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Extended Abstract

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Modulating immune responses with designed glycolipid antigens that target Natural Killer T cells using a structural-functional approach

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Natural Killer T (NKT) cells are a unique T cell population characterized by features of both the innate and adaptive immune response. Two main classes of NKT cells (Type I and II) exist that express different antigen receptors (TCRs) and respond to different glycolipids presented by the shared antigen-presenting molecule CD1d. Type I NKT cells respond rapidly to the prototypical antigen □-galactosylceramide (□-GalCer) and can secrete both pro- and anti-inflammatory cytokines, while Type II NKT cells recognize the self-glycolipid sulfatide and are thought to be controlling autoimmunity. The cytokine profile of Type I NKT cells can be altered using modified synthetic glycolipids to produce the cytokine response of choice. Through biophysical TCR binding affinity measurements, as well as crystallographic studies of how the TCR engages different CD1dpresented glycolipids, we and others have identified the structural basis of glycolipid recognition by NKT cells. The TCR of Type I NKT cells binds to CD1d with a conserved footprint, while inducing structural changes in both CD1d and the glycolipid antigens. This conserved TCR binding mode allows for the design of glycolipid antigens, predominantly analogs of □-GalCer in an attempt to obtain glycolipids that elicit a particular cytokine profile. We are especially interested in identifying novel antigens that elicit pro-inflammatory cytokines, since they have great potential as vaccine adjuvants. I will present our ongoing work on characterizing novel CD1d-restricted antigens, which led us to a surprising discovery. NKT cells are a specialized group of unconventional T-cell lymphocytes, characterized by the co-expression of T-cell antigen receptors (TCRs) together with multiple other surface receptors that are commonly expressed by NK cells (for example, CD161/NK1.1, NKG2D and members of the Ly-49 family). NKT cells modulate the activation and phenotype of other immune cell types and hence affect the responses against a vast array of diseases, including cancer, infections, autoimmunity and allergy. This has led to substantial interest in these cells as targets for potential immunotherapeutic strategies. In addition, they participate in the homeostasis of the immune system and under normal circumstances have been proposed to have a regulatory role. As their name implies, NKT cells display features of both T cells and NK cells and have a range of effector functions that include the secretion of multiple cytokines and the ability to mediate cytotoxicity. Unlike classical NK cells, NKT cells derive from the T-cell lineage and develop throughout a process that is dependent on thymic selection and specific TCR-mediated recognition. However, their ability to respond rapidly and strongly without prior antigen priming indicates that they also function as part of the innate immune system. In contrast to conventional CD8 and CD4 T cells, whose TCRs recognize peptides bound to class I and class II major histocompatibility complex (MHC) molecules, respectively, TCRs of NKT cells recognize lipid antigens bound to CD1d, a non-polymorphic MHC-I-like molecule. CD1d is expressed by all hematopoietic cells as well as some epithelia and other non-hematopoietic cell types, although expression levels are highest in immunologically relevant antigen-presenting cells, such as dendritic cells (DCs) and B lymphocytes. Current classification schemes broadly define CD1d-dependent NKT cells into two broad classes, referred to as type I and type II NKT cells. Type I NKT cells express an invariant TCRα chain (Vα14Jα18 in mice and Vα24Jα18 in humans). These are paired with a moderately diverse repertoire of TCRβ chains using predominantly Vβ8, Vβ7 and Vβ2 in mice and Vβ11 in humans. Because of their characteristic invariant TCRα chain, the type I NKT cells are also known as invariant NKT cells (iNKT cells). These cells recognize lipids and glycolipid antigens bound to CD1d, and their activation has many potential effects on pro- and anti-inflammatory immune responses. Although much less studied, type II NKT also respond to lipids and glycolipids presented by CD1d and have been shown to have a range of different immunomodulatory functions. In contrast to iNKT cells, type II NKT cells express a diverse repertoire of TCRs, possibly as diverse as those of conventional T cells and thus are also referred to as diverse NKT cells (dNKT cells). Although less well studied than iNKT cells, dNKT cells appear to respond to different lipids than those recognized by iNKT cells and are likely to perform different roles in the immune system. In this article, we focus exclusively on the immunomodulatory effects of iNKT cells and their glycolipid ligands. Despite the great potential of NKT cells for immunomodulation, their relatively low frequency in the blood, lymphoid organs and tissues has made their study difficult in humans. On the other hand, mice display much higher frequencies of total NKT cells, a different tissue distribution and altered ratios of iNKT/dNKT cells as compared with humans, making them a useful but imperfect model of their human counterparts. Although human and mouse NKT cells have many conserved features, the major difference in frequency makes it difficult to extrapolate findings from mouse to humans for NKT-cell-based immunotherapy. Some attempts to overcome this problem have considered the use of non-human primates, as they display NKT cell frequencies that are close to those seen in humans. However, these studies are limited by sample size, available tools, high costs and the inability to perform genetic manipulations. These limitations have encouraged the development of humanized mouse models, such as the recently reported human CD1d knock-in mouse, which displays NKT cell frequencies and tissue distribution similar to humans. The NKT cells in this mouse model show a ratio of iNKT to dNKT subsets that mirrors the ratio in normal humans and retain substantial immunomodulatory functions in a variety of in vitro and in vivo assays.

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