Review Article

Effects of Invariant NKT Cells on Parasite Infections and Hygiene Hypothesis

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Invariant natural killer T (iNKT) cells are unique subset of innate-like T cells recognizing glycolipids. iNKT cells can rapidly produce copious amounts of cytokines upon antigen stimulation and exert potent immunomodulatory activities for a wide variety of immune responses and diseases. We have revealed the regulatory effect of iNKT cells on autoimmunity with a serial of publications. On the other hand, the role of iNKT cells in parasitic infections, especially in the recently attractive topic “hygiene hypothesis,” has not been clearly defined yet. Bacterial and parasitic cell wall is a cellular structure highly enriched in a variety of glycolipids and lipoproteins, some of which may serve as natural ligands of iNKT cells. In this review, we mainly summarized the recent findings on the roles and underlying mechanisms of iNKT cells in parasite infections and their cross-talk with Th1, Th2, Th17, Treg, and innate lymphoid cells. In most cases, iNKT cells exert regulatory or direct cytotoxic roles to protect hosts against parasite infections. We put particular emphasis as well on the identification of the natural ligands from parasites and the involvement of iNKT cells in the hygiene hypothesis.

1. Introduction

Natural killer T (NKT) cells are recently discovered innate-like subset of lymphocytes expressing both NK and T cell markers. NKT cells are a phenotypically and functionally diverse subset of T cells that recognize self- and microbial lipids [1, 2]. Most NKT cells are restricted by MHC-I like molecule CD1, which can further be distributed into two major subsets: type I and type II NKT cells (Table 1). Type I NKT cells are also called invariant NKT (iNKT), expressing exclusively limited T cell receptor α (TCRα) and TCRβ receptors, that is, Vα14-Jα18 predominately paired with Vβ8.2, Vβ7, or Vβ2 in mice and Vα24-Jα18 paired with Vβ11 in human [2, 3]. iNKT cells secrete a wide array of cytokines and chemokines immediately upon activation through TCR engagement by glycolipids. iNKT cells exert their regulatory and cytotoxic activities also through direct contact, granzyme B, or FasL-induced mechanisms [4–6]. Hence, iNKT cells exert both regulator and effector cell function and bridge the innate and adaptive immune responses [7]. Recently, iNKT cells have been further classified into NKT1, NKT2, and NKT17 lineages based on their cytokine profiles and distinct transcription factors, T-Bet, Gata-3, and Rorγt, as conventional T helper 1 (Th1), Th2, and Th17 cells [8, 9]. On the other hand, type II NKT cells, which are also called non-iNKT or variant NKT (vNKT) cells, express more diverse TCRα and TCRβ receptors [10]. There still exists a minor group of CD1 nonrestricted NKT cells, referred to as NKT-like cells [11, 12]. The functions of vNKT and NKT-like cells are relatively unknown.

A hallmark of iNKT cells is their capacity to rapidly produce copious amounts of cytokines and chemokines upon TCR stimulation, which endows these cells with potent immunomodulatory activities for a wide variety of immune responses and diseases (Figure 1). iNKT cells exhibit potent effector functions and play critical roles in antimicrobial defense, cancer immunosurveillance, and modulation of...
NKT cells are involved in the pathogenesis of parasitic infections, with particular emphasis on the role of iNKT cells during parasite infections. Recent findings indicate that iNKT cells exhibited an activated phenotype. Hepatic iNKT cells produced both interferon-γ (IFN-γ) and IL-4 following schistosome egg deposition in the liver [22]. Further studies revealed that *S. mansoni* activated both iNKT and non-iNKT cells in vivo. iNKT cells contributed to Th1 cell differentiation, whereas non-iNKT cells might be mostly implicated in Th2 cell differentiation in response to this parasite [23]. Luo and colleagues reported that NK and NKT cells were activated and expanded from draining mesenteric lymph node (MLN) in mice 5–7 wk after infection with *S. japonicum*. These cells produce IL-4 and IL-17 [24]. However, the kinetics of NKT cells and their precise roles in immunomodulation during schistosome infections remain unclear. This is also true to nematode infections, where NKT cells remains ill-defined in their pathogenesis [19]. A pioneer work from Balmer and colleagues found an expansion of NKT (CD3<sup>+</sup>NK1.1<sup>+</sup>) as early as 24 hours following the infection with *Brugia pahangi* [25]. However, depletion of NK1.1-expressing cell had no effect on the Th2 development during the gastrointestinal nematode *Trichuris muris* infection [26].

### 2. NKT Cells in Parasitic Infections

Albeit being widely studied during viral and bacterial infections, the role of iNKT cells during parasite infections remains largely unexplored. As helminth infections can usually induce Th2-dominated immune responses and iNKT cells can rapidly produce copious amounts of various cytokines including interleukin-4 (IL-4), these cells might be important players in the initial steps leading to Th2 responses during helminthiasis [19]. Recent reports have indicated that NKT cells are involved in the pathogenesis of several parasite infections in animal models and patients, playing, in most cases, protective or regulatory roles towards hosts.

#### 2.1. NKT Cells in Helminth Infections

Schistosomiasis remains a severe public health problem in many developing countries in endemic areas. It is caused by digenetic blood trematodes, of which there are three main species: *Schistosoma mansoni*, *S. japonicum*, and *S. haematobium*. Previous studies by others and us indicated that egg deposit in the liver was a determining factor to drive Th2 response in *S. mansoni* and *S. japonicum* infections in mice [20, 21]. NKT cells may contribute to regulating the cytokine secretion profiles during infections. In mice infected with *S. mansoni*, iNKT cells exhibited an activated phenotype. Hepatic iNKT cells produced both interferon-γ (IFN-γ) and IL-4 following schistosome egg deposited in the liver [22]. Further studies revealed that *S. mansoni* activated both iNKT and non-iNKT cells in vivo. iNKT cells contributed to Th1 cell differentiation, whereas non-iNKT cells might be mostly implicated in Th2 cell differentiation in response to this parasite [23]. Luo and colleagues reported that NK and NKT cells were activated and expanded from draining mesenteric lymph node (MLN) in mice 5–7 wk after infection with *S. japonicum*. These cells produce IL-4 and IL-17 [24]. However, the kinetics of NKT cells and their precise roles in immunomodulation during schistosome infections remain unclear. This is also true to nematode infections, where NKT cells remains ill-defined in their pathogenesis [19]. A pioneer work from Balmer and colleagues found an expansion of NKT (CD3<sup>+</sup>NK1.1<sup>+</sup>) as early as 24 hours following the infection with *Brugia pahangi* [25]. However, depletion of NK1.1-expressing cell had no effect on the Th2 development during the gastrointestinal nematode *Trichuris muris* infection [26].

#### 2.2. NKT Cells in Protozoan Infections

iNKT cells have been reported playing crucial roles in the pathogenesis of protozoan infections. In *malaria*, early interactions between blood-stage *Plasmodium* parasites and cells of the innate immune system, including innate-like NKT cells, are important in the timely control of parasite replication and in the subsequent elimination and resolution of the infection [27]. The lipid extracts from murine malaria parasites could actually be loaded onto CD1 molecules to stimulate iNKT cell by the use of artificial antigen-presenting beads [28]. The level of protective antimalaria immunity was greatly enhanced by
coadministration of α-galactosylceramide (α-GalCer) with suboptimal doses of irradiated sporozoites or recombinant viruses expressing a malaria antigen in mice [29], iNKT cells were increased in numbers and played critical roles through the secretion of IFN-γ in reducing liver-stage burden to a secondary infection by murine malaria Plasmodium yoelii [30]. α-C-GalCer displayed a superior inhibitory activity against the liver stages of the rodent malaria parasite P. yoelii compared to its parental glycolipid, α-GalCer [31]. α-GalCer and its analogs have also been used as adjuvants for malaria vaccine. This adjuvant effect depended on NKT cell activation, which was able to boost IFN-γ production by NK cells and memory CD8+ T cells [32].

Visceral leishmaniasis (Kala-azar) is a deadly disease caused by the parasitic protozoa Leishmania donovani. iNKT cells are involved in the pathogenesis of leishmaniasis. In patients with visceral leishmaniasis, bone-marrow-derived non-iNKT cells dominantly produced IFN-γ in response to L. donovani antigen in vitro [33]. Post-kala-azar dermal leishmaniasis is a chronic dermal infection that occurs usually after recovery from visceral leishmaniasis. There was a raised proportion of circulating NKT cells in these patients compared to health controls [34]. Karmakar and colleagues isolated a natural ligand of NKT cells, β-(1–4)-galactose terminal glycosphingophospholipid (GSPL) from this parasite to treat infected BALB/c mice. This immunotherapy with GSPL induced IFN-γ through the cooperative action of TLR4 and NKT cells, which alleviated intestinal lesions and secreted cytokines towards a Th2 profile and a dramatic increase in Treg cells in MLNs, which alleviated intestinal lesions and increased survival of mice [40]. On the other hand, iNKT cells may negatively regulate the immune response against T. gondii infection possibly by producing IL-4 and suppressing the induction of heat shock protein 65. The latter is induced in host macrophages by γδ T cells and plays an essential role in protective immunity in this infection [41].

NKT cells are involved in the pathogenesis of some other protozoan infections, providing protection against infections in most cases. CD8+ NKT cells were able to activate macrophages to kill Trypanosoma congolense through the production of nitrogen oxides, whereas Treg cells prevented the activation of the CD8+ NKT cells [42]. However, another report indicated that loss of iNKT cells did not affect the susceptibility or resistance in CD1d−/− C57BL/6 mice to the infections with virulent African trypanosomes, T. congolense or T. brucei [43]. Lotter and colleagues identified a lipopeptidophosphoglycan from Entamoeba histolytica membranes (EhLPPG) as a possible iNKT natural ligand. EhLPPG treatment, similar to α-GalCer application, induced protective IFN-γ but not IL-4 production from iNKT cells and significantly reduced the severity of amebic liver abscesses in mice infected with E. histolytica [44]. By the use of CD1d KO mice, it was found that iNKT cells contributed to resistance against this protozoan and to the control of inflammation in the colitis induced by the infection [45]. iNKT cells play important roles in the pathogenesis of some other parasitic diseases, as well as of a wide range of microbe infections, as seen in recent nice reviews [10, 46, 47].

### 2.3. Underlying Mechanisms

NKT cells play protective role against a wide range of parasite infections as discussed above, whereas the underlying molecular mechanisms are not fully elucidated. Shifting of host’s cytokine secretion profiles may account for the protective or, in some cases, pathogenic effects of NKT cells on parasitic infections. Activated iNKT cells can also transactivate many other immune cells or attract these cells to the sites of infection to exert their regulatory roles. Like NK cells, activated NKT cells can also mediate cytotoxic activity, possibly involving both perforin/granzyme and Fas/FasL pathways [5, 6, 48]. This function could be relevant to immunity against intracellular microorganisms and tumors [49]. Parasites are enriched in lipid, which may contain natural ligands for NKT cells as discussed in the next section. Therefore, it is not surprising that iNKT cells participate in the pathogenesis of a range of different parasitic infections. Further detailed studies are needed before developing iNKT-based therapy to parasite infections. The role of iNKT cells in some parasitic infections and possible effect mechanisms are summarized in Table 2.

### 3. Contribution of NKT Cells to Hygiene Hypothesis

#### 3.1. Hygiene Hypothesis

The “hygiene hypothesis” was proposed in 1989 by Strachan [17] to explain the dramatic increase in the prevalence of autoimmune and allergic diseases over the past two to three decades [18]. According to this hypothesis, reduced exposure to microorganisms and parasites in childhood is the main cause for the increased incidence of both Th1-mediated autoimmune diseases and
3.2. Parasites and Hygiene Hypothesis. Helminths, as long-lived parasites, are remarkable for their ability to manipulate host immunity, protecting themselves from elimination and minimizing severe pathology in the host [53, 56, 59, 60]. Immunomodulation by parasitic helminths is a general phenomenon that is conserved across species, classes, and even phyla [61]. Therefore, parasitic infections are a major theme in the hygiene hypothesis. Allergies and autoimmune diseases are less prevalent in countries with higher burdens of helminths and other parasitic organisms [55]. There are strong epidemiological evidences to support the premise that the dramatic increase in atopic disease in the developed world is a direct consequence of the eradication of helminth infections [58]. At least some helminthes seem to have antiallergic or anti-inflammatory effects in humans. Experimental evidences have also shown the significant suppression for the development of airway hyperresponsiveness (AIR) in mice infected with numerous helminths, including blood fluke *Schistosoma japonicum* [62], filaria *Litomosoides sigmodontis* [63], nematode *Heligmosomoides polygyrus* [64], and *Nippostrongylus brasiliensis* [65]. These mice show attenuated airway inflammation with reduced infiltration of eosinophilia in the BAL and lung and allergen-specific IgE in sera. Many studies have also demonstrated that helminth infections lower the risk of autoimmunity. Experimental studies have also shown protective effects of helminth infections in animal models of autoimmunity. Surprisingly, helminths have been shown to suppress various types of autoimmune disease, such as collagen-induced arthritis, experimental autoimmune encephalomyelitis, and type 1 diabetes in murine models as reviewed recently [51]. Helminth infections might be beneficial to the induction of multiple regulatory mechanisms, including various regulatory cell populations, inhibitory receptors, blocking antibodies, and two prominent cytokines: IL-10 and TGF-β [61, 66]. Thus, it is not surprising that helminths can modulate immunopathology, whether in

### Table 2: Summary of NKT cells on parasite infections.

| Parasites            | Host          | Model or treatment | Effect-mechanism | NKT overall function | Ref. |
|----------------------|---------------|--------------------|------------------|----------------------|------|
| *Schistosoma mansoni*| C57BL/6       | CD1 KO             | IL-4 ↑           | Activated            | [22, 23] |
| *Schistosoma japonicum*| C57BL/6    | WT                 | IL-4 ↑           | Activated            | [24]  |
| *Brugia pahangi*     | C57BL/6       | WT                 | IL-4 ↑           | Activated            | [25]  |
| *Trichuris muris*    | B10.BR        | NKT deletion       | IL-4 ~           | Protective           | [26]  |
| *Plasmodium yoelii*  | BALB/c        | CD1 KO             | IFN-γ ↑          | Protective           | [27]  |
| *Leishmania donovani*| patient       |                    |                  | Protective           | [33]  |
| *Leishmania donovani*| BALB/c        | Jα8 KO, α-GalCer   | IL-4 ↑ and/or IFN-γ ↑ | Protective           | [35–37] |
| *Leishmania donovani*| C57BL/6       | α-GalCer           | IFN-γ ↑          | Pathogenic           | [38]  |
| *Toxoplasma gondii*  | BALB/c        | CD1 KO, α-GalCer   | IFN-γ ↑          | Protective           | [39, 40] |
| *Trypanosoma congoense*| BALB/c      | Anti-CD1d, CD1 KO  |                  | Protective or suppressive | [42] |
| *Entamoeba histolytica*| C57BL/6      | Jα8 KO, CD1 KO     | IFN-γ ↑          | Protective           | [44, 45] |

→: induce; ↑: increase; and ∼: no change.
the context of allergic inflammation or autoimmune disease, either directly or indirectly [55].

Infections by protozoan, like helmhinct, also modulate host immune system. A study shows that serum antibodies to Toxoplasma gondii tend to be negatively associated with allergic sensitization to food and aeroallergens in children from different geographical areas in Greece, Netherlands, China, India, and Russia [67]. A negative association also exists between T. gondii infection and the presence of multiple sclerosis [68].

3.3. iNKT Cells in Hygiene Hypothesis. Nevertheless, the roles of iNKT cells in this hypothesis is limited regarding the involvement of iNKT cells in this hypothesis. On the other hand, many microorganisms and parasites contain various lipids in their structures. The bacterial and parasitic cell wall is a cellular structure highly enriched in a variety of glycolipids and lipoproteins [49]. Along with α-GalCer, growing evidences suggest that some microorganisms, including Mycobacteria, Sphingomonas, Borrelia, Helicobacter pylori, Streptococcus pneumoniae, and Group B streptococcus, can produce CD1d-restricted ligands capable of activating a proportion of iNKT cells [2]. Hence, iNKT cells can respond directly by recognizing the glycolipid antigens expressed by these bacteria. iNKT cells can also respond indirectly to many other bacteria such as Salmonella enterica and Staphylococcus aureus [18]. Of note, some protozoan and helminthic parasites also contain natural ligands of NKT cells and several candidates have been successfully isolated. The excretory and secretory (ES) products, which are often glycosylated, are found in the bloodstream of infected hosts and dictate particular functional immune responses that allow persistence of the parasite, typically by inducing Th2-associated cytokines and expansion of various regulatory cell subsets, including NKT cells [22, 56, 69]. The adult worms of Schistosoma mansoni express a range of glycoconjugates, such as galactosylceramide and glucosylceramide [70], which may contain natural ligands of NKT cells. Infection with S. mansoni or exposure to eggs from this helmhinct inhibited the development of type 1 diabetes in NOD mice [71]. In addition, soluble extracts from worms or eggs of this schistosome possess the similar ability as infection to prevent the onset of diabetes if injection is given at early age (4 wk old). Soluble adult worm antigen or soluble egg antigen may expand the iNKT cell population in NOD mice, although the lipids binding to iNKT cells have not been targeted in this study [71]. Lipid extracts from murine malaria parasites can actually be loaded onto CD1 molecules to expand iNKT cells [28]. Lotter and colleagues have identified a lipopeptidophosphoglycan from E. histolytica membranes as a possible iNKT natural ligand, which can stimulate iNKT cells to produce IFN-γ to exert protective role against this infection [44]. Karmakar and colleagues isolated a natural ligand of NKT cells, β-(1–4)-galactose terminal glycosphingophospholipid (GSP1), from L. donovani to treat infected BALB/c mice [35]. These investigations pave the way to identify natural ligands of iNKT cells for the development of novel therapeutic agents.

iNKT cells may exert their immunomodulatory effects in hygiene hypothesis through the interaction with Treg, Th17, and other immune cells. Upon activation with microbial and parasitic lipid antigens, iNKT cells rapidly produce a wide range of cytokines and chemokines, transactivating many immune cell types, such as Th1, Th2, and Treg. In EAE model, iNKT cells were found necessary for maintaining the mesenteric Th17 cells. Th17 cells in the MLNs are greatly reduced in CD1d−/− mice or Jα281−/− mice [72], which lack iNKT cells. iNKT cells induce the conversion of naïve diabetogenic BDC2.5 T cells into Foxp3(+) Treg cells in the pancreatic lymph nodes accumulating in the pancreatic islets [73]. In addition, iNKT cells can suppress both antigen-induced acute arthritis and collagen-induced chronic arthritis, likely via inhibition of arthritogenic Th1 cells [74]. In Toxoplasma gondii infection, activation of iNKT cells by α-GalCer can lead to a shift to Th2 cytokine profile and a significant increase in Treg cells in MLNs, which exerts protective role and increases survival of mice [40]. The recently defined innate lymphoid cells (ILC) [75] share some features with iNKT cells. Upon activation without the need of prior sensitization, both cells can release copious amounts of Th1, Th2, and/or Th17 cytokines that shape subsequent innate and adaptive immune responses [76]. Although sparse up to now, there exists experimental evidence for direct interactions of ILCs and NKT cells possibly via their effector cytokines [77]. For example, NKT cells, as well as alveolar macrophages, secrete endogenous IL-33 that enhance IL-5 production from ILC2 in lungs during influenza virus infection [78]. The interaction of iNKT cells with other T cell subsets and underlying mechanisms remain to be elucidated.

Taken together, microbe and parasite infections, especially at early lifetime, may sincerely modulate the host’s immune system. Parasitic worms are able to survive in their mammalian host for many years due to their ability to manipulate the immune response. The underlying mechanisms regarding how infections affect the immunity of hosts remain to be clarified. Upregulation of regulatory T cell subsets, such as Treg, and induction of inhibitory cytokines and/or chemokines are the common findings. The involvement of NKT cells in the hygiene hypothesis mostly remains elusive. Given the fact that many microbes and parasites are enriched in lipid antigens and NKT cells are unique T cell subset that can recognize lipid antigens, it is reasonable to speculate that NKT cells play key roles in this hypothesis (Figure 2). Further studies are needed to verify this idea.

4. Conclusions

iNKT cells are unique innate-like T cell subset that bridge between innate and acquired immunity systems. iNKT cells exert both effector and regulatory functions through direct contact or quick secretion of copious amounts of cytokines, chemokines, and other mediators upon their TCR engagement by glycolipid antigens. These cytokines and chemokines critically regulate the downstream differentiation of Th1, Th2, Th17, and other cells. Therefore, iNKT cells have been postulated to have an important proximal immunoregulatory role and influence both innate and acquired immune systems. iNKT cells play crucial regulatory roles in autoimmunity,
allergy, and infections. They participate in the host’s immunity and immunopathogenesis of a wide range of parasite infections as discussed above. More thorough investigation is clearly necessary to better define their mode of activation and their regulatory functions in parasitic infections. Although the involvement of iNKT cells in the hygiene hypothesis and the contribution to autoimmunity and allergic inflammation remains to be fully elucidated, exploiting iNKT cells in helminth immunomodulatory mechanisms may lead to opening a new avenue to develop novel safer therapeutic agents for these diseases based on the manipulation of iNKT cell function.

**Competing Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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