metabolism during the priming phase of liver regeneration [20]. Complement activation increases complement effector proteins, C3a and C5a, which not only are central to complement-mediated inflammation [21,22], but also bind to the nearby Kupffer cells to release TNF-α [23], which subsequently binds to receptors on hepatocytes to initiate the MAPK pathway and its downstream immediate early genes. This leads to activation of acute-phase proteins that can replace lipoprotein in high-density lipoprotein (HDL) to form acute-phase HDL. Acute phase HDL promotes lower cholesterol efflux more than native HDL, which causes hepatocytes to respond by activating liver X receptor (LXR) through oxysterols to reduce cholesterol biosynthesis and stabilizing cholesterol. Reduced cholesterol biosynthesis allows hepatocytes to use cellular resources to meet other metabolic demands required for prolonged proliferation during liver regeneration [20]. C3 is needed for normal liver regeneration but how C3 activation participates in this process is unclear [24].When C4-dependent complement pathway (classical and lectin cascades), factor B dependent complement pathway (alternative signaling), or all three were disturbed, liver regeneration was not impaired. *In vitro* analysis confirmed that plasmin might be essential to complement activation [24]. A similar deterioration in hepatic regenerative response appeared in C5-deficient mice treated with CCL_4. Compared to wild-type mice, C5-deficient mice had more serious hepatic necrosis, apoptosis, and more lipids after CCL_4 injection. C5-deficient mice treated with murine C5 or C5a had less injury than wild-type mice after CCL_4 injection and regenerative responses were restored [25]. The authors Mastellos D et al. confirmed that hepatic regeneration was abated in wild type mice when C5aR was blocked with an antagonist, suggesting that the interaction between C5a and C5aR was implicated in stimulating liver regeneration [25].

Another report revealed that C5a receptors were present on regenerating hepatocytes and C5a receptor expression was increased after liver resection. C5a/C5aR interaction up-regulated hepatocyte growth factor (HGF) and the HGF receptor c-MET mRNA [26], which are involved in mitosis and hepatic regeneration [6]. C3 and C5 are individually needed for liver regeneration and together they may have a synergistic effect on hepatocyte proliferation. More severe hepatic injury was observed in double-deficient C3 and C5 mice compared to single-deficient C3 or C5 mice [27]. The importance of C3a and C5a in liver regeneration has been confirmed with single (C3 or C5) or double (C3 and C5) restoration in double-deficient C3 and C5 mice after hepatectomy. Hepatic regenerative ability was partly but not completely restored after a single treatment of C3a or C5a; but when C3a and C5a were both reconstituted, liver regeneration in C3/C5-/- mice were rescued [27]. Several studies confirmed that C3a and C5a are involved in early signaling and the transcriptional network of hepatocyte proliferation mediated by Kupffer cells [28-30]. Binding of C3a or C5a to their individual receptors located on Kupffer

cell surfaces, Toll-like receptor 4 (TLR4) signaling stimulate Kupffer cells to release TNF-α and IL-6, as well as activate NF-κB and STAT3 signaling in hepatocytes. This induces immediate-early genes involved in hepatocyte regeneration [31-33].

Targeting Complement Cascade Could Regulate Liver Regeneration

Complement is necessary for normal liver regeneration. Rat liver ischemia and reperfusion injury (IRI) experiments indicate that controlling complement activation with CR1 reduces liver injury [34-36]; however, products and MAC from complement activation have detrimental effects on liver tissues and cause neutrophil accumulation, microvascular dysfunction and cell death [37,38]. A damaged liver's regenerative ability and hepatic dysfunction is related to the degree of IRI and there may be a balance between liver injury and regeneration, all of which are mediated by the complement signaling pathway.

Several studies confirmed that liver regeneration could be ameliorated with complement inhibitors. For example, the protease inhibitor, C1-esterase inhibitor (C1-INH), is a serpin superfamily member that can inhibit the classical and lectin complement pathways and the purpose of this is to activate complement spontaneously [39-41]. Administration of C1-INH (human) can promote liver regeneration in mice, and 400 IU/kg is the most effective dose that causes the least elevation of hepatic function enzymes and IL-6 and offers best histology scores. Even so, there was no apparent dose-dependent effect of C1-INH on liver regeneration [42].

Similar results were found with another complement inhibitor, CR2-Crry (complement receptor 2 (CR2)-complement receptor 1-related protein y (Crry)) [43]. CR2 is a C3 binding protein family member and matured B cells and follicular dendritic cells express CR2 [44]. iC3b, C3dg, C3d, and cell-bound products cleaved from C3 are present at complement activating sites and are natural ligands targeting the CR2 moiety [45]. As a structural and functional orthologue of human soluble CR1, soluble Crry is a murine protein that inhibits the activation of C3. The effect and characteristics of CR2-Crry were first tested in a mouse intestine IRI model, and tissue localization of CR2-Crry was at the activating sites of complement. CR2-Crry was more effective in complement inhibition compared to Crry-Ig, which is used as a counterpart systemically [46]. In a complicated model combined with IRI and hepatectomy, CR2-Crry at a lower dose could prevent liver damage and enhance liver proliferation and this involved IL-6, STAT3, and Akt signaling. However, CR2-Crry at higher doses or C3 knock out resulted in steatosis, liver injury, and more death [43]; thus, complement must be balanced for liver health.

MAC is the last step of complement activation. CD59 is a MAC inhibitor, and soluble CD59 is a poor inhibitor but can function effectively if positioned where complement was activated and MAC was formed [47]. The fusion protein of CR2-CD59 is a mouse-specific inhibitor targeting MAC production, which is the terminal signaling event in the activated complement system. However, unlike CR2-Crry, CR2-CD59 is a specific inhibitor targeting cells opsonized by C3 and reduces MAC production. It has no or little effect on C3 activation, so CR2-CD59 is more specific to the complement system [48], it does not affect C3a and C5a production, which are essential for liver regeneration. Furthermore, CR2-CD59 significantly reduces hepatic IRI and enhances liver regeneration by multiple mechanisms that involve elevation of TNF and IL-6, activation of STAT3 and AKT signaling pathways, blockade of mitochondrial depolarization, and restoration of ATP [48].

CONCLUSION

Complement is involved in inflammatory injury and regenerative response, excessive activation of complement aggravates hepatic IRI and deteriorates hepatic regeneration. Inhibitors used in the complement system may be clinically beneficial for augmenting liver regeneration by modulating excessive of complement activation and may represent a promising targeted strategy for balancing hepatic inflammatory responses and cellular regeneration.

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