

EDITORIAL

Neutrophil Extracellular Traps Enhance Liver Inflammation and Fibrin Deposition in Fulminant Viral Hepatitis

Fulminant viral hepatitis remains a rare but devastating illness that may culminate in acute liver failure and the need for liver transplantation. Viral hepatitis is the most common cause of acute liver failure in developing countries, where access to liver transplantation is limited.¹ Certain populations, including immunosuppressed patients and pregnant women, are at increased risk of developing liver failure related to infection with particular viruses, including herpes simplex virus and hepatitis E virus. Given the limited access to liver transplantation in developing countries and persistent organ shortages worldwide,² elucidating the pathophysiology of fulminant viral hepatitis is critical in devising novel therapeutics to prevent acute liver failure and avoid the need for liver transplantation. The study by Li et al³ proposed a mechanism whereby expression of fibrinogen-like protein 2 (Fgl2) by neutrophils in the setting of fulminant viral hepatitis enhances formation of neutrophil extracellular traps through an autophagy-based mechanism. They found that neutrophil extracellular traps exacerbated fulminant viral hepatitis in a mouse model of murine hepatitis virus strain-3 infection by enhancing intrahepatic fibrin deposition and inflammation.

Neutrophil extracellular traps comprise a framework of extracellular decondensed nuclear DNA that is expelled by a neutrophil and subsequently binds to a variety of nuclear and granular proteins, some of which have antimicrobial properties.⁴ Neutrophil extracellular traps are thrombogenic structures that also contribute to immune defense by binding and neutralizing pathogens. Although other immune cells, such as T cells and natural killer cells, are implicated in the pathogenesis of viral hepatitis, the role of neutrophils and neutrophil extracellular traps in human viral hepatitis is not well established. CD8 T-cell responses have been implicated in the pathogenesis of acute liver failure owing to many hepatotropic viruses, including hepatitis A and E.^{5,6} Similarly, lysis of infected hepatocytes mediated by the cytotoxic T-cell response is a significant driver of fulminant hepatitis B virus infection.⁷ Recent studies in a murine model of hepatitis B virus showed that neutrophil depletion does not impact the recruitment of cytotoxic T cells, but does ameliorate liver damage by decreasing the recruitment of antigen-nonspecific cells into the liver, which amplify and perpetuate the T-cell-mediated inflammatory response.⁸ Neutrophils similarly have been implicated in exacerbation of hepatitis resulting from adenoviral infection.^{9,10} These recent studies, in conjunction with this study by Li et al,³ showed a multifaceted and previously overlooked role of neutrophils in the pathogenesis of fulminant viral hepatitis. Thus, neutrophils constitute a potential therapeutic target

that may curtail hepatotoxicity while circumventing the T-cell-driven immune response to the virus.

Li et al³ studied a mouse model of fulminant viral hepatitis, but its applicability to human disease is unclear, in part because of the significant heterogeneity that characterizes the human viral hepatitis syndromes and pathogens. As noted earlier, recent studies have shown that neutrophil depletion decreases liver damage in a murine model of hepatitis B virus infection.⁷ Interestingly, Li et al³ observed minimal change after neutrophil depletion in their murine model of fulminant viral hepatitis, which likely was owing at least in part to differences in the models of viral hepatitis used. These discrepant findings suggest a nuanced, context-specific role of neutrophils in the pathogenesis of viral hepatitis syndromes and the need for disease-specific studies of each hepatotropic virus.

Li et al³ proposed that neutrophil extracellular traps enhance intrahepatic fibrin deposition, which characterizes fulminant hepatitis through Fgl2 activation. Fgl2 converts prothrombin to thrombin and thereby contributes to fibrin deposition.¹¹ Fgl2 deficiency has been shown previously to improve survival in murine models of fulminant hepatitis,¹² thereby confirming the role of intrahepatic fibrin deposition in its progression. Although previous studies have focused on Fgl2 production by liver sinusoidal endothelial cells,¹³ Li et al³ here found that Fgl2 expression by neutrophils is critical in promoting neutrophil extracellular trap formation. They collected peripheral neutrophils from patients with acute liver injury/acute liver failure resulting from hepatitis B virus infection and found a significant increase in messenger RNA levels of Fgl2, suggesting a direct impact of hepatitis B virus on neutrophil populations. Li et al³ postulated that Fgl2-induced neutrophil extracellular trap formation also contributes to the systemic coagulopathy seen in acute liver injury/acute liver failure resulting from hepatitis B virus infection. The thrombogenic impact of neutrophil extracellular traps on the microenvironment in the liver in the setting of the systemic coagulopathy that characterizes acute liver failure is a complex and interesting dichotomy that merits further study.

Overall, this article provides helpful big-picture insights into the role of neutrophils and neutrophil extracellular traps in promoting intrahepatic fibrin deposition, which is a known contributor to the pathogenesis of acute liver failure. We look forward to more nuanced studies that clarify the interaction of neutrophils and neutrophil extracellular traps with other immune cell populations and the role of neutrophils in the pathogenesis of individual viral hepatitis syndrome.

117 MOIRA B. HILSCHER, MD
 118^{Q12} Division of Gastroenterology and Hepatology
 119 Department of Medicine
 120 University of Pennsylvania
 121 Philadelphia, Pennsylvania
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References

- 125 1. Lee WM. Etiologies of acute liver failure. *Semin Liver Dis* 2008;28:142–152.
- 126 2. Muhammad H, Zaffar D, Tehreem A, Ting PS, Simsek C,
 127 Turan I, Alqahtani S, et al. An update on usage of high-
 128 risk donors in liver transplantation. *J Clin Med* 2021;
 129 11:215.
- 130^{Q10} 3. Li X, Gao Q, Wu W, Hai S, Hu J, You J, Huang D, et al.
 131 FGL2-MCOLN3-autophagy axis-triggered neutrophil
 132 extracellular traps exacerbate liver injury in fulminant viral
 133 hepatitis. *Cell Mol Gastroenterol Hepatol* 2022. Epub
 134 ahead of print.
- 135^{Q11} 4. Brinkmann V, Reichard U, Goosmann C, Fauler B,
 136 Uhlemann Y, Weiss DS, Weinrauch Y, et al. Neutrophil
 137 extracellular traps kill bacteria. *Science* 2004;
 138 303:1532–1535.
- 139 5. Prabhu SB, Gupta P, Durgapal H, Rath S, Gupta SD,
 140 Acharya SK, Panda SK. Study of cellular immune
 141 response against hepatitis E virus (HEV). *J Viral Hepat*
 142 2011;18:587–594.
- 143 6. Fleischer B, Fleischer S, Maier K, Wiedmann KH,
 144 Sacher M, Thaler H, Vallbracht A. Clonal analysis of
 145 infiltrating T lymphocytes in liver tissue in viral hepatitis
 146 A. *Immunology* 1990;69:14–19.
- 147 7. Wright TL, Mamish D, Combs C, Kim M, Donegan E,
 148 Ferrell L, Lake J, et al. Hepatitis B virus and apparent
 149 fulminant non-A, non-B hepatitis. *Lancet* 1992;
 150 339:952–955.
- 151 8. Sitia G, Isogawa M, Kakimi K, Wieland SF, Chisari FV,
 152 Guidotti LG. Depletion of neutrophils blocks the recruit-
 153 ment of antigen-nonspecific cells into the liver without
 154
 155
 156
 157
 158
 159
 160
 161
 162
 163
 164
 165
 166
 167
 168

- affecting the antiviral activity of hepatitis B virus-specific
 cytotoxic T lymphocytes. *Proc Natl Acad Sci U S A* 2002;
 99:13717–13722. 169
 170
 171
9. Maher JJ, Scott MK, Saito JM, Burton MC. Adenovirus-
 mediated expression of cytokine-induced neutrophil
 chemoattractant in rat liver induces a neutrophilic hep-
 atitis. *Hepatology* 1997;25:624–630. 172
 173
 174
 175
10. Muruve DA, Barnes MJ, Stillman IE, Libermann TA.
 Adenoviral gene therapy leads to rapid induction of
 multiple chemokines and acute neutrophil-dependent
 hepatic injury in vivo. *Hum Gene Ther* 1999;10:965–976. 176
 177
 178
 179
11. Ding JW, Ning Q, Liu MF, Lai A, Leibowitz J,
 Peltekian KM, Cole EH, et al. Fulminant hepatic failure in
 murine hepatitis virus strain 3 infection: tissue-specific
 expression of a novel fgl2 prothrombinase. *J Virol*
 1997;71:9223–9230. 180
 181
 182
 183
 184
12. Marsden PA, Ning Q, Fung LS, Luo X, Chen Y,
 Mendicino M, Ghanekar A, et al. The Fgl2/fibroleukin
 prothrombinase contributes to immunologically medi-
 ated thrombosis in experimental and human viral hepa-
 titis. *J Clin Invest* 2003;112:58–66. 185
 186
 187
 188
 189
13. Liu J, Tan Y, Zhang J, Zou L, Deng G, Xu X, Wang F, et al.
 C5aR, TNF-alpha, and FGL2 contribute to coagulation
 and complement activation in virus-induced fulminant
 hepatitis. *J Hepatol* 2015;62:354–362. 190
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Correspondence

Address correspondence to: Moira Hilscher, MD, Division of Gastroenterology
 and Hepatology, Department of Medicine, University of Pennsylvania, 914
 Biomedical Research Building II/III, 421 Curie Boulevard, Philadelphia,
 Pennsylvania 19104. e-mail: Moira.hilscher@penmedicine.upenn.edu.

Conflicts of interest

The author discloses no conflicts.

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