Systemic inflammation and disorders of hemostasis in the AD-ACLF syndrome

Lisman, Ton; Luyendyk, James P.

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To the Editor:

With great interest we read the recent paper by Arroyo and coworkers in *Journal of Hepatology*, in which they propose that systemic inflammation plays a central role in the transition from compensated to decompensated cirrhosis, and the development of acute decompensation and acute-on-chronic liver failure (ACLF)[1] We fully concur with the authors that this intriguing hypothesis will create new research perspectives, and would like to propose one such research theme, not directly addressed by the authors.

It has been well established that inflammatory responses are accompanied by activation of coagulation, and vice versa.[2] Thus, if inflammatory responses drive clinical deterioration in patients with liver disease, there is likely exaggeration of coagulation activation in decompensating patients. We propose a number of potential consequences of an inflammation-induced activation of coagulation in patients with decompensating disease.

First, intrahepatic activation of hemostasis with deposition of platelets and fibrin has been demonstrated in animal models of liver disease.[3] This intrahepatic activation of coagulation was demonstrated to propagate disease progression by 1) inducing local ischemia, 2) activation of hepatic cells by coagulation proteases, 3) effects of fibrin on modulating cellular inflammatory responses.[3,4] We propose that inflammation-induced aggravation of coagulation will worsen intrahepatic deposition of fibrin and platelets and in this way hasten the progression of liver injury.

Second, systemic inflammation will likely lead to systemic activation of hemostasis, which may result in fibrin deposition in extrahepatic tissues, leading to failure of other organs as is seen in patients with ACLF. Disseminated intravascular coagulation (DIC) may lead to multiple organ failure by a thrombotic mechanism.[5] It has long been debated whether patients with cirrhosis develop DIC, but the systemic inflammation hypothesis would suggest that (low-grade) DIC will develop in the decompensating patient, consistent with the concept that inflammation-mediated activation of coagulation could contribute to multiple organ failure in ACLF. In patients without underlying liver disease, inflammation is thought to result in upregulation of coagulation, impairment of natural anticoagulant mechanisms, and downregulation of fibrinolysis.[2] In patients with compensated liver disease, these changes are already apparent, and inflammation-affiliated mechanisms are likely to aggravate these changes, potentially to a more thrombotic phenotype. This prothrombotic state could promote intraorgan microthrombosis that may contribute to multiple organ failure.[6] In addition, the thrombotic state could precipitate macrovascular events such as venous thrombosis and portal vein thrombosis.

Third, local or systemic activation of coagulation would lead to consumption of coagulation factors. In this way, systemic inflammation may contribute to the further decline in hepatocyte-derived coagulation proteins by consumption, perhaps in addition to the decrease in coagulation factor synthesis. In this way, systemic inflammation may form the basis of the progressing hemostatic changes in decompensating patients.[7]

Forth, although downregulation of fibrinolysis is a hallmark of systemic inflammation in patients without underlying liver disease, the picture is more complicated in decompensating patients with cirrhosis.[8] Mixed fibrinolytic patterns are observed in patients with acute decompensation and ACLF, with upregulation of fibrinolysis in acutely decompensating patients and downregulation of fibrinolysis in particular in those patients with sepsis. In acutely ill patients without underlying liver disease, the fibrinolytic system was uniformly downregulated.[9] There may indeed be divergent effects of liver injury and systemic inflammation on the fibrinolytic system, with additional study required as to whether the inflammatory response overrules the profibrinolytic effects of liver injury.

Fifth, systemic inflammation with concomitant activation of coagulation will activate additional processes that may propagate injury to the liver and other organs. Such processes include the generation of neutrophil extracellular traps that may be formed in response to activation of hemostasis, and activation of complement that is also known to communicate with the coagulation system.[2,10] Both of these processes have established roles in organ injury and their connection to the systemic inflammation hypothesis should not be overlooked.

Overall, we propose that reciprocal connections between the hemostatic system and systemic inflammatory response may contribute to hepatic and extrahepatic injury and clinical deterioration in patients through enhancement of micro- or macrovascular thromboses. It will be of considerable interest to investigate whether anti-inflammatory or antithrombotic strategies (or a combination thereof) will halt clinical deterioration. Indeed, anticoagulant therapy reduced the risk of portal vein thrombosis and decompensation in a small randomized controlled trial,[11] although these data require validation before this concept can be clinically applied.

As a final remark, we suggest a need for precise definitions of systemic inflammation in this context. Classifying elevated circulating markers of inflammation as a true measure of systemic inflammation is challenging, as this could also be a readout of massive hepatic inflammation. This will be critical as we seek

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to understand whether a switch from hepatic to systemic inflammation is a cause or consequence of extrahepatic organ injury. It is also possible that the proportion of patients with genuine systemic inflammation in studies like PREDICT is unintentionally overestimated. This is because many inflammatory markers measured are cleared by the liver,[12] creating a scenario in which hepatic dysfunction indirectly elevates inflammatory biomarkers.

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Conflict of interest
The authors have no conflicts of interest to declare.

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Authors' contributions
TL and JPL jointly wrote the manuscript.

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Author names in bold designate shared co-first authorship

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Ton Lisman[1,*]
James P. Luyendyk[2]
[1]Surgical Research Laboratory, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[2]Department of Pathobiology and Diagnostic Investigation, Michigan State University, East Lansing, Michigan, USA
[*]Corresponding author. Address: Ton Lisman, University Medical Center Groningen, Department of Surgery, BA33, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. Tel.: +31-50-3619028, Fax: +31-50-3632796.
E-mail address: j.a.lisman@umcg.nl (T. Lisman)

Reply to: "Systemic inflammation and disorders of hemostasis in the AD-ACLF syndrome"

To the Editor:

We are grateful to Drs. Lisman and Luyendyk for their interest in our hypothesis proposing systemic inflammation as the common mechanism of the major complications of cirrhosis.[1] The core of the hypothesis consists of a variety of systemic disorders induced by systemic inflammation (immunopathology, systemic metabolic dysregulation and immunosuppression) which, operating in synergy with organ-specific mechanisms (hyperammonemia, sinusoidal portal hypertension and cardiocirculatory dysfunction), form a complex pathophysiological network that explains the systemic nature of the acute decompensation-acute-on-chronic liver failure (AD-ACLF) syndrome.[2] The hypothesis is based on solid pathophysiological arguments, mostly elaborated within the past decades, chronological studies assessing the temporal relationship between mechanisms and clinical events, and recent studies derived from omics investigations.[2–4] These latest studies indicate that, as in severe sepsis, acute decompensation of cirrhosis occurs in the setting of an intense shift of metabolism from peripheral (non-immune) organs to the immune system, which may cause multiorgan dysfunction or failure,[5] and of simultaneous activation of the innate immune system and downregulation of the adaptive immune system, which may explain the coincidence of

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