Increased Killing of Liver NK Cells by Fas/Fas Ligand and NKG2D/NKG2D Ligand Contributes to Hepatocyte Necrosis in Virus-Induced Liver Failure

Yong Zou,* 1 Tao Chen,* 1 Meifang Han,* Hongwu Wang,* Weiming Yan,* Ge Song,* Zeguang Wu,* Xiaojing Wang,* Chuanlong Zhu,‡ Xiaoping Luo,‡ and Qin Ning*

The role of liver NK cells in virus-induced severe viral hepatitis and, subsequently, hepatic failure is not well defined. In this study, we investigated the role of liver NK cells in the development of hepatocyte necrosis in fulminant hepatic failure (FHF) and acute-on-chronic liver failure (ACLF) because of viral infection. A mouse model of FHF induced by murine hepatitis virus strain 3 (MHV-3) was used to study the role of liver NK cells. Samples from patients with hepatitis B virus-related ACLF (HBV-ACLF) were examined. After MHV-3 infection, the number of NK cells in livers of BALB/cJ mice increased markedly, peaked at 48 h postinfection, and remained at a high level until sacrifice. In peripheral blood, spleen, and bone marrow, this number decreased significantly. Expression of CD69, cytotoxic activity, and intracellular IFN-γ and TNF-α production by liver NK cells at 48 h postinfection were all significantly upregulated. Depletion of NK cells 24 h post-MHV-3 infection increased the mice survival from 0 of 18 (0%) to 4 of 18 (22.2%). Highly activated liver NK cells were cytotoxic to MHV-3-infected hepatocytes and this effect was markedly inhibited by anti-Fas ligand (FasL) plus anti-NKG2D mAbs. Furthermore, the accumulation of hepatic NK cells and increased expression of FasL and natural cytotoxicity receptors (Nkp30 and Nkp46) on the peripheral NK cells from patients with HBV-ACLF were correlated with disease progression. These results indicate that liver NK cells play a pivotal role in the pathogenesis of FHF and HBV-ACLF, in which process Fas/FasL and NKG2D/NKG2D ligand pathway contribute to the liver NK cell-mediated hepatocyte injury. The Journal of Immunology, 2010, 184: 466–475.

†Y. Z. and T. C. contributed equally to this work.

Received for publication March 4, 2009. Accepted for publication October 29, 2009.

This work was supported by the National Key Basic Research Program of China (2007CB512900, 2005CB522901, 2005CB522507), the National Science Fund of China (NSFC30672380, 30571643), and 11th Five-Year Plan Key Project Key Project (2006BAI05A07) and Key Project from Ministry of Health of China.

Address correspondence and reprint requests to Dr. Qin Ning, Department of Infectious Disease, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan; and Department of Infectious Disease, Affiliated Provincial Hospital, Anhui Medical University, Hefei, China.

Abbreviations used in this paper: ACLF; acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BM, bone marrow; CHB, chronic hepatitis B; FasL, Fas ligand; FHF, fulminant hepatic failure; HBsAg, hepatitis B e antigen; HBV-ACLF, hepatitis B virus-related ACLF; HCV, hepatitis C virus; MHV-3, mouse hepatitis virus strain 3; MNC, mononuclear cell; NCR, natural cytotoxicity receptor; NKG2DL, NKG2D ligand; PTA, prothrombinase time; PT, prothrombinase activity.

Copyright © 2009 by The American Association of Immunologists, Inc. 0022-1767/10/5/184/466;10.

www.jimmunol.org/cgi/doi/10.4049/jimmunol.0900687