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Dissecting the Roles of Natural Killer T cells in Autoimmune Disorders and Malignancy

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Abstract

Natural killer T (NKT) cells are a heterogeneous group of T cells that share properties of both T cells and natural killer (NK) cells. Many of these cells recognize the non-polymorphic CD1d molecule, an antigen-presenting molecule that binds self and non-self glycolipids and lipids. NKT cells are able to influence autoimmune and cancer diseases, thanks to their innate and adaptative immune properties. A hallmark of NKT cells is their ability to express pro- and anti-inflammatory T helper(h)1 and Th2 cytokines upon antigenic stimulation, and to modify both inflammatory mediators and late stage T cell responses. Thus, NKT cells are considered critical cells in regulatory events that direct the inflammatory response. Additionally, NKT cells can regulate the functions of other NKT subsets. The purpose of this review is to highlight the importance of NKT cells as regulators of autoimmunity disorders and cancer.

Keywords: Natural Killer T cells; Autoimmune disorders; Cancer; Inflammation; Allergy

Introduction

Natural killer T (NKT) cells are a heterogeneous group of T cells that share properties of both T cells and natural killer (NK) cells. It has been demonstrated that NKT are involved in the regulation of immune responses by bridging the innate and adaptive immune system cells. Many of these cells recognize the non-polymorphic CD1d molecule, an antigen-presenting molecule that binds self and non-self glycolipids and lipids [1]. NKT cells are able to rapidly produce large amounts of pro- and anti-inflammatory T helper (Th)1,Th2, Th3 and/or Th17 cytokines upon antigenic stimulation, which endows these cells with strong immunomodulatory activities [2]. Thanks to their innate and adaptative properties, the NKT cells are implicated in the regulation of immune responses, including infections, tumors, transplants, allergic and inflammatory reactions, autoimmune diseases and infectious diseases ranging from bacteria and viruses to fungi and parasites [3]. In cancer, NKT cells play a protective role, but can also inhibit tumor immune surveillance as well as cancer immunotherapy [4]. The purpose of this review is to highlight the importance of NKT cells as regulators of autoimmunity disorders and cancer.

The Biology of Natural Killer T cells

NKT cells constitute a unique lymphocyte population. These cells are divided in two subsets, type I and type II. Differently from conventional $CD4^+$ T helper (Th) cells that recognize peptide antigens bounded to major histocompatibility complex (MHC) molecules, both subsets of NKT cells recognize lipid antigens bounded to CD1d molecules [5-7]. Type I NKT cells (or invariant NKT cells) express an invariant T cell receptor (TCR; Vα14Jα18 in mice and Vα24Jα18 in humans), while type II NKT cells (or non-invariant NKT cells) express variable TCRs [6,8,9]. The TCRs present on type I NKT cells recognize the antigen α-galactosylceramide (α-GalCer). Within this group, distinguishable subpopulations have been identified, including $CD4^+CD8^-$ cells and $CD4^-CD8^-$ cells that are present in mice and humans, and $CD4^-CD8^+$ cells that are found only in humans [10]. Type I NKT cells share a similar distribution between human and mice. These cells, as type II NKT cells, are present in tissues in which lymphocytes are present, such as thymus, spleen, blood, bone marrow, lymph node and liver. The frequency of type I NKT cells is much lower in humans compared to mice [11,12]. Less is known about type II NKT cells, which express a wider range of TCR alpha chains and do not recognize the α-GalCer antigen. These cells represent the majority of NKT cells present in humans, differently from mice, in which are prevalently present type I NKT cells [13]. NKT cells arise in the thymus from a common precursor pool of $CD4^+CD8^+$ double positive thymocytes, that have undergone random TCR-β gene rearrangement and expression [14]. Expression of TCR that binds to self-peptide–MHC class II or I molecules on thymic epithelial cells (TECs), leads to the positive selection of conventional $CD4^+$ or $CD8^+$ T cells, respectively. Thymocytes that express TCR interacting with CD1d bounded to self-glycolipid, expressed by other double positive thymocytes, enter the NKT-cell lineage. Once selected, NKT-cell precursors undergo a series of differentiation steps, resulting in the immature NKT-cell pool. Most of immature NKT-cell pool emigrates from the thymus to the periphery. Finally NKT cells undergo a maturation step, at the end of which, these cells are phenotypically and functionally modified. Some mature thymic NKT cells migrate to the periphery, but many remain as long-term thymus-resident cells [15]. It has been demonstrated that mouse and human NKT cells follow similar thymic development and peripheral maturation steps [16-21]. After the maturation process, NKT cells are activated and this step is mediated by CD1d, a glycolipid antigens presented in the monomorphic MHC I-like molecule [22]. The CD1d molecule is expressed on thymocytes, B cells, dendritic

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cells (DC), and macrophages [23]. The CD1d trafficking has been well described by studies performed on mouse models. CD1d assembled with β2-microglubulin in the endoplasmic reticulum, is transported, via the secretory pathway, from the Golgi to the plasma membrane. CD1d cytoplasmic tail regulates the internalization of glycolipids from the plasma membrane and directs trafficking of endosomes to lysosomes [24]. The discovery of α-GalCer, which is able to bind the CD1d molecule and to activate selectively both mouse and human NKT cell, has improved the research on NKT cells. A contribute to better elucidate the NKT cell development and NKT cell immune function, was also given by studies performed with OCH [(2S,3S,4R)-1-O-(-D-galatopyranosyl)-Ntetracosanoyl-2amino-1,3,4-naonanetriol], the glycosylphosphatidylinositol (GPI), the disialoganglioside GD3 and the lysosomal glycosphingolipid iGb3 [25-29]. NKT cells can have either protective or deleterious effects on autoimmune disorders and malignancy, due to their abilities to produce cytokines that promote either inflammation or immune tolerance. As a result, they contribute to antibacterial and antiviral immune responses, promote tumor-related immune surveillance or immunosuppression, and inhibit or promote the development of autoimmune diseases. In table 1, the role of NKT cells are summarized.

NKT cells Play Protective and Pathogenic Roles in Autoimmune and Allergic Disorders

Autoimmune disorders are diseases that occur when the body produces an inappropriate immune response against self-tissues. This causes a prolonged inflammation and subsequent tissue destruction. Autoimmune disorders are classified into organ-specific (directed mainly at one organ) and non-organ-specific (widely spread throughout the body). Examples of autoimmune disorders are: type 1 diabetes, inflammatory bowel diseases, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis scleroderma, hemolytic anemia, Graves' disease and Sjögren's syndrome. These disorders share underlying defects in the immune response leading the body to attack its own organs and tissues. All ages are affected, with onset from childhood to late adulthood. Most of these diseases disproportionately affect women. Allergic disorders are a group of disorders caused by an allergic response to an allergen. They include asthma, atopic dermatitis, allergic rhinitis, food allergy, pet allergy, pollen and insect sting allergies. Protective and pathogenic roles of NKT cells in autoimmune and allergic diseases have been described [2,30]. In most cases, the protective role of NKT cells to autoimmune disease is dependent on the production of interferon (IFN)-γ. In the following paragraphs, we review significant studies providing evidences that NKT cells can regulate autoimmune and allergic disorders (results are summarized in table 1).

Type I diabetes

The most evidence that NKT cells are implicated in autoimmune regulation, has been provided by studies of Type 1 diabetes (T1D). T1D also named insulin-dependent diabetes mellitus or juvenile diabetes, is caused by T cell-mediated destruction of the pancreatic β-cells producing insulin. In the pathogenesis of T1D are implicated both $CD8^+$ and $CD4^+$ T cells. Clinical studies, have demonstrated that the status of NKT cells in TD1 diabetes is controversial [31]. It has been reported that the frequency of peripheral blood NKT cells in TD1 patients decrease [32,33], increase [34] or remain the same [35] if compared to normal control patients. Animal models classically used for diabetes study, are the non-obese diabetic (NOD) mice which develop the spontaneous disease [36]. NOD mice display a reduction in numbers of thymic and splenic NKT cells. In these mice, NKT cells exhibit defects in both their frequency and cytokine production [37]. Several studies have demonstrated that adoptive transfer or transgenic overexpression of the invariant TCR or CD1d can prevent the development of diabetes in NOD mice [37-39]. It has been reported that the protective role of NKT cells in diabetes was associated with Th2 shift within the pancreatic islet. Specifically, NKT cells are able to impair the differentiation of anti-islet reactive T cells into Th1 effector cells in a cell–cell contact dependent mechanism, without Th2 cytokine production or CD1d recognition [40]. Additionally, NKT cells accumulating in the pancreas, can indirectly suppress diabetogenic $CD4^+$ T cells by producing IFN-γ [41]. These findings indicate that NKT play a protective role in diabetes by preventing the differentiation of auto reactive T cells into effector cells. Other studies have reported that activation of NKT cells by administration of α-GalCer prevented autoimmune diabetes in NOD mice and that the protection was associated with the recruitment and induction of dendritic cell subsets [42-44]. In addition it has been reported that treatment of mice with synthetic glycolipid OCH, also prevented diabetes development in NOD mice [45]. Studies on mouse diabetes model established by the adoptive transfer of diabetogenic $CD8^+$ T cells, demonstrated that NKT cells may have a dual role in the modulation of diabetogenic $CD8^+$ and $CD4^+$ T cells. In details, NKT cells may inhibit the development and the progression of diabetes, but they can promote the pathogenesis of $CD8^+$ cells when these cells become diabetogenic. All these findings indicate that protective roles of NKT cells in diabetes may depend on many conditions such as the NKT-cells subset being studied, the stage

Diseases	Model	Type NKT cells	Implicated Mechanism	References
Diabetes	NOD	I	IL-4, IL-10 production Inhibition development pathogenic T cells Selective recruitment of tolerogenic DC	[44,100] [40] [43]
Multiple sclerosis	EAE	I	IL-4, IL-10 production Reduced INF-γ production	[26,101,102] [48,101-103]
Myasthenia gravis	EAMG	I	Reduced INF-γ Reduced Acetylcholine-specific antibody $CD4^+$, $CD25^+$ regulatory T cells	[62] [63]
Rheumatoid arthritis	CIA *CD1d*- and *Jα18*-knockout mice	I I	Induction of IL-4 and IL-10 expression Production of IL-4 and IFN- γ	[75,76,78,104]
Allergic Asthma	OVA challenged $Ja18^{-/-}$ mice Mice treated with DPPE-PEG	I I	IL-13, IL-4 production; Production of IFN-γ; Production of IL-4	[68] [70,105]

Table 1: Roles of NKT cells in autoimmune disorders and asthma.

of disease and the genetic background of the host or animal model used for study.

Multiple sclerosis and experimental autoimmune encephalomyelitis

Multiple sclerosis (MS) is a chronic inflammatory disorder, which affects the central nervous system leading to a progressive paralysis. T cells mediate the inflammatory process, by interaction with myelin antigens. It has been demonstrated that MS patients exhibit a reduction in the frequency of NKT cells in the peripheral blood and are not able to produce interleukin-4 (IL-4) [46,47]. Myelin oligodendrocyte glycoprotein (MOG35–55)-immunized NOD mice, develop experimental autoimmune encephalomyelitis (EAE), a disease similar to MS. EAE can be induced in some strains such as SJL/L (which lack expression of the most common Vβ8 chain used by murine NKT cells), C57BL/6 mice. For these reason these mice are used to study MS. It has been demonstrated that MOG35–55-immunized NOD mice overexpressing NKT cells, developed less severe EAE. This was related to inhibition of antigen specific INF-γ production independently from IL-4. Specifically it has been suggested that NKT cells may alleviate EAE by inhibition of pathogenic Th1 cells through Th2 showing of the immune response [26,48-50]. Additional studies demonstrated that NKT cells can alleviate EAE via interaction of CD1 antigenic signaling and dendritic cells (DCs) [51,52]. All these studies suggest that NKT play a protective role on EAE and that this process is antigen independent for type 1 NKT cells while is antigen dependent for type II NKT cells.

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune chronic and progressive cholestatic disease of the liver. The major pathology of this disease is a destruction of the small-to-medium bile ducts, which leads to progressive cholestasis and often end-stage liver disease. PBC is characterized by the presence of antibodies directed against the mitochondrial enzyme pyruvate dehydrogenase complex E2. It has been demonstrated that the frequency of NKT cells and the CD1d expression are both increased in the liver of patients with PBC [53-55]. Two experimental models have been developed to investigate the role of NKT cells in primary biliary cirrhosis [56]. The first model employed transgenic mice expressing a dominant negative TGF-β receptor, which spontaneously developed primary biliary cirrhosis [57]. These animals exhibited CD1d-deficiency and hyperactive NKT cells within hepatic tissues and resulted in reduced cholangitis and decreased hepatic lymphoid infiltrates [58]. The second model was generated by using infection with *Novosphingobium aromaticivorans*, a gram-negative microorganism that produces an enzyme recognized by the signature autoantibodies observed in primary biliary cirrhosis. It has been demonstrated that *N. aromaticivorans*, which activates NKT cells *via* cell wall α- glycuronosylceramides, induced cholangitis in wild-type but not CD1d-deficient animals (Mattner, Savage et al.). In another model of PBC, induced by immunizing mice with 2-octynoic acid coupled with bovine serum albumin, exposure to α-GalCer resulted in a dramatic exacerbation of autoimmune cholangitis [59]. Collectively, these findings revealed a role of NKT cells in the initiation of primary biliary cirrhosis in mice however, the precise mechanisms underlying this process, remain to be determined.

Myasthenia gravis

Myasthenia gravis (MG) is a chronic neuromuscular disease characterized by several degrees of weakness of the skeletal muscles. Patients with MG displayed an increased number of NKT cells in their peripheral blood [60] and possibly the hyperplastic thymus [61]. It has been demonstrated, that these changes in NKT cell numbers in the blood of MG patients returned to normal after therapy [62]. Studies on mice, showed that while CD1d-deficiency in mice was not associated with alterations in susceptibility to experimental autoimmune myasthenia gravis (EAMG) (Shi, Wang et al.), α-GalCer was able to protect mice against the development of EAMG [63]. This suppression was associated with reduced acetylcholine-specific antibody responses and reduced IFN-γ but not IL-4 production by acetylcholine receptor-specific T cells. Studies performed with anti-CD25 antibodies established a key role of $CD4^+CD25^+$ regulatory T cells in mediating myasthenia gravis prevention.

Allergic asthma

Asthma is an immunological disease with many inflammatory and clinical phenotypes, characterized by symptoms of shortness of breath, wheezing and coughing due to airway hyper reactivity (AHR). In allergic asthma, the most common form of asthma, airway inflammation is mediated by adaptive immune recognition of protein allergens by Th2 cells. This process results in airway eosinophilia [64]. The pathogenesis of bronchial asthma is complex and involves multiple cell types and several distinct cellular and molecular pathways. These pathways include adaptive and innate immunity and involve Th2 cells, mast cells, basophils, eosinophils, neutrophils, airway epithelial cells, NKT cells and NOS isoforms. $eNOS^{(-/-)}$ mice are a good transgenic model to study asthma and disease of the respiratory system. In fact it has been demonstrated that these mice, were more hyper responsive to inhaled methacholine and less sensitive to NOS inhibitor compared to control mice, suggesting that NO derived from eNOS plays a physiological role in controlling airway reactivity [65]. Additionally it has been showed that eNOS, plays also a role in the initiation and promotion of cell proliferation [66]. Key regulators in development of autoimmune and allergic disease and cancer are the NKT cells. In the case of asthma, an indication that type I NKT cells are involved in the development of disease, was given by the observation that type I NKT cells were predominantly present in the lungs of patients with allergic asthma [67]. Studies performed with animal models, tried to dissect the role of NKT cells in the development and regulation of asthma. Severe AHR and induction of Th2 cytokines IL-13 and IL-4 are produced by challenging mice with ovalbumin (OVA) antigen. Specifically, OVA challenged $J\alpha18^{(-/-)}$ mice, without type I NKT cells, did not developed AHR and did not elevated IL-13 or IL-4 expression [68]. AHR was reconstituted in $J\alpha18^{(-/-)}$ mice, which received an adoptive transfer of type I NKT cells from wild-type mice. In addition, it has been demonstrated that NKT cells can be activated through an apoptotic sensor pathogen-associated molecular pattern, called TIM-1 [69]. Other studies demonstrated that the activation of type I NKT cells with α-GalCer, suppressed Th2 responses and allergic airway inflammation by the production of IFN-γ [70]. Moreover, it has been showed that the treatment of sensitized mice with di-palmitoyl-phosphatidyl-ethanolamine polyethylene (DPPE-PEG), a CD1d-binding lipid antagonist, inhibited by type I NKT cells of cytokine production such as IL-4 and IFN-γ. As a consequence, the development of AHR in a murine model using OVA was blocked [70]. Another study demonstrated that transfer of bone marrow dendritic cells (BMDCs) treated with α-GalCer, prevented the development of lung allergic responses, and this was dependent on IFN-γ production by recipient type I NKT cells [71]. All these findings suggest novel therapeutic strategies for asthma by eliminating or skewing type I NKT cells toward Th1 functions.

Other autoimmune diseases

NKT cell number is decreased in a wide variety of diseases that are characterized by autoreactive tissue damage, including rheumatoid arthritis (RA) [47]. RA is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible (synovial) joints. This process is mediated by pathogenic T cells producing pro-inflammatory cytokinesis. It has been demonstrated that the number of NKT cells is reduced in the peripheral blood [47,72,73] and synovial [74] of RA patients. The most commonly used animal model for RA, is induced by immunization of susceptible mouse strains with heterologous type-II collagen (CIA). Several studies suggest that NKT cells play a pathogenic role in CIA [75]. Studies performed with different mouse models for RA, have demonstrated that NKT play two opposite roles in arthritis, probably due to functional differences between type I NKT and type II NKT cells. In fact type II NKT suppress arthritis while type I NKT cells play a pathogenic role in this disease [75-78]. Systemic lupus erythematosus (SLE) is mediated by autoantibodies directed against nuclear antigens a process controlled by autoreactive T helper cells and regulatory T cells. It has been reported that many patients with SLE have a reduced frequency of NKT cells. These cells may have pathogenic and/or protective roles in SLE and this process seems to be related to their interactions with disease promoting, autoreactive B cells, depending on antigenic signals [79]. Finally, it has been demonstrated that NKT cells are implicated in the regulation of a murine model of colitis [80] as well as Wegener's granulotomatosis [81] and in inflammatory bowel disease [47].

The Role of NKT cells in Cancer

Studies performed with chemical mutagenesis demonstrated that NKT cell subsets play a role in natural tumor immunosurveillance [82] which is a part of a dynamic process of interaction between abnormal cells and the host immune system. Specifically, experiments performed with stimulation of α-GalCer in several tumor mice models, demonstrated that type 1 NKT cells protected mice from tumor growth [83-85] The mechanism of α-GalCer-mediated tumor protection, involves a Th1-skewed immune response. This process also requires IFN-γ, IL-12, IFN- γ activated NK cells and activated $CD4^+$ or $CD8^+$ T cells [86-88]. Additionally, it has been demonstrated that NKT cells play an important protective role in immunosurveillance against methylcholanthrene-induced tumors [89]. In humans, *in vitro* studies, demonstrated that type 1 NKT cells are able to lyse solid-tumor cell-lines [90,91] or CD1d-expressing leukemia cell lines [92]. On the other hand, NKT cells are also implicated in the suppression of antitumor immune responses. This function is played mainly by type II NKT cells and involves Th2-skewed immune responses [93]. These data indicate, that NKT cells can inhibit or promote the development of protective autoimmune responses, establishing a regulatory axis between tumor immunosurveillance and escape (Figure 1) (reviewed in [94]).Several studies have been demonstrated that NKT cells are also involved in the induction or maintenance of immune tolerance. Specifically, it has been reported that NKT cells are required in the induction of allograft and xenograft tolerance [95-97]. In addition, a role for NKT cells in prevention of autoimmunity has been described [98].

NKT Cell-based Treatment of Human Autoimmune Disorder and Cancer

The NKT/CD1d system is highly conserved among mammalian species. This allows using α-GalCer as therapeutic agent in human autoimmune disorders [22]. It is important to underline that the treatment efficacy of α-GalCer can be influenced by a variety of parameters, including the dose administration route, frequency of injections, the specific chemical utilized, the experimental model employed, and genetic effects. Treatments of α-GalCer in cancer patients and patients chronically infected with hepatitis C virus have not found any evidence for severe side-effects [99]. It is important to underline that some of the functions of NKT cells in mice might not be recapitulated in humans. The alterations in NKT cell numbers and functions that have been observed in multiple human autoimmune diseases and cancer might further complicate treatment [94]. In order to translate the mouse studies to the clinic, a better understanding of the mechanisms involved in the control of autoimmunity and cancer by NKT cells will be needed.

Conclusions

NKT cells are a subset of regulatory T cells with innate properties. Numbers and functions of these cells are perturbed in a variety of autoimmune, allergic diseases and cancer. In multiple mouse models for autoimmunity, NKT cell-deficiency exacerbates disease, although in some models NKT cell-deficiency had no effect or ameliorated disease, suggesting complex relationships between NKT cells and autoimmunity. The protective role of NKT cells in tumor immunosurveillance and immunity has been well documented but paradoxically, there are also studies ascribing a suppressive role to these cells. This paradox was resolved by assuming distinct roles for the two types of NKT cells, whereby type I NKT cells enhance anti-tumor responses and type II NKT cells suppress these responses. The finding of cross-regulation between the two types of NKT cells suggests an immunoregulatory axis. Consideration of the cross-talk of NKT cells along with the well-defined suppression by regulatory T cells could provide new insights into cancer immunotherapy. In order to translate the mouse studies to the clinic, a better understanding of the mechanisms involved in the control of autoimmunity and cancer by NKT cells will be needed.

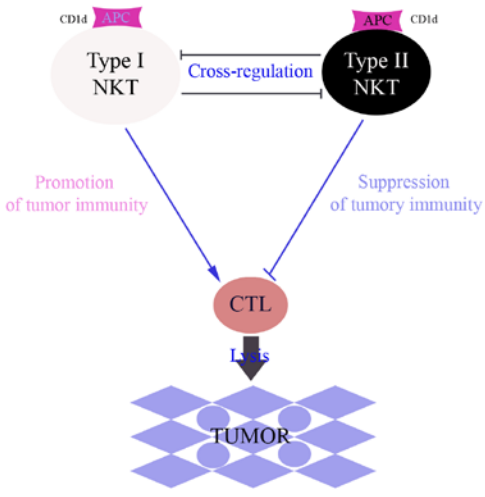

Figure 1: Cross-regulation of type I and type II NKT cells in tumor immunosurveillance and immunity. Type I NKT cells promote tumor immunity mediated by $CD8^+$ T cells, while type II NKT cells suppress tumor immunity by $CD8^+$ T cells. Type I and type II NKT cells also cross-regulate each other.

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References

1. van der Vliet HJ, Molling JW, von Blomberg BM, Nishi N, Kölgen W, et al. (2004) The immunoregulatory role of CD1d-restricted natural killer T cells in disease. Clin Immunol 112: 8-23.
2. Wu L, Gabriel CL, Parekh VV, Van Kaer L (2009) Invariant natural killer T cells: innate-like T cells with potent immunomodulatory activities. Tissue Antigens 73: 535-545.
3. Wu L, Van Kaer L (2009) Natural killer T cells and autoimmune disease. Curr Mol Med 9: 4-14.
4. Terabe M, Berzofsky JA (2008) The role of NKT cells in tumor immunity. Adv Cancer Res 101: 277-348.
5. Zeng Z, Castaño AR, Segelke BW, Stura EA, Peterson PA, et al. (1997) Crystal structure of mouse CD1: An MHC-like fold with a large hydrophobic binding groove. Science 277: 339-345.
6. Bendelac A, Savage PB, Teyton L (2007) The biology of NKT cells. Annu Rev Immunol 25: 297-336.
7. Cohen NR, Garg S, Brenner MB (2009) Antigen Presentation by CD1 Lipids, T Cells, and NKT Cells in Microbial Immunity. Adv Immunol 102: 1-94.
8. Behar SM, Podrebarac TA, Roy CJ, Wang CR, Brenner MB (1999) Diverse TCRs recognize murine CD1. J Immunol 162: 161-167.
9. Chiu YH, Jayawardena J, Weiss A, Lee D, Park SH, et al. (1999) Distinct subsets of CD1d-restricted T cells recognize self-antigens loaded in different cellular compartments. J Exp Med 189: 103-110.
10. Gumperz JE, Miyake S, Yamamura T, Brenner MB (2002) Functionally distinct subsets of CD1d-restricted natural killer T cells revealed by CD1d tetramer staining. J Exp Med 195: 625-636.
11. Kenna T, Golden-Mason L, Porcelli SA, Koezuka Y, Hegarty JE, et al. (2003) NKT cells from normal and tumor-bearing human livers are phenotypically and functionally distinct from murine NKT cells. J Immunol 171: 1775-1779.
12. Berzins SP, Smyth MJ, Baxter AG (2011) Presumed guilty: natural killer T cell defects and human disease. Nat Rev Immunol 11: 131-142.
13. Exley MA, Tahir SM, Cheng O, Shaulov A, Joyce R, et al. (2001) A major fraction of human bone marrow lymphocytes are Th2-like CD1d-reactive T cells that can suppress mixed lymphocyte responses. J Immunol 167: 5531-5534.
14. MacDonald HR (2002) Development and selection of NKT cells. Curr Opin Immunol 14: 250-254.
15. Godfrey DI, Berzins SP (2007) Control points in NKT-cell development. Nat Rev Immunol 7: 505-518.
16. Chun T, Page MJ, Gapin L, Matsuda JL, Xu H, et al. (2003) CD1d-expressing dendritic cells but not thymic epithelial cells can mediate negative selection of NKT cells. J Exp Med 197: 907-918.
17. Pellicci DG, Uldrich AP, Kyparissoudis K, Crowe NY, Brooks AG, et al. (2003) Intrathymic NKT cell development is blocked by the presence of alpha-galactosylceramide. Eur J Immunol 33: 1816-1823.
18. Baev DV, Peng XH, Song L, Barnhart JR, Crooks GM, et al. (2004) Distinct homeostatic requirements of CD4+ and CD4- subsets of Valpha24-invariant natural killer T cells in humans. Blood 104: 4150-4156.
19. Berzins SP, Uldrich AP, Pellicci DG, McNab F, Hayakawa Y, et al. (2004) Parallels and distinctions between T and NKT cell development in the thymus. Immunol Cell Biol 82: 269-275.
20. Borowski C, Bendelac A (2005) Signaling for NKT cell development: the SAP-FynT connection. J Exp Med 201: 833-836.
21. Pasquier B, Yin L, Fondanèche MC, Relouzat F, Bloch-Queyrat C, et al. (2005) Defective NKT cell development in mice and humans lacking the adapter SAP, the X-linked lymphoproliferative syndrome gene product. J Exp Med 201: 695-701.
22. Godfrey DI, Hammond KJ, Poulton LD, Smyth MJ, Baxter AG (2000) NKT cells: facts, functions and fallacies. Immunol Today 21: 573-583.
23. Exley M, Garcia J, Wilson SB, Spada F, Gerdes D, et al. (2000) CD1d structure and regulation on human thymocytes, peripheral blood T cells, B cells and monocytes. Immunology 100: 37-47.
24. Jayawardena-Wolf J, Benlagha K, Chiu YH, Mehr R, Bendelac A (2001) CD1d endosomal trafficking is independently regulated by an intrinsic CD1d-encoded tyrosine motif and by the invariant chain. Immunity 15: 897-908.
25. Joyce S, Woods AS, Yewdell JW, Bennink JR, De Silva AD, et al. (1998) Natural ligand of mouse CD1d1: cellular glycosylphosphatidylinositol. Science 279: 1541-1544.
26. Miyamoto K, Miyake S, Yamamura T (2001) A synthetic glycolipid prevents autoimmune encephalomyelitis by inducing TH2 bias of natural killer T cells. Nature 413: 531-534.
27. De Silva AD, Park JJ, Matsuki N, Stanic AK, Brutkiewicz RR, et al. (2002) Lipid protein interactions: the assembly of CD1d1 with cellular phospholipids occurs in the endoplasmic reticulum. J Immunol 168: 723-733.
28. Wu DY, Segal NH, Sidobre S, Kronenberg M, Chapman PB (2003) Cross-presentation of disialoganglioside GD3 to natural killer T cells. J Exp Med 198: 173-181.
29. Zhou D, Mattner J, Cantu C 3rd, Schrantz N, Yin N, et al. (2004) Lysosomal glycosphingolipid recognition by NKT cells. Science 306: 1786-1789.
30. Matangkasombut P, Marigowda G, Ervine A, Idris L, Pichavant M, et al. (2009) Natural killer T cells in the lungs of patients with asthma. J Allergy Clin Immunol 123: 1181-1185.
31. Chatenoud L (2002) Do NKT cells control autoimmunity? J Clin Invest 110: 747-748.
32. Wilson SB, Kent SC, Patton KT, Orban T, Jackson RA, et al. (1998) Extreme Th1 bias of invariant Valpha24JalphaQ T cells in type 1 diabetes. Nature 391: 177-181.
33. Kis J, Engelmann P, Farkas K, Richman G, Eck S, et al. (2007) Reduced CD4+ subset and Th1 bias of the human iNKT cells in Type 1 diabetes mellitus. J Leukoc Biol 81: 654-662.
34. Oikawa Y, Shimada A, Yamada S, Motohashi Y, Nakagawa Y, et al. (2002) High frequency of valpha24(+) vbeta11(+) T-cells observed in type 1 diabetes. Diabetes Care 25: 1818-1823.
35. Lee PT, Putnam A, Benlagha K, Teyton L, Gottlieb PA, et al. (2002) Testing the NKT cell hypothesis of human IDDM pathogenesis. J Clin Invest 110: 793-800.
36. Anderson MS, Bluestone JA (2005) The NOD mouse: a model of immune dysregulation. Annu Rev Immunol 23: 447-485.
37. Fletcher MT, Baxter AG (2009) Clinical application of NKT cell biology in type I (autoimmune) diabetes mellitus. Immunol Cell Biol 87: 315-323.
38. Lehuen A, Lantz O, Beaudoin L, Laloux V, Carnaud C, et al. (1998) Overexpression of natural killer T cells protects Valpha14- Jalpha281 transgenic nonobese diabetic mice against diabetes. J Exp Med 188: 1831-1839.
39. Wang B, Geng YB, Wang CR (2001) CD1-restricted NK T cells protect nonobese diabetic mice from developing diabetes. J Exp Med 194: 313-320.
40. Beaudoin L, Laloux V, Novak J, Lucas B, Lehuen A (2002) NKT cells inhibit the onset of diabetes by impairing the development of pathogenic T cells specific for pancreatic beta cells. Immunity 17: 725-736.
41. Cain JA, Smith JA, Ondr JK, Wang B, Katz JD (2006) NKT cells and IFN-gamma establish the regulatory environment for the control of diabetogenic T cells in the nonobese diabetic mouse. J Immunol 176: 1645-1654.
42. Hong S, Wilson MT, Serizawa I, Wu L, Singh N, et al. (2001) The natural killer T-cell ligand alpha-galactosylceramide prevents autoimmune diabetes in non-obese diabetic mice. Nat Med 7: 1052-1056.
43. Naumov YN, Bahjat KS, Gausling R, Abraham R, Exley MA, et al. (2001) Activation of CD1d-restricted T cells protects NOD mice from developing diabetes by regulating dendritic cell subsets. Proc Natl Acad Sci U S A 98: 13838-13843.

44. Sharif S, Arreaza GA, Zucker P, Mi QS, Sondhi J, et al. (2001) Activation of natural killer T cells by alpha-galactosylceramide treatment prevents the onset and recurrence of autoimmune Type 1 diabetes. Nat Med 7: 1057-1062.

45. Mizuno M, Masumura M, Tomi C, Chiba A, Oki S, et al. (2004) Synthetic glycolipid OCH prevents insulitis and diabetes in NOD mice. J Autoimmun 23: 293-300.

46. Illés Z, Kondo T, Newcombe J, Oka N, Tabira T, et al. (2000) Differential expression of NK T cell V alpha 24J alpha Q invariant TCR chain in the lesions of multiple sclerosis and chronic inflammatory demyelinating polyneuropathy. J Immunol 164: 4375-4381.

47. van der Vliet HJ, von Blomberg BM, Nishi N, Reijm M, Voskuyl AE, et al. (2001) Circulating V(alpha24+) Vbeta11+ NKT cell numbers are decreased in a wide variety of diseases that are characterized by autoreactive tissue damage. Clin Immunol 100: 144-148.

48. Mars LT, Laloux V, Goude K, Desbois S, Saoudi A, et al. (2002) Cutting edge: V alpha 14-J alpha 281 NKT cells naturally regulate experimental autoimmune encephalomyelitis in nonobese diabetic mice. J Immunol 168: 6007-6011.

49. Oki S, Tomi C, Yamamura T, Miyake S (2005) Preferential T(h)2 polarization by OCH is supported by incompetent NKT cell induction of CD40L and following production of inflammatory cytokines by bystander cells in vivo. Int Immunol 17: 1619-1629.

50. Mars LT, Gautron AS, Novak J, Beaudoin L, Diana J, et al. (2008) Invariant NKT cells regulate experimental autoimmune encephalomyelitis and infiltrate the central nervous system in a CD1d-independent manner. J Immunol 181: 2321-2329.

51. Wiethe C, Schiemann M, Busch D, Haeberle L, Kopf M, et al. (2007) Interdependency of MHC class II/self-peptide and CD1d/self-glycolipid presentation by TNF-matured dendritic cells for protection from autoimmunity. J Immunol 178: 4908-4916.

52. Brandl C, Ortler S, Herrmann T, Cardell S, Lutz MB, et al. (2010) B7-H1-deficiency enhances the potential of tolerogenic dendritic cells by activating CD1d-restricted type II NKT cells. PLoS One 5: e10800.

53. Tsuneyama K, Kono N, Hoso M, Sugahara H, Yoshida K, et al. (1998) aly/aly mice: a unique model of biliary disease. Hepatology 27: 1499-1507.

54. Kita H, Naidenko OV, Kronenberg M, Ansari AA, Rogers P, et al. (2002) Quantitation and phenotypic analysis of natural killer T cells in primary biliary cirrhosis using a human CD1d tetramer. Gastroenterology 123: 1031-1043.

55. Chuang YH, Lian ZX, Tsuneyama K, Chiang BL, Ansari AA, et al. (2006) Increased killing activity and decreased cytokine production in NK cells in patients with primary biliary cirrhosis. J Autoimmun 26: 232-240.

56. Joyce S, Van Kaer L (2008) Invariant natural killer T cells trigger adaptive lymphocytes to churn up bile. Cell Host Microbe 3: 275-277.

57. Oertelt S, Lian ZX, Cheng CM, Chuang YH, Padgett KA, et al. (2006) Anti-mitochondrial antibodies and primary biliary cirrhosis in TGF-beta receptor II dominant-negative mice. J Immunol 177: 1655-1660.

58. Chuang YH, Lian ZX, Yang GX, Shu SA, Moritoki Y, et al. (2008) Natural killer T cells exacerbate liver injury in a transforming growth factor beta receptor II dominant-negative mouse model of primary biliary cirrhosis. Hepatology 47: 571-580.

59. Wu SJ, Yang YH, Tsuneyama K, Leung PS, Illarionov P, et al. (2011) Innate immunity and primary biliary cirrhosis: activated invariant natural killer T cells exacerbate murine autoimmune cholangitis and fibrosis. Hepatology 53: 915-925.

60. Suzuki Y, Onodera H, Tago H, Saito R, Ohuchi M, et al. (2005) Altered populations of natural killer cell and natural killer T cell subclasses in myasthenia gravis. J Neuroimmunol 167: 186-189.

61. Nagane Y, Utsugisawa K, Obara D, Tohgi H (2001) NKT-associated markers and perforin in hyperplastic thymuses from patients with Myasthenia gravis. Muscle Nerve 24: 1359-1364.

62. Shi FD, Wang HB, Li H, Hong S, Taniguchi M, et al. (2000) Natural killer cells determine the outcome of B cell-mediated autoimmunity. Nat Immunol 1: 245-251.

63. Liu R, La Cava A, Bai XF, Jee Y, Price M, et al. (2005) Cooperation of invariant NKT cells and CD4+CD25+ T regulatory cells in the prevention of autoimmune myasthenia. J Immunol 175: 7898-7904.

64. Meyer EH, DeKruyff RH, Umetsu DT (2008) T cells and NKT cells in the pathogenesis of asthma. Annu Rev Med 59: 281-292.

65. Feletou M, Lonchampt M, Coge F, Galizzi JP, Bassoullet C, et al. (2001) Regulation of murine airway responsiveness by endothelial nitric oxide synthase. Am J Physiol Lung Cell Mol Physiol 281: L258-267.

66. Barbieri A, Palma G, Rosati A, Giudice A, Falco A, et al. (2012) Role of endothelial nitric oxide synthase (eNOS) in chronic stress-promoted tumour growth. J Cell Mol Med 16: 920-926.

67. Akbari O, Faul JL, Hoyte EG, Berry GJ, Wahlström J, et al. (2006) CD4+ invariant T-cell-receptor+ natural killer T cells in bronchial asthma. N Engl J Med 354: 1117-1129.

68. Akbari O, Stock P, Meyer E, Kronenberg M, Sidobre S, et al. (2003) Essential role of NKT cells producing IL-4 and IL-13 in the development of allergen-induced airway hyperreactivity. Nat Med 9: 582-588.

69. Lee HH, Meyer EH, Goya S, Pichavant M, Kim HY, et al. (2010) Apoptotic cells activate NKT cells through T cell Ig-like mucin-like-1 resulting in airway hyperreactivity. J Immunol 185: 5225-5235.

70. Cui J, Watanabe N, Kawano T, Yamashita M, Kamata T, et al. (1999) Inhibition of T helper cell type 2 cell differentiation and immunoglobulin E response by ligand-activated Valpha14 natural killer T cells. J Exp Med 190: 783-792.

71. Matsuda H, Takeda K, Koya T, Okamoto M, Shiraishi Y, et al. (2010) Plasticity of invariant NKT cell regulation of allergic airway disease is dependent on IFN-gamma production. J Immunol 185: 253-262.

72. Yanagihara Y, Shiozawa K, Takai M, Kyogoku M, Shiozawa S (1999) Natural killer (NK) T cells are significantly decreased in the peripheral blood of patients with rheumatoid arthritis (RA). Clin Exp Immunol 118: 131-136.

73. Kojo S, Adachi Y, Keino H, Taniguchi M, Sumida T (2001) Dysfunction of T cell receptor AV24AJ18+, BV11+ double-negative regulatory natural killer T cells in autoimmune diseases. Arthritis Rheum 44: 1127-1138.

74. Maeda T, Keino H, Asahara H, Taniguchi M, Nishioka K, et al. (1999) Decreased TCR AV24AJ18+ double-negative T cells in rheumatoid synovium. Rheumatology (Oxford) 38: 186-188.

75. Coppieters K, Dewint P, Van Beneden K, Jacques P, Seeuws S, et al. (2007) NKT cells: manipulable managers of joint inflammation. Rheumatology (Oxford) 46: 565-571.

76. Kim HY, Kim HJ, Min HS, Kim S, Park WS, et al. (2005) NKT cells promote antibody-induced joint inflammation by suppressing transforming growth factor beta1 production. J Exp Med 201: 41-47.

77. Ohnishi Y, Tsutsumi A, Goto D, Itoh S, Matsumoto I, et al. (2005) TCR Valpha14 natural killer T cells function as effector T cells in mice with collagen-induced arthritis. Clin Exp Immunol 141: 47-53.

78. Teige A, Bockermann R, Hasan M, Olofsson KE, Liu Y, et al. (2010) CD1d-dependent NKT cells play a protective role in acute and chronic arthritis models by ameliorating antigen-specific Th1 responses. J Immunol 185: 345-356.

79. Forestier C, Molano A, Im JS, Dutronc Y, Diamond B, et al. (2005) Expansion and hyperactivity of CD1d-restricted NKT cells during the progression of systemic lupus erythematosus in (New Zealand Black x New Zealand White)F1 mice. J Immunol 175: 763-770.

80. Shibolet O, Kalish Y, Klein A, Alper R, Zolotarov L, et al. (2004) Adoptive transfer of ex vivo immune-programmed NKT lymphocytes alleviates immune-mediated colitis. J Leukoc Biol 75: 76-86.

81. Takagi D, Iwabuchi K, Iwabuchi C, Nakamaru Y, Maguchi S, et al. (2004) Immunoregulatory defects of V alpha 24V+ beta 11+ NKT cells in development of Wegener's granulomatosis and relapsing polychondritis. Clin Exp Immunol 136: 591-600.

82. Smyth MJ, Thia KY, Street SE, Cretney E, Trapani JA, et al. (2000) Differential tumor surveillance by natural killer (NK) and NKT cells. J Exp Med 191: 661-668.

83. Kawano T, Cui J, Koezuka Y, Toura I, Kaneko Y, et al. (1998) Natural killer-like nonspecific tumor cell lysis mediated by specific ligand-activated Valpha14 NKT cells. Proc Natl Acad Sci U S A 95: 5690-5693.

84. Hayakawa Y, Takeda K, Yagita H, Van Kaer L, Saiki I, et al. (2001) Differential regulation of Th1 and Th2 functions of NKT cells by CD28 and CD40 costimulatory pathways. J Immunol 166: 6012-6018.

85. Ambrosino E, Terabe M, Halder RC, Peng J, Takaku S, et al. (2007) Cross-regulation between type I and type II NKT cells in regulating tumor immunity: a new immunoregulatory axis. J Immunol 179: 5126-5136.

86. Fuji N, Ueda Y, Fujiwara H, Toh T, Yoshimura T, et al. (2000) Antitumor effect of alpha-galactosylceramide (KRN7000) on spontaneous hepatic metastases requires endogenous interleukin 12 in the liver. Clin Cancer Res 6: 3380-3387.

87. Chiodoni C, Stoppacciaro A, Sangaletti S, Gri G, Cappetti B, et al. (2001) Different requirements for alpha-galactosylceramide and recombinant IL-12 antitumor activity in the treatment of C-26 colon carcinoma hepatic metastases. Eur J Immunol 31: 3101-3110.

88. Osada T, Nagawa H, Shibata Y (2004) Tumor-infiltrating effector cells of alpha-galactosylceramide-induced antitumor immunity in metastatic liver tumor. J Immune Based Ther Vaccines 2: 7.

89. Crowe NY, Smyth MJ, Godfrey DI (2002) A critical role for natural killer T cells in immunosurveillance of methylcholanthrene-induced sarcomas. J Exp Med 196: 119-127.

90. Kawano T, Nakayama T, Kamada N, Kaneko Y, Harada M, et al. (1999) Antitumor cytotoxicity mediated by ligand-activated human V alpha24 NKT cells. Cancer Res 59: 5102-5105.

91. Mattarollo SR, Kenna T, Nieda M, Nicol AJ (2006) Chemotherapy pretreatment sensitizes solid tumor-derived cell lines to V alpha 24+ NKT cell-mediated cytotoxicity. Int J Cancer 119: 1630-1637.

92. Metelitsa LS, Weinberg KI, Emanuel PD, Seeger RC (2003) Expression of CD1d by myelomonocytic leukemias provides a target for cytotoxic NKT cells. Leukemia 17: 1068-1077.

93. Terabe M, Matsui S, Noben-Trauth N, Chen H, Watson C, et al. (2000) NKT cell-mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway. Nat Immunol 1: 515-520.

94. Subleski JJ, Jiang Q, Weiss JM, Wiltrout RH (2011) The split personality of NKT cells in malignancy, autoimmune and allergic disorders. Immunotherapy 3: 1167-1184.

95. Ikehara Y, Yasunami Y, Kodama S, Maki T, Nakano M, et al. (2000) CD4(+) Valpha14 natural killer T cells are essential for acceptance of rat islet xenografts in mice. J Clin Invest 105: 1761-1767.

96. Seino KI, Fukao K, Muramoto K, Yanagisawa K, Takada Y, et al. (2001) Requirement for natural killer T (NKT) cells in the induction of allograft tolerance. Proc Natl Acad Sci U S A 98: 2577-2581.

97. Sonoda KH, Taniguchi M, Stein-Streilein J (2002) Long-term survival of corneal allografts is dependent on intact CD1d-reactive NKT cells. J Immunol 168: 2028-2034.

98. Godfrey DI, Kronenberg M (2004) Going both ways: immune regulation via CD1d-dependent NKT cells. J Clin Invest 114: 1379-1388.

99. Duwaerts CC, Gregory SH (2011) Targeting the diverse immunological functions expressed by hepatic NKT cells. Expert Opin Ther Targets 15: 973-988.

100. Laloux V, Beaudoin L, Jeske D, Carnaud C, Lehuen A (2001) NK T cell-induced protection against diabetes in V alpha 14-J alpha 281 transgenic nonobese diabetic mice is associated with a Th2 shift circumscribed regionally to the islets and functionally to islet autoantigen. J Immunol 166: 3749-3756.

101. Jahng AW, Maricic I, Pedersen B, Burdin N, Naidenko O, et al. (2001) Activation of natural killer T cells potentiates or prevents experimental autoimmune encephalomyelitis. J Exp Med 194: 1789-1799.

102. Singh AK, Wilson MT, Hong S, Olivares-Villagómez D, Du C, et al. (2001) Natural killer T cell activation protects mice against experimental autoimmune encephalomyelitis. J Exp Med 194: 1801-1811.

103. Pál E, Tabira T, Kawano T, Taniguchi M, Miyake S, et al. (2001) Costimulation-dependent modulation of experimental autoimmune encephalomyelitis by ligand stimulation of V alpha 14 NK T cells. J Immunol 166: 662-668.

104. Chiba A, Kaieda S, Oki S, Yamamura T, Miyake S (2005) The involvement of V(alpha)14 natural killer T cells in the pathogenesis of arthritis in murine models. Arthritis Rheum 52: 1941-1948.

105. Lombardi V, Stock P, Singh AK, Kerzerho J, Yang W, et al. (2010) A CD1d-dependent antagonist inhibits the activation of invariant NKT cells and prevents development of allergen-induced airway hyperreactivity. J Immunol 184: 2107-2115.

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