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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Unravelling the Role of Neutrophil Extracellular Traps in Acute Liver Failure

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Q6 Q4 Acute liver failure (ALF) is a life-threatening disease that often requires organ support, admission to an intensive care facility, and urgent liver transplantation. Patients develop complex changes in their hemostatic system and massive systemic activation of inflammatory responses. The exact pathologic mechanisms of ALF are incompletely understood, and there is a need for targeted treatment strategies.[1] A study by Ye et al[2] published in this issue of *Cellular and Molecular Gastroenterology and Hepatology* improves the understanding of the role of neutrophils in the onset and progression of ALF, and provides novel therapeutic targets that could be further explored.

Neutrophils accumulate in the injured liver and are considered key players in ALF- associated liver injury. On activation, such as by platelets or danger-associated molecular patterns, a neutrophil can release its internal components to form a neutrophil extracellular trap (NET). NETs consist of unfolded DNA structures to which granular enzymes, such as neutrophil elastase (NE), are bound, which trap and remove pathogens. NETs have a host-protective function, but have also been implicated as drivers of diseases, such as sepsis and autoimmune diseases.[3] In addition, NETs have been shown to promote thrombosis in various ways. NETs bind and activate platelets, promote activation of coagulation, bind fibrinogen to inhibit its degradation, and stabilize thrombi.[4,5] Because of these characteristics, NETs might provide a connection between the profound activation of the hemostatic system and the immune system that is seen in patients with ALF, making it an interesting subject of study in this disease.

We have recently shown in a large cohort of patients with ALF that plasma markers of NETs were elevated and associated with death or the need for urgent liver transplantation.

Moreover, histologic analyses of explanted livers obtained from a small proportion of these patients showed NET formation in the liver.[6] These findings underline a potential role for NETs in the progression of ALF that warrant mechanistic studies.

In this issue, a well-designed study by Ye et al[2] investigated the potential role for NETs in ALF in a galactosamine-lipopolysaccharide-induced ALF mouse model, and specifically studied the contribution of microRNA-223 and NE to disease progression. The authors demonstrated a protective role for microRNA-223 and detrimental effects of NE in ALF by modulating neutrophil recruitment to the liver, NET formation, and hepatic injury. Interestingly, pharmacologic and genetic blockage of NE resulted in decreased NET formation and hepatic injury that could at least in part be attributed to the decreased neutrophil recruitment to the liver in NE-deficient mice. These results are in line with a previous experimental study in septic mice that showed that inhibition of NE resulted in significantly decreased NET formation and was more efficient in reducing hepatic injury than inhibition of NET formation alone.[7] In addition, in this study the necrotic areas in the liver of untreated septic mice colocalized with the proteolytic activity of NE,[7] suggesting direct cytotoxic effects of NE. Whether NETs, and specifically NE, mainly inflict hepatic injury in ALF by direct cytotoxic effects or whether other mechanisms, such as (local) activation of the hemostatic system and consequent ischemic injury, are involved should be further explored. NET-induced activation of the hemostatic system has been shown to contribute to chronic liver disease progression by formation of (micro)thrombi in the liver in a mouse model of portal hypertension.[8] Moreover, NE contributes to thrombus formation by activating platelets through proteinase-activated receptor-1,[9] and by degradation of tissue factor pathway inhibitor.[10] These mechanisms may explain why neutrophil influx and NET formation is decreased in the absence of NE, because activated platelets and fibrin can bind and activate neutrophils. Therefore, we think that the interplay of NE, NETs, and the hemostatic system in ALF is of definite interest for future study.

In conclusion, the results of the study by Ye et al[2] improve the understanding of this difficult to treat disease, and provide rationale to explore targeted treatment strategies. In addition to this study, others have demonstrated that the removal or inhibition of NETs and NE by for example DNase I or sivelestat, which are both clinically available compounds, reduced liver injury and thrombosis in experimental models.[7,11] It is, however, important to acknowledge the vital role of NETs in pathogen clearance, and that blocking NETs might further increase the risk of infection in patients with ALF. However, there is experimental evidence that inhibition of NETs does not increase bacterial dissemination, and it was suggested that other cell types, such as macrophages and Kupffer cells, compensate for the loss of (immune) function of NETs.[12] We look forward to future studies that unravel the role of neutrophils and NETs in ALF, and explore its therapeutic potential.

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References

1. Stravitz RT, Lee WM. Acute liver failure. Lancet 2019; 394:869–881.
2. Ye D, Yao J, Du W, Chen C, Yang Y, Yan K, et al. Neutrophil extracellular traps mediate acute liver failure in regulation of miR-223/neutrophil elastase signaling in mice. Cell Mol Gastroenterol Hepatol 2022;XX:XXX–XXX.
3. Kaplan MJ, Radic M. Neutrophil extracellular traps: double-edged swords of innate immunity. J Immunol 2012;189:2689–2695.
4. Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD Jr, et al. Extracellular DNA traps promote thrombosis. Proc Natl Acad Sci U S A 2010; 107:15880–15885.
5. Gould TJ, Vu TT, Stafford AR, Dwivedi DJ, Kim PY, Fox-Robichaud AE, et al. Cell-free DNA modulates clot structure and impairs fibrinolysis in sepsis. Arterioscler Thromb Vasc Biol 2015;35:2544–2553.
6. von Meijenfeldt FA, Stravitz RT, Zhang J, Adelmeijer J, Zen Y, Durkalski V, et al. Generation of neutrophil extracellular traps in patients with acute liver failure is associated with poor outcome. Hepatology 2022;75: 623–633.
7. Kolaczkowska E, Jenne CN, Surewaard BG, Thanabalasuriar A, Lee WY, Sanz MJ, et al. Molecular mechanisms of NET formation and degradation revealed by intravital imaging in the liver vasculature. Nat Commun 2015;6:6673.
8. Hilscher MB, Sehrawat T, Arab JP, Zeng Z, Gao J, Liu M, et al. Mechanical stretch increases expression of CXCL1 in liver sinusoidal endothelial cells to recruit neutrophils, generate sinusoidal microthombi, and promote portal hypertension. Gastroenterology 2019; 157:193–209.
9. Mihara K, Ramachandran R, Renaux B, Saifeddine M, Hollenberg MD. Neutrophil elastase and proteinase-3 trigger G protein-biased signaling through proteinase-activated receptor-1(PAR1). J Biol Chem 2013;288: 32979–32990.
10. Massberg S, Grahl L, von Bruehl ML, Manukyan D, Pfeiler S, Goosmann C, et al. Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases. Nat Med 2010;16:887–896.
11. Brill A, Fuchs TA, Savchenko AS, Thomas GM, Martinod K, de Meyer SF, et al. Neutrophil extracellular traps promote deep vein thrombosis in mice. J Thromb Haemost 2012;10:136–144.
12. Carestia A, Davis RP, Davis L, Jenne CN. Inhibition of immunothrombosis does not affect pathogen capture and does not promote bacterial dissemination in a mouse model of sepsis. Platelets 2020;31:925–931.

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Conflicts of interest
The authors disclose no conflicts.

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