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Cells in focus

Natural killer T cells: rapid responders controlling immunity and disease

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Abstract

Natural killer T (NKT) cells are a subset of T cells that share properties of natural killer cells and conventional T cells. They are involved in immediate immune responses, tumor rejection, immune surveillance and control of autoimmune diseases. Most NKT cells express both an invariant T cell antigen receptor and the NK cell receptor NK1.1, and are referred to as invariant NKT cells. This invariant T cell receptor is restricted to interactions with glycolipids presented by the non-classical MHC, CD1d. These NKT cells rapidly produce high levels of interleukin (IL)-2, IFN-γ, TNF-α, and IL-4 upon stimulation through their TCR. Most also have cytotoxic activity similar to NK cells. NKT cells are involved in a number of pathological conditions, and have been shown to regulate viral infections in vivo, and control tumor growth. They may also play both protective and harmful roles in the progression of certain autoimmune diseases, such as diabetes, lupus, atherosclerosis, and allergen-induced asthma.

Cell facts

- NKT cells express both T and NK cell markers, and most carry an invariant T cell receptor restricted to interactions with CD1d.
- NKT cells respond to TCR stimulation by rapidly producing high levels of pro- as well as anti-inflammatory cytokines.
- NKT cells are involved in the rapid immediate immune response to infection and are important for the clearance of a number of pathogens.
- NKT cells play a dual role both in controlling certain diseases while exacerbating others.

Keywords: Cytokines; Interleukin-4; α-Galactosylceramide; CD1d; Immune response

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1. Introduction

Natural killer T (NKT) cells represent a specialized subset of thymus-derived T cells that express the T cell receptor (TCR) as well as NK cell markers, such as NK1.1 (NKRP1C) and Ly-49. A large majority of NKT cells express an invariant TCR consisting of the Vα14–Jα18 (previously named Jα281) α-chain (Vα24–JαQ in humans) paired with a Vβ8 or Vβ2 β-chain, and so these cells are referred to as invariant NKT (iNKT) or Vα14 NKT cells (Berzins et al., 2004). This review will, therefore, focus on these cells, and refer to them as NKT cells. The invariant TCR expressed by these NKT cells is unique in that it interacts with the non-classical MHC molecule CD1d (or the human homologue of CD1d), and mice lacking CD1d or Jα18 of the TCR α-chain lack these cells (reviewed in Godfrey, Hammond, Poulton, Smyth, & Baxter, 2000). CD1d has a deep, hydrophobic antigen-binding pocket that allows it to present lipid and glycolipid antigens rather than peptide antigens. While the natural ligand presented to NKT cells by CD1d in vivo has previously been unclear, and thought to be a glycosylphosphatidylinositol, Zhou et al. recently reported that isoglobotrihexosylceramide (iGb3) may be an endogenous ligand for these cells (Hansen & Schofield, 2004; Zhou et al., 2004). One particular synthetic glycolipid, α-galactosylceramide (α-GalCer), has proven to be a useful tool for analyzing NKT cell responses. α-GalCer, derived from marine sponges has been identified as a specific ligand for both mouse and human NKT cells. The use of α-GalCer has been a powerful tool for analyzing NKT cell function in vivo since conventional T cells do not recognize this molecule (Crowe et al., 2003). Stimulation of NKT cells with α-GalCer or using antibodies against the TCR results in a vigorous response marked by proliferation, expression of activation molecules, increased cytotoxic activity, and secretion of various cytokines, in particular large amounts of TNF-α, interleukin-2 (IL-2), the T_H1 cytokine IFNγ and the T_H2 cytokine interleukin-4 (IL-4). Their ability to produce large quantities of these cytokines both in vitro and in vivo has been well characterized. The aim of this review is to give a brief view of a cell population that appears to be pivotal, if not required for immediate responses to most infections, as well as in prevention of certain autoimmune diseases and cancer. As much of the work on NKT cells has been performed in mice the information presented here will be referring to mice unless specified.

2. The origins of NKT cells

NKT cells were originally identified for their ability to rapidly produce IL-4 and IFN-γ upon stimulation using anti-CD3 antibodies. NKT cells, like T cells arise from thymocyte progenitor cells (Fig. 1). Currently, it is unclear how early, prior to TCR expression, progenitor cells become committed to the NKT lineage since they are identified by their TCR specificity. Following TCR expression, CD1d restricted cells can be identified even before NK1.1 expression based on the ability to bind α-GalCer/CD1d tetramers (Gumperz, Miyake, Yamamura, & Brenner, 2002). Based on expression of the cell surface marker DX5, CD1d reactive NKT cells have been divided into four stages of development. The first two stages are immature, with the most immature stage lacking both DX5 and NK1.1. These cells are highly $CD4^+$ as are cells in the next stage, $DX5^+/NK1.1^-$. Mature NKT cells are divided almost equally into $DX5^+/NK1.1^+$ and $DX5^-/NK1.1^+$ cells (Gadue & Stein, 2002). In contrast to conventional T cells, which develop in the fetus and are present at birth, NKT cells are not found until approximately 5

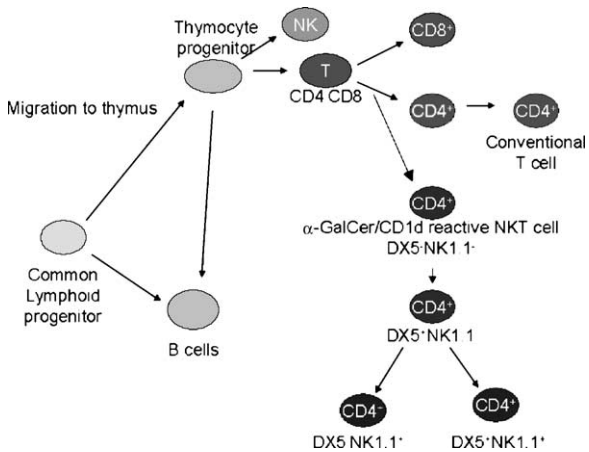

Fig. 1. Development of NKT cells. NKT cells develop in the thymus from thymocyte progenitor cells. Following commitment to the T cell lineage Vα14Jα18 TCR bearing, CD1d reactive $CD4^+$ T cells can be identified. Immature NKT cells are $DX5^-NK1.1^-$ and develop into $DX5^+NK1.1^-$ cells. Mature NKT cells are equally divided into $DX5^-NK1.1^+$ and $DX5^+NK1.1^+$ cells.