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

Bimonte Sabrina*, Barbieri Antonio1, Palma Giuseppe1,2, Turco Maria Caterina2 and Arra Claudio1

1Struttura Semplice Dipartimentale Sperimentazione Animale, Istituto Nazionale dei Tumori, IRCCS “Fondazione G. Pascale”, Via Mariano Semmola, 80131, Naples, Italy
2Istituto di Endocrinologia e Oncologia Sperimentale del Consiglio Nazionale delle Ricerche c/o Dipartimento di Biologia e Patologia Cellulare e Molecolare “L. Califano”, Università degli Studi di Napoli “Federico II”, Via Pansini 5, 80121 Napoli, Italy
3University of Salerno, Fisciano (SA), Italy

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 [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 powerful immunomodulatory activities [2]. NKT cells are implicated in the regulation of immune responses, including infections, tumors, transplants, allergic and inflammatory reactions, autoimmunity 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.

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 powerful immunomodulatory activities [2]. NKT cells are implicated in the regulation of immune responses, including infections, tumors, transplants, allergic and inflammatory reactions, autoimmunity 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 bound to major histocompatibility complex (MHC) molecules, both subsets of NKT cells recognize lipid antigens bound 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 bound 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

*Corresponding author: Bimonte Sabrina, Struttura Semplice Dipartimentale Sperimentazione Animale, Istituto Nazionale dei Tumori,IRCCS “Fondazione G. Pascale”, Via Mariano Semmola, 80131, Naples, Italy, E-mail: s.bimonte@istitutotumori.na.it

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we review significant studies providing evidences that NKT cells can protect the production of interferon (IFN)-γ. In the following paragraphs, the protective role of NKT cells to autoimmune disease is dependent on allergies. Protective and pathogenic roles of NKT cells in autoimmune disorders model type NKT cells implicated mechanism references

**Diseases**

| Disease          | Model          | Type NKT cells | Implicated Mechanism                                    | References |
|------------------|----------------|----------------|--------------------------------------------------------|------------|
| Type I diabetes  | Diabetes       | I              | IL-4, IL-10 production                                 | [44,100]   |
|                  | Multiple sclerosis | I           | IL-4, IL-10 production                                 | [26,101,102] |
|                  | Myasthenia gravis     | I            | Reduced INF-γ production                               | [261,101-103] |
|                  | Rheumatoid arthritis | I            | Induction of IL-4 and IL-10 expression                  | [75,76,78,104] |
|                  | Allergic Asthma     | I             | IL-13, IL-4 production                                 | [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 antigen 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 transgenic mice expressing a dominant negative TGF-β receptor, 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 antigen 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.

### 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 1 NKT cells are involved in the development of disease, was given by the observation that type 1 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 Jα18(-/-) mice, without type 1 NKT cells, did not developed AHR and did not elevated IL-13 or IL-4 expression [68]. AHR was reconstituted in Jα18(-/-) mice, which received an adoptive transfer of type 1 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 1 NKT cells with α-GalCer, suppressed Th2 responses and allergic airway inflammation by the production of IFN-γ [70]. Moreover, it has been shown that the treatment of sensitized mice with di-palmitoyl-phosphatidyl-ethanolamine polyethylene (DPPE-PEG), a CD1d-binding lipid antagonist, inhibited by type 1 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 1 NKT cells [71]. All these findings suggest novel therapeutic strategies for asthma by eliminating or skewing type 1 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 cytokines. 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 granulomatosis [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 I 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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