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EDITORIAL

The Role of Natural Killer Cells in Nonalcoholic Steatohepatitis: An Ongoing Debate

Nonalcoholic fatty liver disease ranges from benign infiltration of fat in the liver to nonalcoholic steatohepatitis (NASH) where the fat infiltration is accompanied by lobular inflammation that can lead to cirrhosis and end-stage liver disease.[1] NASH cirrhosis represents an increasing clinical concern and is now an important indication for liver transplantation in Western countries.[2,3] Natural killer (NK) cells are a key component of the innate immune system that are highly enriched in the liver and hence perform critical functions in most liver inflammatory diseases. However, their functions in NASH remain unclear.

There has been a long debate regarding a pathogenic or protective role of NK cells in NASH. Studies have shown increased NK cells with more activated phenotypes in patients with NASH and mouse models.[4] Furthermore, a pathogenic function is suggested because NK cells promote chronic inflammation in a spontaneous NASH model.[5] In contrast to these findings, other studies have been unable to replicate these observations and also suggest that NK cells are protective against NASH by attenuating hepatic fibrosis.[4,6] These apparently contradictory results make the functional role of NK cells in NASH pathogenesis controversial. Determining experimentally the contribution of NK cells in NASH is therefore a prerequisite before attempting new therapeutic strategies for NASH with targeting of NK cells.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Wang et al[7] add to this debate by thoroughly examining the role of NK cells in the development of NASH by using 3 different mouse models with slightly different pathogenesis (methionine- and choline-deficient diet [MCD], choline-deficient high-fat diet, and high-fat diet with streptozotocin injection). Consistent higher expression of NKG2D, CD107a, and interferon-γ, but decreased NKG2A on NK cells were observed in all the examined models, adding strong support to the proposed abnormal activation of NK cells in NASH. An important strength of these observations is the use of different models that in large recapitulates the same results. The pathogenic role of NK cells was directly demonstrated using the NK cell–deficient *Nfil3*$^{-/-}$ mouse model, which developed less disease under MCD- and choline-deficient high-fat diet compared with control mice. This observation was corroborated by experiments using NK cell depletion with a neutralization antibody PK136 alleviating disease severity in MCD-fed mice, an approach that highlights an important translational potential into human medicine. Intriguing mechanistic insights were also uncovered that specific cytokines produced by NK cells are likely to activate JAK-STAT1/3 and nuclear factor-κB signaling in hepatocytes, leading to increased reactive oxygen species (ROS) level and apoptosis in these cells.

In contrast to other studies that have used the MCD model, the present study surprisingly observed that NK cell–deficient mice developed less disease. The previous study by Young S. Hahn's group showed that NK cell–deficient mice exhibited more severe NASH disease phenotype.[6] This apparent contradiction might be explained by the different NK cell–deficient models used in the studies. The current study used *Nfil3*$^{-/-}$ mice that lack conventional NK (cNK) cells but with retained liver-resident NK (lrNK) cells (Table 1, *Nfil3*$^{-/-}$). In contrast, the previous study used NKp46-depleted mice that lack both cNK and lrNK cells (Table 1, NKp46-depleted). Thus, it seems that the disease in MCD model is ameliorated after "solo" cNK depletion, and exacerbated when both cNK and lrNK cells are depleted, suggesting a promising protective role for lrNK cells in addition to the pathogenic role for cNK cells in fatty liver diseases. If this hypothesis holds true, it is surprising that PK136 antibodies depleting both cNK and lrNK cells still resulted in ameliorated disease phenotypes, pointing to remaining important distinctions here that need to be determined. One possible explanation might be that natural killer T (NKT) cells are depleted at the same time by PK136 antibodies (Table 1, PK136 Abs). Therefore, the present paper along with the previous report also implies a pathogenic role for NKT cells that might be regulated by lrNK in this model. Interestingly, the pathogenic role for NKT cells is supported by observations showing NKT-deficient mice (*Cd1d*$^{-/-}$ and *Ja18*$^{-/-}$) are protected against NASH fibrosis.[8] Further investigations exploring the interplay and regulatory mechanisms among these "natural killer family" cells are needed to provide a clear answer to the role of NK cells, both cNK and lrNK, in NASH.

XIAOJUN JIANG, PHD
Norwegian PSC Research Center
Division of Surgery, Inflammatory Diseases and Transplantation
Oslo University Hospital Rikshospitalet
Oslo, Norway
Research Institute of Internal Medicine
Oslo University Hospital Rikshospitalet
Oslo, Norway
Institute of Clinical Medicine, University of Oslo
Oslo, Norway

Table 1. Illustration of the Impact of Different NK Depletion Methods on cNK, lrNK, and NKT Cells

	cNK	lrNK	NKT	Disease in MCD model
Nfil3$^{-/-}$	Depleted	Retained	Retained	Ameliorated[7]
NKp46-depleted	Depleted	Depleted	Retained	Exacerbated[6]
PK136 Abs	Depleted	Depleted	Depleted	Ameliorated[7]
Suggested role	Pathogenic	Protective	Pathogenic	

NOTE. The reported outcome regarding the disease severity in MCD mouse model is specified for each method. Based on these findings, the pathogenic or protective role for each cell type is suggested.
Abs, antibodies; cNK, conventional NK; lrNK, liver-resident NK; MCD, methionine- and choline-deficient diet; NK, natural killer cells; NKT, natural killer T cells.

ESPEN MELUM, MD, PHD
Norwegian PSC Research Center
Division of Surgery, Inflammatory Diseases and Transplantation
Oslo University Hospital Rikshospitalet
Oslo, Norway
Research Institute of Internal Medicine
Oslo University Hospital Rikshospitalet
Oslo, Norway
Institute of Clinical Medicine, University of Oslo
Oslo, Norway
Section of Gastroenterology, Department of Transplantation Medicine
Division of Surgery, Inflammatory Diseases and Transplantation
Oslo University Hospital Rikshospitalet
Oslo, Norway
Hybrid Technology Hub-Centre of Excellence
Institute of Basic Medical Sciences
Faculty of Medicine, University of Oslo
Oslo, Norway

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Correspondence
Address correspondence to: Espen Melum, MD, PhD, Norwegian PSC Research Center, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital Rikshospitalet, 0424 Oslo, Norway. e-mail: espen.melum@medisin.uio.no.

Conflicts of interest
The authors disclose no conflicts.

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