cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Complement in Acute Liver Failure: The Right Timing to Give a Sincere Compliment

The complement system is a system of plasma proteins that are part of the innate immune response and hereby responsible for the regulation of inflammatory processes.[1] It comprises 9 glycoproteins (C1-C9) that are synthesized in the liver and circulate throughout the blood. The complement component C5 is a small anaphylatoxin that is cleaved into C5a and C5b on activation. C5a can bind to 2 different receptors on the cell surface (ie, C5aR and C5L2). The activation and function of the complement system have been shown to be relevant for many human diseases including blood disorders, such as paroxysmal nocturnal hemoglobinuria, and renal and hepatic diseases.

Hepatic fibrosis is the common consequence of all chronic liver diseases that induce inflammation and tissue injury. When inflammatory cells enter the liver, a wound healing process and the deposition of extracellular matrix proteins are initiated, leading to the repair of liver tissue but also the formation of fibrotic scars. The fact that the complement system is involved in liver diseases has been known for decades.[2] In 2005 Hillebrandt et al.[3] identified the gene encoding complement factor C5 (*Hc*) as a fibrosis susceptibility gene in genetic analyses of experimental crosses of inbred mouse lines, with C5-deficient mice being more fibrosis-resistant than mice with a functional *Hc* gene.[3] They also showed that high serum levels of C5 were associated with *C5* risk genotypes in humans. C5 receptors are expressed in different cells of the liver, in particular Kupffer cells and activated myofibroblasts, linking C5 function to inflammation and fibrogenesis.[4] Besides its role in hepatic fibrosis, the complement system is also involved in other liver diseases, such as alcohol-associated liver disease, where it contributes to pathogenesis across the whole disease spectrum from fatty liver disease to acute alcoholic hepatitis and alcoholic cirrhosis.[5] There is also a link between complement activation and autoimmune hepatitis, indicating an important functional role of the complement system not only in toxic but also in immune-mediated and systemic diseases.[6]

In the present study Kusakabe et al.[7] investigated the potential therapeutic role of C5 inhibition on acute liver failure in a distinct preclinical murine model. Acute liver failure represents a life-threatening pathologic condition with no treatment options for severe cases other than liver transplantation, and to date the role of the complement system in acute liver failure has not been defined. Kusakabe et al[7] induced acute liver failure in wild-type and C5-deficient mice, and as treatment option the authors also used an anti-C5 antibody. C5-deficiency and antibody treatment in wild-type mice significantly reduced liver damage, as demonstrated by preserved Kupffer cells, fewer infiltrating macrophages, and the repression of hepatic proinflammatory genes. Furthermore, better survival was noted in this model, implying a relevant role of C5 in acute liver failure. The paper shows nicely that there is a therapeutic effect of C5 inhibition in acute liver failure, which could easily be translated to the clinic, because eculizumab, a humanized monoclonal antibody to C5, is already licensed for the treatment of paroxysmal nocturnal hemoglobinuria.[8] Currently, there are several clinical studies ongoing recruiting patients for treatment with eculizumab, including for liver-related conditions, such as HELLP syndrome or COVID-19 (hhtps://www.clinicaltrials.gov). Furthermore, it has recently been demonstrated that the C5a-C5a receptor (C5aR) axis is crucial in the pathogenesis of severe COVID-19.[9] High C5a plasma levels were found in patients to correlate with COVID-19 severity, and increased complement activity was further confirmed by transcriptomic analyses of peripheral blood. These findings indicate that it is necessary to define the dynamics of complement activation and its beneficial and deleterious effects in multiple human diseases. Studies like the current one improve the understanding of the roles of the complement system in complex diseases. Taken together, because of the difficulty of treating patients with acute liver failure and the lack of success of recent randomized controlled trials, inhibiting complement factors should be considered and evaluated in pilot studies.

SUSANNE N. WEBER, PhD
FRANK LAMMERT, MD, PhD
Department of Medicine II, Saarland University Medical Center
Saarland University
Homburg, Germany

References

1. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. Nat Immunol 2010;11:785–797.
2. Koleva M, Schlaf G, Landmann R, Götze O, Jungermann K, Schieferdecker HL. Induction of anaphylatoxin C5a receptors in rat hepatocytes by lipopolysaccharide in vivo: mediation by interleukin-6 from Kupffer cells. Gastroenterology 2002;122:697–708.
3. Hillebrandt S, Wasmuth HE, Weiskirchen R, Hellerbrand C, Keppeler H, Werth A, Schirin-Sokhan R, Wilkens G, Geier A, Lorenzen J, Köhl J, Gressner AM, Matern S, Lammert F. Complement factor 5 is a quantitative trait gene that modifies liver fibrogenesis in mice and humans. Nat Genet 2005;37:835–843.
4. Schlaf G, Schmitz M, Rothermel E, Jungermann K, Schieferdecker HL, Götze O. Expression and induction of

anaphylatoxin C5a receptors in the rat liver. Histol Histopathol 2003;18:299–308.
5. Zhou Y, Yuan G, Zhong F, He S. Roles of the complement system in alcohol-induced liver disease. Clin Mol Hepatol 2020;26:677–685.
6. Biewenga M, Farina Sarasqueta A, Tushuizen ME, de Jonge-Muller ESM, van Hoek B, Trouw LA. The role of complement activation in autoimmune liver disease. Autoimmun Rev 2020;19:102534.
7. Kusakabe J, Hata K, Miyauchi H, Tajima T, Wang Y, Tamaki I, Kawasoe J, Okamura Y, Zhao X, Okamoto T, Tsuruyama T, Uemoto S. Complement-5 inhibition deters progression of fulminant hepatitis to acute liver failure in murine models. Cell Mol Gastroenterol Hepatol 2021;11:1351–1367.
8. Hillmen P, Hall C, Marsh JCW, Elebute M, Bombara MP, Petro BE, Cullen MJ, Richards SJ, Rollins SA, Mojcik CF, Rother RP. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2004;350, 552–529.
9. Carvelli J, Demaria O, Vély F, Batista L, Chouaki Benmansour N, Fares J, Carpentier S, Thibult ML, Morel A, Remark R, André P, Represa A, Piperoglou C, Assante Miranda L, Baron W, Belaid N, Caillet C, Caraguel F, Carrette B, Carrette F, Chanuc F, Courtois R, Fenis A, Giordano M, Girard-Madoux M, Giraudon-Paoli M, Gourdin N, Guillot F, Habif G, Jaubert S, Lopez J, Le Van M, Lovera N, Mansuy M, Bonnet E, Sansaloni A, Reboul A, Mitry E, Nekkar-Constant C, Péri V, Ricaut P, Simon L, Vallier JB, Vétizou M, Zerbib R, Ugolini S, Etiennot M, Galluso J, Lyonnet L, Forel JM, Papazian L, Velly L, André B, Briantais A, Faucher B, Jean E, Seguier J, Veit V, Harlé JR, Pastorino B, Delteil C, Daniel L, Boudsocq JP, Clerc A, Delmond E, Vidal PO, Savini H, Coutard B, Cordier PY, Le Dault E, Guervilly C, Simeone P, Gainnier M, Morel Y, Ebbo M, Schleinitz N, Vivier E. Association of COVID-19 inflammation with activation of the C5a–C5aR1 axis. Nature 2020; 588:146–150.

Correspondence
Address correspondence to: Susanne N. Weber, PhD, Department of Medicine II, Saarland University Medical Center, Saarland University, Kirrberger Str. 100, D 66421 Homburg, Germany. e-mail: susanne.weber@uks.eu.

Conflicts of interest
The authors disclose no conflicts.


Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2021.02.011