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Natural killer T cells and non-alcoholic fatty liver disease: Fat chews on the immune system

Michael Kremer, Ian N Hines

Michael Kremer, Department of Surgery, University of Heidelberg, Heidelberg 69120, Germany
Ian N Hines, Department of Medicine, University of North Carolina at Chapel Hill, CB 7525, United States
Correspondence to: Michael Kremer, MD, Department of Surgery, Mail Box # B5, University of Heidelberg, Heidelberg 69120, Germany. michael_kremer@med.unc.edu
Telephone: +49-6221-5639494 Fax: +49-6221-565450
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Abstract

Natural killer T cells (NKT) are an important subset of T lymphocytes. They are unique in their ability to produce both T helper 1 and T helper 2 associated cytokines, thus being capable of steering the immune system into either inflammation or tolerance. Disruption of NKT cell numbers or function results in severe deficits in immune surveillance against pathogens and tumor cells. Growing experimental evidence suggests that hepatosteatosis may reduce resident hepatic as well as peripheral NKT cells. Those models of hepatosteatosis and the change in NKT cell numbers are associated with a disruption of cytokine homeostasis, resulting in a more pronounced release of proinflammatory cytokines which renders the steatotic liver highly susceptible to secondary insults. In this letter to the editor, we focus on recently published data in the *World Journal of Gastroenterology* by Xu and colleagues demonstrating reduced peripheral NKT cells in patients with non-alcoholic fatty liver disease, compare those findings with ours and others in different animal models of hepatosteatosis, and hypothesize about the potential underlying mechanism.

Key words: Obesity; Hepatosteatosis; Metabolic syndrome

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TO THE EDITOR

We are excited to read a recent report in the *World Journal of Gastroenterology* by Xu and colleagues demonstrating a reduction in the numbers of peripheral natural killer T cell (NKT) cells in patients with non-alcoholic fatty liver disease[1]. A growing body of experimental data demonstrates a link between hepatosteatosis and defects in NKT numbers and/or function. Over the past years, reductions in NKT cell numbers was reported in the fatty liver by a number of groups including ours[2-4]. Observations by our group show an inverse correlation between hepatic NKT cell numbers with the accumulation of hepatic lipid using the choline-deficient diet model of hepatosteatosis[4]. Although different animal models of diet-induced hepatic steatosis using high fat, high sucrose and choline-deficient diet or leptin deficient *ob/ob* mice showed depletion or decrease in hepatic NKT cell numbers[2-4], it has remained unclear if those findings were relevant to human fatty liver disease.

NKT cells play a critical role both in the liver and peripherally in the regulation of the innate and adaptive immune response. Decreased hepatic NKT cell numbers correlate with increased local production of pro-inflammatory T helper 1-associated cytokines[4,5]. We and others have shown that T helper 1-associated cytokines, such as tumor necrosis factor alpha, interleukin 12 and interferon gamma, are significantly elevated in steatotic livers in mouse models of obesity[3-5]. Similar findings have been reported in obese individuals with low levels of adiponectin and increased levels of circulating tumor necrosis factor alpha[6,7], although those studies did not examine hepatic or peripheral NKT cell numbers. NKT cells are unique in their ability to produce both T helper 1- and T helper 2-associated cytokines. The loss of NKT cells likely contributes to disrupted cytokine balance within the liver[5,8,9]. Consistent with their function as a regulator of the immune response, loss of NKT cell-associated interleukin 4 production promotes beta cell destruction in the *db/db* mouse model of type I diabetes[10]. Finally, NKT cells also function to clear tumor cells within the liver, as NKT cell activation promotes tumor cell clearance in several mouse models of hepatic metastasis[11]. Therefore, it is apparent that NKT cells play an important immunological and potentially regulatory role in both the liver and peripheral organs. The ability of hepatic lipid accumulation to alter this multifunctional cell population may have important and widespread pathophysiological consequences.

It remains unclear how hepatosteatosis reduces hepatic

and peripheral NKT cells. Previous studies implicated that interleukin 12 is a key activator of NKT cells, a process which is linked to activation-induced cell death of this cell population[12]. Therefore, it is likely that increased levels of interleukin 12 in fatty livers directly reduce the viability of NKT cells. We hypothesize that increased interleukin 12 expression in combination with hepatic lipid accumulation might be directly responsible for the reduced NKT cell population in non-alcoholic fatty liver disease (NAFLD).

The current study by Xu and colleagues is the first of its kind to establish this inverse relationship between NKT cell numbers and hepatosteatosis in humans and provides strong support to animal models of steatotic liver disease and immune cell dysfunction. Future research should focus on hepatic resident NKT cell numbers in humans suffering from NAFLD, and the relationship between hepatic and systemic cytokine levels of those patients should be monitored.

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