Reply

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Reply

We thank Dr. Liu and colleagues for their interest in our manuscript. We agree that the lower plasma levels of the neutrophil extracellular trap (NET)-marker, myeloperoxidase (MPO)-DNA complex, in patients with acetaminophen-induced acute liver failure (ALF) might be explained by the shorter duration of disease at blood sampling compared with non-acetaminophen-induced ALF. We disagree, however, that it has been established at what stage in human acetaminophen-induced ALF neutrophil influx in the liver takes place and would like to emphasize that the data referred to by Dr. Liu and colleagues are derived from studies in mice. It would be of interest to assess NET formation in serial blood samples to document NET formation over time and its possible contribution to progression of disease.

We agree that subsets of neutrophils are involved in tissue repair after liver injury, but when neutrophils are activated to form NETs, these beneficial features are likely lost.[1] Our study suggests that in ALF, NET formation primarily causes damage, as high plasma levels of MPO-DNA complexes were associated with poor outcome. Notably, the vast majority of studies on the role of neutrophils in liver injury and repair have used mouse models of liver injury. Whether these results are relevant for ALF in humans should be further explored.

The second comment raised on the activation of coagulation by NETs in liver disease is important and has been the subject of studies in our group. There is convincing evidence from experimental studies that NETs activate coagulation, but there is limited evidence that NETs are involved in activation of coagulation in patients with liver disease. We previously showed that MPO-DNA complex levels were not associated with markers of coagulation activation in patients with acute-on-chronic liver failure[2] and in patients undergoing liver transplantation.[3] It has also been demonstrated that NETs inhibit the fibrinolytic system in vitro, but it is unclear whether this mechanism plays a role in fibrinolysis regulation in vivo. We recently demonstrated that coagulation or fibrinolytic potential in patients with ALF were not associated with outcome.[4] Thus, it may be that the mechanism by which NETs contribute to progression of ALF is not through activation of coagulation. We agree that additional (histological) studies to explore the role of NETs in progression of liver disease and their link to coagulation are of interest.

CONFLICT OF INTEREST

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