EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

NKT-cell subsets: Promoters and protectors in inflammatory liver disease

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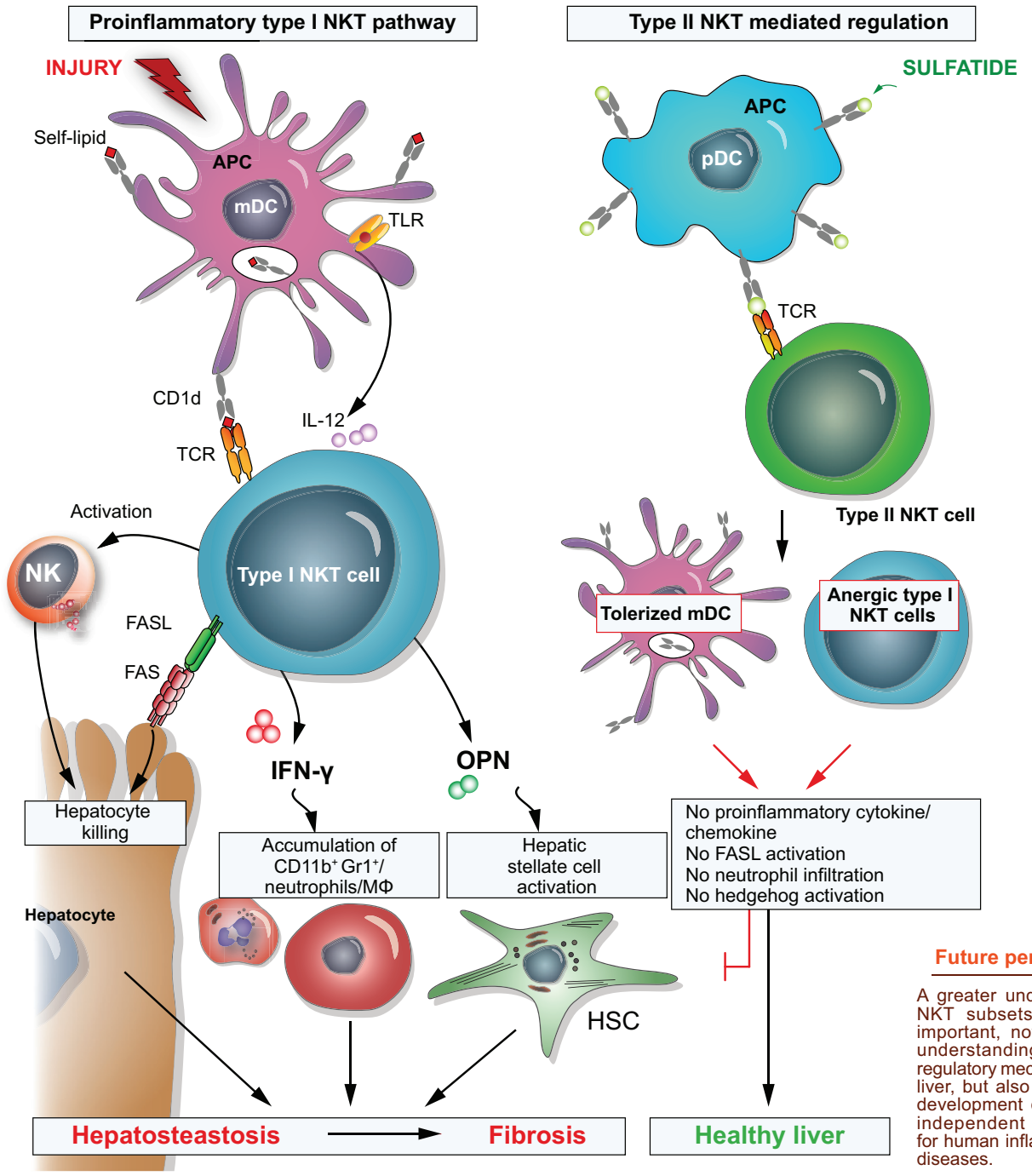
Key facts

Natural killer T cells (NKT) recognize lipid antigens in the context of CD1d, a non-polymorphic MHC class I-like molecule. Activation of NKT cells has a profound influence on the immune response against tumors and infectious organisms and in autoimmune diseases.

Recent evidence suggests that NKT cell subsets (iNKT/type I and type II) can play opposing roles early in non-microbial liver inflammation.



Future perspective

A greater understanding of NKT subsets' interplay is important, not only for the understanding of immune regulatory mechanisms in the liver, but also to enable the development of novel HLA-independent therapeutics for human inflammatory liver diseases.

Keywords: NK T cells, Sulfatide, Hepatitis, Inflammation.
Received 1 November 2012; received in revised form 20 February 2013; accepted 27 February 2013.
Abbreviations: MHC, major histocompatibility complex; NK, natural killer cells; NKT, natural killer T cells; TCR, T cell receptor; αGalCer, α-galactosylceramide; DC, dendritic cells; ConA, concavalin A; IRI, ischemic reperfusion injury; KC, Kupffer cells; OPN, osteopontin; MCD, methionine choline deficient diet; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; SCD, sickle cell disease; TAA, thioacetamide.

Hepatology Snapshot

Summary

Natural killer T cells (NKT) are innate-like cells which are abundant in liver sinusoids and express the cell surface receptors of NK cells (e.g., NK1.1 (mouse) or CD161+/CD56+(human)) as well as an antigen receptor (TCR) characteristic of conventional T cells. NKT cells recognize lipid antigens in the context of CD1d, a non-polymorphic MHC class I-like molecule. Activation of NKT cells has a profound influence on the immune response against tumors and infectious organisms and in autoimmune diseases. NKT cells can be categorized into at least two distinct subsets: iNKT or type I use a semi-invariant TCR, whereas type II NKT TCRs are more diverse. Recent evidence suggests that NKT-cell subsets can play opposing roles early in non-microbial liver inflammation in that type I NKT are proinflammatory whereas type II NKT cells inhibit type I NKT-mediated liver injury.

Type I NKT cells are proinflammatory and can promote liver injury

Although type I NKT cells can recognize self-lipids, most also recognize a marine sponge-derived lipid α-galactosylceramide (αGalCer) and are best identified using αGalCer/CD1d multimers. NKT cells in the liver respond very rapidly to injury following either direct recognition of cognate lipids or indirectly by TLR ligands and cytokine secretion (e.g., IL-12) by activated antigen-presenting cells (APC), such as Kupffer cells (KC), hepatocytes, and myeloid dendritic cells (mDC). Notably, the cytokine secretion profile (Th1/Th2/Th17-like) of type I NKT is influenced by the nature of the APC as well as the lipid ligands, e.g., they predominantly secrete IFN-γ following ischemia or toxin-induced injury, but secrete both IFN-γ and IL-4 in response to αGalCer [1,2]. Rapid secretion of pro-inflammatory cytokines and chemokines by type I NKT cells leads to accumulation of CD11b+Gr-1+ cells including neutrophils and macrophages in the liver. Accordingly, these cells do not accumulate in type I NKT-deficient mice, which are resistant to liver injury following ischemic reperfusion injury (IRI), concavalin A (ConA), or high-fat diet [1–3]. Type I NKT cells can promote fibrogenesis involving the Hedgehog (Hh) pathway and cytokines, including osteopontin (OPN), leading to hepatic stellate cell (HSC) activation [4]. Activated type I NKT cells can also kill hepatocytes directly (FAS/FASL) or indirectly by activating NK cells. Collectively, recent studies suggest a proinflammatory role of type I NKT cells in liver injury following ischemic reperfusion or in sickle cell disease, ConA- or thioacetamide (TAA)-induced hepatitis, primary biliary cirrhosis, and NAFLD [1,2,4–7]. Though their role remains controversial in obesity [8], hepatic type I NKT cells become activated and also secrete IFN-γ following a high-fat diet. Since microbial exposure during early life has a profound impact on the number and function of NKT cells [9], housing and food may influence experimental results in different laboratories.

A major type II NKT subset cross-regulate type I NKT activity and protect from liver injury

A major subset of type II NKT cells express oligoclonal TCRs with distinct molecular recognition features and can recognize sulfatide, a self-glycolipid enriched in the CNS, kidney, and liver [10]. Interestingly, anti-sulfatide immune responses are present in multiple sclerosis, type 1 diabetes, as well as in hepatitis C virus-associated mixed cryoglobulinemia [11], but how sulfatide or other self-lipids are presented physiologically has not been investigated yet.

Type II NKT cells are more abundant in humans than in mice. A novel regulatory mechanism in the liver is orchestrated following activation of type II NKT cells by sulfatide, which limits tissue damage [1,2]. Sulfatide administration results in activation of plasmacytoid DC (pDC), but tolerization of mDC followed by anergy induction in type I NKT cells [2]. Both anergic type I NKT cells and tolerized mDC also inhibit expansion of adaptive immunity. Tolerized mDC may also control inflammation through IL-10 secretion and they are abundant in the human liver as well. Thus, a cascade of proinflammatory events is inhibited following sulfatide-mediated activation of type II NKT cells. Other type II NKT cells may contribute to HBV-induced hepatitis [12]. Thus, differential activation of type II NKT subsets depends upon the lipid antigen and state of APCs leading to an exacerbated or diminished inflammatory response. Since NKT cells orchestrate changes in other cells including DC, NK cells, and adaptive B and T cells, they can radically affect the outcome of liver inflammation

Future perspectives

Though animal models may not represent all aspects of human liver disease, it is likely that some key immune pathways are conserved among species. Since CD1d and NKT-cell systems are extensively similar between mice and humans, a greater understanding of NKT subsets' interplay in experimental models is important, not only for the understanding of immune regulatory mechanisms in the liver, but also to enable the development of novel HLA-independent therapeutics for human inflammatory liver diseases. Several key questions still need to be addressed: (1) are there similarities in the biological roles of type I and type II NKT cells in mice and humans in liver disease? (2) Can self-lipid/human CD1d-multimers be utilized for the characterization of human NKT cells? (3) Are OPN levels in liver following injury modulated by type I NKT cells? (4) Can inhibition of type I NKT cells be beneficial in ALD or NAFLD?

Financial support

This work was supported by grants from the National Institutes of Health (R01 CA100660 and R01 AA020864), Juvenile Diabetes Research Foundation (24-2007-362) and Multiple Sclerosis National Research Institute.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Fig. A proinflammatory and protective role of type I and a major type II NKT subset, respectively, in non-microbial liver inflammatory disease. APC, antigen-presenting cells; mDC and pDC, myeloid and plasmacytoid dendritic cells; Hh, Hedgehog pathway; OPN, osteopontin; HSC, hepatic stellate cells.

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