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Review

Physiology and Potential Application of NKT Cells: A Minireview

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Abstract

CD1d-restricted T (NKT) cells are potent regulators of autoimmunity, tumor immunity, and transplantation-related immunity. NKT cells are a subset of innate lymphocytes that recognize endogenous or exogenous glycolipids in the context of CD1d molecules. Recent progress in the research of NKT cells has proved that NKT cells function as a bridge between innate and adaptive immunity in anticancer immunity. Furthermore, NKT cells also function as a bridge to tolerance or rejection of grafts in organ transplantation. Harnessing the function of NKT cells, and trying to put it into clinical application in the treatment of autoimmune disease, anticancer cell immunotherapy, and organ transplantation are the dreams of immunologists. This minireview will focus on the physiology of NKT cells and potential clinical application.

Key Words: NKT cells, anticancer immunotherapy

Introduction

Natural killer T (NKT) cells are unique population of dynamic T cells capable of regulating a broad range of immune responses, including infection, autoimmunity, and tumor immunity (12). NKT cells are a subset of innate lymphocytes, defined by the canonical $V_\alpha14$-$J_\alpha18$ T cell receptor (TCR)-α chain in mice ($V_\alpha24$-$J_\alpha18$ in humans), recognize lipid antigens in the context of CD1d and mediate potent immune regulatory functions *via* the rapid production of interferon-γ (a Th-1 cytokine) and interleukin-4 (a Th-2 cytokine) (30). Note that, among the cells that have been postulated to link the innate immunity and adaptive immunity, CD1d-restricted NKT cells are compelling candidates, being able to respond rapidly and subsequently to activate other cell types (32). Despite its being non-polymorphic, CD1d can still bind a variety of antigens because of its narrow and deep hydrophobic antigen-binding groove. These include the α-galactoceramide (α-GalCer) (derived from marine sponge), certain α-linked bacterial glycosphingolipids, and bacterial-derived diacylglycerols (Table 1) (21). Two α-GalCer analogs, c-glycoside (α-C-GalCer) and OCH, have been particularly reported to bias the Th1 or Th2 cytokine profiles, respectively.

There is convincing evidence that NKT cells belong to a separate lineage of T lymphocytes in the thymic cortex. NKT precursor cells segregate from the mainstream of thymocyte development at the $CD4^+CD8^+$ double-positive stage. However, it is still in debate whether NKT cells seen at sites other than the thymus (*e.g.* the liver, spleen, and bone marrow) are of thymic origin or extrathymic origin (11, 22, 33). The traditional classification of NKT cells has

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Table 1. Glycosphingolipid ligands of NKT cells presented in the context of CD1d molecule

Glycosphingolipid Ligands	Biased Th Response (cytokine production)
α-Galactosylceramide (α-GalCer)	
Truncated α-GalCer	Biased Th2 response (IL-4)
C-glycoside	Biased Th1 response (IFN-γ)
Bacterial recognition	
Sphingomonas related	
α-glucuronosylceramide (GSL-1)	Th1/Th2 responses (IFN-γ/IL-4)
α-galacturonosylceramide (GS-1')	
Self-antigen recognition	
Isoglobotrihexosylceramide (iGb3)	Th1/Th2 responses (IFN-γ/IL-4)

been complicated by the fact that NKT cells were defined in many different ways (i) $CD3^+NK1.1^+$ cells, (ii) $V_\alpha14^+$ cells, (iii) cells reactive to CD1d tetramers conjugated with α-GalCer. However, several lines of evidence have pointed out that the definition of NKT cells by the coexpressing of CD3/NK1.1 is imprecise because a significant set of $V_\alpha14^+$ cells do not express NK1.1. Further, NK 1.1 marker was down-regulated after NKT activation (3, 10). Because classical $V_\alpha14^+$ ($V_\alpha24^+$ in humans) are highly reactive to α-GalCer and were defined as type I NKT cells independent of their expression of NK1.1, whereas non-classical nonvariant, $V_\alpha14^-$ NKT cells were defined as type II NKT cells. Both cell types are restricted by CD1d and are absent in β2-microglobulin (β2m)-deficient or CD1d-deficient mice (34).

In contrast to conventional T cells, NKT cells respond within minutes after TCR ligation and do not depend on clonal expansion, differentiation, and migration to the target organ. The effector/memory phenotype of NKT cells, and their constitutive expression of mRNA for IL-4 and IFN-γ, suggested that they undergo a strong antigenic stimulation during their differentiation. This is consistent with the hypothesis that true TCR agonists mediate their positive selection (21). These unique characteristics render NKT cells perfect first-line defense microbial pathogens (37). The current paper tried to review the updated lines of evidence of physiology of NKT cells and the future potential clinical application.

To date, two models of NKT cell activation have been proposed. The first proposes hat NKT cells actually have two subsets: Th1-like NKT and Th2-like NKT. The second suggests that NKT cells are a homogenous population that attains functional phenotypes according to different cytokine environment (37).

Pathophysiology of NKT Cells in the Digestive Tract

The first demonstration of CD1d function in the intestine occurred more than 10 years ago, when it was first shown that intestinal epithelial cells can activate T cells in a CD1d-restricted manner and that oligoclonal T cells with a biased TCR repertoire reside in the intestinal compartment (27). CD1d molecule is synthesized in the endoplasmic reticulum where it associates with microsomal triglyceride transfer protein, which assists in loading endogenous antigens into the CD1d groove before transport of CD1d to the cell surface (4). Intriguingly, saposins and GM2 protein can assist in loading exogenous glycolipids into CD1d once it reaches the cell surface. According to several reports, up to 4% of intraepithelial lymphocytes in small intestine, 10% in large intestine coexpress the TCR^+/CD3ε and NK cell receptors (NK 1.1 in mice and CD161 in humans) (17, 18). However, direct analysis of NKT cells by detection of $V_\alpha14$ in mice and $V_\alpha24$ in humans or by staining with α-GalCer-loaded CD1d tetramers revealed considerably lower numbers of NKT ranging from 0-2% in humans and mice (9, 23, 28).

Conventional NKT cells produce large amounts of both IL-4 and IFN-γ upon *in vitro* administration of anti-CD3 mAb. NKT cells are involved with several pathophysiological changes in the digestive tract. Among these diseases, inflammatory bowel disease (IBD), which is characterized by inflammatory response to antigens derived from the gut lumen, was most often investigated. Several studies have demonstrated that NKT cells played an important role in the protection effect in patients with IBD as NKT cells have been found to be reduced in numbers in patients with Crohn's disease (15, 35). Interestingly, intraepithelial lymphocytes-mediated presentation of α-GalCer leading to NKT cell secretion of Th2 cytokines was suggested as a protective mechanism of disease amelioration (37). Furthermore, in contrast to Th2-mediated types of intestinal inflammation, the role of NKT cells in Th1 diseases is less obvious. Although the percentage of $CD3^+NK1.1^+$ cells in the intestinal lamina propria is similar in Crohn's disease

as compared with ulcerative colitis, these cells are not CD1d-restricted (9).

Relationships between NKT Cells and Autoimmune Disease

Extensive works in the 90s have found that NKT cells are important in the regulation of Th2 immune response. Following quasi-invariant TCR engagement, these cells produce immediate large amounts of IL-4, which drives the differentiation and growth of Th2 cells (1). Moreover, studies in mice lacking NKT cells have suggested that NKT cells are indeed important sources of Th2 differentiation and IgE production (36).

The connection of NKT cells and asthma has been investigated. In patients with bronchial asthma, large numbers of NKT cells were found in the bronchoalveolar-lavage fluid. Further immunohistochemical studies revealed that a significant portion of $CD4^+$ T cells coexpressed invariant TCR, indicating that they were actually NKT cells (12). Intriguingly, NKT cells in these patients produced prominent amounts of IL-4 and IL-13, whereas the values were normal in normal healthy subjects.

Systemic lupus erythematous (SLE) is a multiorgan involved autoimmune disease. Studies have indicated that Th1 cytokine IFN-γ plays an important role in the pathogenesis of SLE, since disease severity can be reduced by anti-IFN-γ therapy. Because NKT cells are well-known IFN-γ producers, the relationship between SLE and NKT cells have been investigated (13). CD1d-tetramer-positive $CD4^+$ NKT cells are required for the *in vitro* augmentation of IgM and IgM anti-dsDNA antibody secretion. Furthermore, auto-reactive B cells are stimulated to secrete IgM and then IgG autoantibodies by $CD4^+$ NKT cells (38).

Another common autoimmune disease-diabetes mellitus also has been studied on the relationship with NKT cells. A significant deficiency of NKT cell numbers and functional capacities in nonobese diabetic (NOD) mice was noted, as evidenced by reduced IL-4 production following TCR ligation (6, 14, 16).

NKT Cells and Antitumor Immunity

NKT cells are important in antitumor immunity. The interaction of dendritic cells with innate lymphocytes represents an additional control mechanism for the induction of adaptive immunity. Innate lymphocytes, like NK or NKT cells, have been implicated to activate dendritic cells by different profiles of cytokines- and cell contact-dependent signals (24).

Alternations in NKT cell function or numbers have been studied in patients with several kinds of malignancies, implicating that NKT cells are important in the rejection of tumors, or alternatively, tumor can induce reduction of numbers or functional impairment in NKT cells. *In vitro* studies have proved that NKT cells stimulated by α-GalCer-pulsed dendritic cells can regain cytotoxic capacities (20). However, there is a report showing that number and/or function of NKT cells in patients with glioma are comparable to those found in healthy individuals (6).

In patients with multiple myeloma, NKT cells from peripheral blood or tumor bed were found to IFN-γ defective. Intriguingly, there is a positive relationship between functional impairment and tumor progression. Importantly, it was demonstrated that this functional impairment could be stimulated by α-GalCer-pulsed dendritic cells (7). Nonetheless, tumor-infiltrated NKT cells have been identified as an important prognostic factor. In patients with colorectal carcinomas, the numbers of tumor-infiltrated NKT cells were reported to be positively implicated with overall survival and disease-free survival (37). NKT cells stimulated by α-GalCer and combined with T cell-activating monoclonal antibody (anti-4-1-BB mAb) and tumor apoptosis-inducing monoclonal antibody (anti-DR5 mAb) have been reported to be very efficiently eradicate large established mammary carcinoma in BALB/c mouse models (31).

However, several lines of evidence have demonstrated that CD1d can regulate immune responses independent of NKT cells. Studies using a 4T1.2 metastatic mammary carcinoma model have demonstrated that tumor metastases are more significant in wild type mice than in CD1d-deficient mice (26). Interestingly, $CD4^+$CD1d-restricted T cells were reported to produce immunosuppressive cytokine IL-13, which acts on $CD11b^+Gr\text{-}1^+$ cells, and in turn triggering these cells to produce TGF-β, which is responsible for cytotoxic T cell suppression (31). In addition, CD1d molecule appears to influence innate NK cell killing, as CD1d overexpressing NK cell targets are protected from lysis by LAK cells (5).

One thing to be noted in antitumor immunity is the fact that balancing antitumor immunity and autoimmunity is important. The more antitumor immunity is evoked , the more autoimmunity is at risk. In antitumor immunity, $CD4^+$ and $CD8^+$ T cells, CD1d-restricted NKT cells, and antibodies are required for tumor protection. In preliminary studies using anti-CTLA-4 antibody to treat B16 melanoma, tumor destruction was evidenced by significant lymphocyte and granulocyte infiltration and accompanied autoimmunity. A key issue of ongoing investigation is to determine whether tumor immunity and autoimmunity can be dissociated (8).

Role of NKT Cells in Transplantation Immunology

The relationship between NKT cells and transplantation immunology is still evolving. In $CD1d^{-/-}$ mice transplanted with sex-mismatched skin grafts, rejection rates were higher than in wild-type mice (25). Moreover, cardiac allografts were accepted in mice treated with anti-LFA-1/ICAM-1 or CD28/B7 monoclonal antibodies (mAbs) but were rejected in $NKT^{-/-}$ mice that received the same antibodies. In addition, graft survival was shown to involve increased immunosuppressive IL-10 production (29). The current hypothesis is that NKT cells may primarily serve to aid regulatory T cell function in transplantation graft tolerance (19, 22).

However, it is still unclear as to the precise role of NKT in transplantation immunology. Different cytokines production in graft microenvironment may bias the NKT differentiation toward graft tolerance or rejection. Further in-depth investigations are imperative to better elucidate role of NKT cells in these very complicated environment.

Potential Clinical Application of NKT Cells

Harnessing NKT cell function to treat different kinds of tumor has already gone into clinical trials (2, 6). These studies have demonstrated that, using α-GalCer to stimulate dendritic cells, NKT cells can be expanded more than 100-fold. In addition, dendritic cells can be effective adjuvant for boosting innate effectors in humans as well, and that this can lead to an increase in adaptive immunity. However, the study subjects in these trials are limited, and the clinical response is still not clear-cut. Furthermore, it has been shown that over-stimulation of NKT cells by repeated α-GalCer injections results in NKT cell anergy, expansion of $CD4^+CD25^+$ regulatory T cells (9). Further studies using larger sample size and better experimental design are needed.

Another thing to be noted in the clinical application of NKT cells is that liver has higher population of NKT cells than other organs. Possible liver injury during the NKT manipulation may pose a potential problem. However, in a dose escalation trial in patients injected with 5 mg/m^2 show no hepatoxicity in the α-GalCer-treated patients. Of interest, despite different binding affinities between α-GalCer and OCH, both compounds were shown to induce comparable dendritic cell maturation and equally protective CTL responses. Therefore, in order to reduce potential NKT-driven immunopathology and tissue injury, using OCH as an alternative to α-GalCer may be a reasonable option.

Conclusions

The ability of CD1d molecules to present structurally diverse glycolipids to T cells has stimulated extensive research. The unusual development pathway of NKT cells in the thymus has focused attention on the underestimated potential of hematopoietic cells to guide T cell selection. Importantly, activation of NKT cells with α-GalCer leads to potent downstream activation of $CD8^+$ T cells, NK cells, and APC, such as dendritic cells and B cells. Bystander activation of these cells is critical to the protective antitumor and antimicrobial immunity.

The involvement of NKT cells in the diverse immune responses to autoimmunity, transplantation, antitumor immunity, and the fact that NKT distribute in different organs with different distribution density, implicating the functional diversity of NKT cells in different pathophysiology changes. Further in-depth studies are imperative to better understand the complexities NKT cells are involved with.

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