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Review article

Understanding the behavior of invariant NKT cells in autoimmune diseases

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Abstract

Invariant NKT (iNKT) cells are a unique subset of lymphocytes that recognize glycolipid antigens presented by a monomorphic glycoprotein CD1d. Numerous works have shown that iNKT cells may serve as regulatory cells in autoimmune diseases including multiple sclerosis (MS). However, recent studies have revealed that the presence of iNKT cells accelerates some inflammatory conditions, implying that their protective role against autoimmunity is not predetermined. Here we review recent information concerning the mechanism of how iNKT cells intervene or promote autoimmune inflammation. Although iNKT cells are thought to be specific for a limited set of glycolipids, they may cross-react to self and non-self ligands. Regarding the response to non-self, it is now known that iNKT cells produce enormous amounts of proinflammatory cytokines during the course of infectious diseases, which is triggered by TCR ligation by microbial lipids, cytokines produced from APCs or both. Whereas the strongly activated iNKT cells play a beneficial role in combating environmental pathogens, they could play a deleterious role in autoimmunity by producing disease-promoting cytokines. However, iNKT cells in the steady state would retain an ability to produce anti-inflammatory cytokines, which is needed for terminating the ongoing inflammation. Though an initial trigger for their regulatory responses remains elusive, our recent work indicates that iNKT cells may start regulating inflammation after sensing the presence of IL-2 in addition to recognizing a ubiquitous endogenous ligand. Understanding of how iNKT cells regulate autoimmunity should lead to a more sophisticated strategy for controlling autoimmune diseases.

Keywords: NKT cells; iNKT cells; Multiple sclerosis

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1. Introduction

Invariant NKT (iNKT) cells are regulatory T lymphocytes reactive to lipid antigen presented by a monomorphic glycoprotein CD1d (Bendelac et al., 2007; Kronenberg, 2005; Taniguchi et al., 2003). Many previous reports have documented that the number or function of iNKT cells is altered in patients with autoimmune diseases such as multiple sclerosis (MS) (Araki et al., 2003; Illés et al., 2000; Kojo et al., 2001; van der Vliet et al., 2001b; Wilson et al., 1998). Studies using transgenic mice that over- or under-express iNKT cells have basically supported the involvement of iNKT cells in the pathogenesis of autoimmune diseases (Miyake and Yamamura, 2007a). Moreover, stimulating iNKT cells with synthetic glycolipids has proven effective for preventing experimental autoimmune encephalomyelitis (EAE) (Miyamoto et al., 2001; Pál et al., 2001) or spontaneous type 1 diabetes (T1D) in NOD mice (Naumov et al., 2001; Sharif et al., 2001), indicating the important role of iNKT cells in controlling pathogenic autoreactivity and maintaining immune homeostasis (Miyake and Yamamura, 2007b). However, more recent studies have shown that iNKT cells may augment inflammatory conditions in models of arthritis (Chiba et al., 2005; Kim et al., 2005; Ohnishi et al., 2005), $CD8^+$ T cell-mediated diabetes (Griseri et al., 2005), experimental colitis (Ronet et al., 2005; Ueno et al., 2005) and airway hypersensitivity reactions (Akbari et al., 2003; Meyer et al., 2007). These results indicate that unlike $CD4^+$ $CD25^+$ regulatory T cells that appear to be a faithful regulator of unwanted immune responses (Sakaguchi and Sakaguchi, 2005), iNKT cells' help is only conditional and would occasionally take part in augmentation of harmful inflammation. How activation of iNKT cells manifests such opposing results and what is an initial trigger for the regulatory iNKT cell responses has remained to be unanswered. Here we review recent advances in the research of iNKT cells that may be relevant for understanding the "Janus-like" behavior of iNKT cells (Wilson and Delovitch, 2003). Our ultimate goal is to seek ways for making iNKT cells serve as a reliable guardian for our health.

2. General properties of iNKT cells

Although iNKT cells express T cell receptor (TCR) α- and β-chains, their TCR diversity is very limited owing to their expression of a single α-chain (Vα14-Jα18 in mice, Vα24-Jα18 in human) coupled with a β-chain rearranged with a limited Vβ gene segments (Vβ8.2, Vβ2 and Vβ7 in mice, Vβ11 in human). Unlike conventional T cells, they constitutively express memory/activated T cell phenotype and are capable of producing enormous amounts of pro- and anti-inflammatory cytokines shortly after TCR engagement (Bendelac et al., 2007; Kronenberg, 2005; Miyake and Yamamura, 2005; Taniguchi et al., 2003). The cytokine burst following iNKT cell activation then triggers a maturation process in downstream cells such as NK cells, dendritic cells (DCs), B cells and T cells, leading to subsequent alteration of a broad range of adaptive immune responses. It is widely accepted that they could behave very much like innate lymphocytes rather than conventional T cells (Mempel et al., 2002), and owing to the rapidity with which they respond to various stimuli, they play an important role in bridging innate and adaptive arms of immune response.

The ability of iNKT cells to produce regulatory cytokines is so outstanding that they could efficiently alter an adaptive immune response. Mouse iNKT cells can produce interferon-γ (IFN- γ), IL-2 (Jiang et al., 2005), -3 (Leite-de-Moraes et al., 2002), -4, -5, -13, -17, -21 (Coquet et al., 2007), GM-CSF (Leite-de-Moraes et al., 2002), and osteopontin (Diao et al., 2004) after an optimal engagement of TCR. However, it does not mean that iNKT cells would purposefully use all the listed cytokines. In fact, it can be assumed that except for extreme conditions (like stimulation with strong agonists), iNKT cells may produce only a set of Th1 or Th2 cytokines in physiological conditions. We support this postulate because the TCR engagement by an endogenous ligand is likely to be modest or suboptimal in most situations (Sakuishi et al., 2007). With regard to their role in balancing immune homeostasis, an organized production of Th1, Th2 or Th17 cytokines is probably required for iNKT cells to conduct meaningful jobs.

3. Exogenous glycolipids stimulatory for iNKT cells

Since a marine sponge-derived glycosphingolipid, α-galactosylceramide (α-GalCer), was discovered as a potent ligand for iNKT cells (Kawano et al., 1997), a synthetic α-GalCer has widely been used for study of iNKT cells as a surrogate ligand (Fig. 1). It is now established that two lipid chains of α-GalCer are inserted to hydrophobic grooves of the CD1d glycoprotein expressed by antigen presenting cells (APCs) (McCarthy et al., 2007), whereas the α-linked sugar moiety is accessible and recognized by the TCR of iNKT cells. Recently, the crystal structure of the invariant TCR and CD1d loaded with α-GalCer has shown a very unique orientation of TCR towards CD1d (Borg et al., 2007), which allows a selective involvement of the invariant α-chain for recognition of the α-linked sugar.

Comparison of α-GalCer with its structurally altered analogues has provided important insights into how iNKT cells may differentially respond to glycosphoingolipids with lipid tail variants (Brutkiewicz, 2006; Miyake and Yamamura, 2007b). As a representative example, we showed previously that an α-GalCer analogue called OCH (Miyamoto et al., 2001; Oki et al., 2004, 2005), with a shorter sphingosine chain (Fig. 1), would selectively stimulate IL-4 production from iNKT cells, whereas α-GalCer stimulation induces both IL-4 and IFN-γ. Accordingly, OCH stimulation of iNKT cells favors a Th2 bias of immune responses *in vivo*, as compared to α-GalCer stimulation.

α-linked sugars such as α-GalCer are not recognized as a product of mammalian cells, implying that α-GalCer is not a physiological ligand for iNKT cells. Currently, it is well recognized that iNKT cells can be activated during infectious diseases (Tupin et al., 2007). Interestingly, it has been reported that α-GalCer-like glycosphingolipids are rather ubiquitously found in the environment, indicating that α-GalCer may be actually derived from bacteria residing with the marine sponge. Whether or not α-GalCer is derived from bacteria, we may ask a number of questions as to whether infectious diseases may influence on autoimmune disease via activation of iNKT cells