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Immune Evasion of the CD1d/NKT Cell Axis

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Abstract

Many reviews on the CD1d/NKT cell axis focus on the ability of CD1d-restricted NKT cells to serve as effector cells in a variety of disorders, be they infectious diseases, cancer or autoimmunity. In contrast, here, we discuss the ways that viruses, bacteria and tumor cells can evade the CD1d/NKT cell axis. As a result, these disease states have a better chance to establish a foothold and potentially cause problems for the subsequent adaptive immune response, as the host tries to rid itself of infections or tumors.

Introduction

Classical antigen presentation in the cellular adaptive immune response occurs via the recognition of peptides presented by the major histocompatibility complex (MHC) class I or class II molecules, to conventional T lymphocytes [1,2]. In contrast, the MHC class I-like CD1d molecule presents lipids to natural killer T (NKT) cells [3]. Invariant NKT cells are defined as those CD1d-specific T cells that have an invariant T cell α chain rearrangement (Vα14-Jα18 in mouse; Vα24-Jα18 in humans). As part of the innate immune response, the CD1d/NKT cell axis has been shown to play various protective roles in anti-microbial and anti-tumor host defense [4–8]. However, several pathogens and tumor cells have various means to impair antigen (Ag) presentation by CD1d and/or NKT cell function.

CD1d acquires the lipid antigens it presents by an intracellular mechanism (Figure 1). CD1d molecules are synthesized in the endoplasmic reticulum and are loaded with a non-antigenic lipid [3,9,10]. Like other glycosylated proteins, they then traverse through the Golgi and are ultimately expressed on the cell surface [11]. However, these CD1d molecules are not loaded with a lipid that can stimulate NKT cells. Instead, thanks to a tyrosine-based endosomal targeting sequence [12], CD1d molecules re-enter the cells and traffic through late endocytic compartments, where the non-antigenic lipid is replaced by one that is. Upon re-expression on the cell surface, NKT cells can be activated [13]. In cancer, this process is metabolically “revved up” [14]. During certain virus infections, the intracellular location of CD1d is

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altered [15]. We measure NKT cell activation in co-cultures (i.e., NKT cells with CD1d+ cells) by the release of cytokines (e.g., IL-2, IFN-γ, IL-4, GM-CSF, etc.) by the NKT cells.

This review will discuss the immune evasion strategies various pathogens and cancer cells use against the CD1d/NKT cell axis, which could provide potential future approaches to counter those measures. Figure 2 shows the different players reported to be able to impair the CD1d/NKT cell axis; many of these mechanisms are multi-functional. We will break down the immune evasion strategies, by discussing the different diseases individually: 1. Viruses; 2. Bacteria; 3. Tumor cells.

Immune evasion by viruses

Viruses have the capacity to impact the CD1d/NKT cell axis at both the CD1d+ antigen presenting cell (APC) and NKT cell levels. In fact, the simple act of a virus infection results in the loss of a large percentage of NKT cells by activation-induced cell death [16,17]. Interestingly, the decrease in NKT cells appears to be IL-12-dependent, yet CD1d-independent [17]; IL-12 itself can cause the apoptotic loss of NKT cells [18]. That being said, administration of the NKT cell activating and CD1d-presented, synthetic glycolipid α-galactosylceramide (α-GalCer; ref. [19]) to mice infected with murine cytomegalovirus (MCMV) or lymphocytic choriomeningitis virus (LCMV), results in enhanced viral clearance [20,21].

On top of this effect, viruses can target APCs. An acute LCMV infection *in vivo* causes a reduction in CD1d expression on dendritic cells and macrophages [22]; this may be due, in part, to alterations in cellular metabolism, resulting in a “danger signal” used by the CD1d/NKT cell axis as part of the innate immune response [23]. Importantly, cytopathic viruses are able to impact the functional expression of CD1d in multiple ways. After a vaccinia virus (VV) or vesicular stomatitis virus (VSV) infection, CD1d molecules are segregated to one side of a cell; this is concomitant with alterations in cell signaling pathways [10,15,24,25]. The VV-encoded proteins, B1R and H5R, and VSV matrix protein, also contribute to impairing Ag presentation by CD1d post-infection [24,25]. Herpes simplex virus-1 (HSV-1) alters the recycling of human CD1d [26,27], likely by inducing the phosphorylation of residues in its cytoplasmic tail [28,29]. Moreover, two HSV-1 encoded proteins, VP22 and US3, have been reported to contribute to the impairment of CD1d-mediated Ag presentation post-HSV-1 infection [30–32]. The inhibition of NKT cell activation by HSV-1 is APC/NKT cell contact-dependent [33]. An MCMV infection results in a substantial reduction in myeloid progenitor cells in the bone marrow and spleen, especially in NKT cell- and CD1d-deficient mice [34]; this could be prevented by the adoptive transfer of NKT cells into wildtype and NKT cell-deficient mice before infection [34].

A human immunodeficiency virus (HIV) infection can target both NKT cells and CD1d+ APCs. NKT cells are reduced following infection with HIV [35–38] or simian immunodeficiency virus (SIV) [39]; this NKT cell loss is reversed quickly upon highly active antiretroviral therapy (HAART) [40]. In APCs, HIV causes a reduction in CD1d expression by the formation of a CD1d/Nef complex [41,42]. In contrast, an HIV-1 infection

of dendritic cells can result in a TLR7-dependent upregulation of CD1d, triggering NKT cell recognition of those cells [43]. The herpesvirus KSHV also affects both CD1d expression and NKT cell numbers [44,45], whereas the human papillomavirus E5 protein inhibits calnexin-dependent trafficking of CD1d [46]. Taken together, the reports indicate that viruses have multiple mechanism(s) whereby they impair CD1d-mediated Ag presentation or directly affect NKT cells.

Bacterial Infections and CD1d

There has been a variety of work describing bacterial infections that can impact the CD1d/NKT cell axis. For the most part, CD1d-mediated Ag presentation to NKT cells helps, rather than hurts, a host's anti-bacterial host defense. An example of this is the requirement for CD1d in anti-*Borrelia* responses [47] and the identification of diacylglycerols from *Borrelia burgdorferi* (causative agent of Lyme Disease) as an NKT cell-stimulating Ag [48]. As indicated above with certain virus infections, α-GalCer has also been shown to protect mice against a *Mycobacterium tuberculosis* infection [49].

In other animal models (e.g., CD1d- or Jα18-deficient mice), the growth of *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Sphingomonas* and *Ehrlichia muris* is exacerbated as compared to wildtype mice [50]. For *Sphingomonas*, this makes sense, as this bacterium contains α-glucoronosylceramide, which can be presented by CD1d and activate NKT cells [51–53]. Additionally, *S. pneumoniae* has diacylglycerol-containing glycolipids that can stimulate NKT cells [54]. Early following a *Listeria monocytogenes* infection, there is a transient reduction in IL-4-producing NKT cells [55,56]. In contrast, IFN-γ-producing NKT cells expand quickly post-infection [57]. Other bacteria, such as *Chlamydia*, have been shown to be less pathogenic in CD1d-deficient mice, in a mouse pneumonitis model [58]. Also in that report and in line with the results in CD1d KO mice, the activation of NKT cells enhanced *Chlamydia* growth *in vivo*. This seemed to be dependent upon the *Chlamydia* species, as the production of Th1 vs. Th2 cytokines upon NKT cell activation *in vivo*, resulted in reduced or enhanced bacterial growth, respectively [59]. Specifically, *C. muridarum* grew better when NKT cells were present, whereas a *C. pneumoniae* infection was controlled by NKT cells *in vivo* [60]. Others have reported that CD1d is degraded in *C. trachomatis*-infected human epithelial cells [61]. The anthrax lethal toxin impairs CD1d-mediated Ag presentation by targeting the ERK1/2 mitogen-activated protein kinase [62]; a signaling pathway that we showed promotes Ag presentation by CD1d [15].

Thus, bacteria have the ability to affect the CD1d/NKT cell axis by either enhancing NKT cell-dependent responses against infection, or by directly altering the functional expression of CD1d on antigen presenting cells.

Immune evasion by cancer

Although the majority of work studying the CD1d/NKT cell axis has been in the innate anti-cancer immune response [63], tumor cells have been notorious for evading the immune system. Thus, overall, how do we develop cancer if our immune system is apparently "OK"? One way in which cancer cells can prevent immune attack by antitumor effector T cells (e.g.,

CD8+ CTL and NKT cells) is by simply downregulating $\beta_2$microglobulin (β_2m). As both MHC class I and CD1d molecules are associated with β_2m, this allows a tumor to kill two birds with one stone and is a common means of immune evasion by melanoma and colorectal carcinoma, for example [64]. CD1d+ tumors have the capacity to evade recognition by NKT cells by shedding glycolipids, which presumably replace endogenous lipids bound to CD1d, and which cannot be recognized by NKT cells. These glycolipids include gangliogtriaosylceramide shed by the murine T cell lymphoma line, L5178Y-R [14], or the ganglioside GD3 by human ovarian cancer cells [65]. Cells that constitute the blood cancer multiple myeloma are CD1d+ [66]; however, as the disease progresses, the level of CD1d is decreased [67]. Additionally, MM patients have defects in NKT cell function *in vivo*; this is "reversible", in that α-GalCer can activate these NKT cells *ex vivo* [66]. Moreover, advanced prostate cancer patients have a reduction in circulating NKT cells; those that do exist are defective in their ability to produce IFN-γ [68].

Immune responses to tumors are not generally polarized toward a single arm (e.g., only innate). Both the innate and adaptive immune responses will work together as a network with one arm regulating another and vice versa [69]. Overall, immune evasion mechanisms can impair one or more elements of the immunological network; alternatively, the tumors themselves can shed immunosuppressive (or CD1d blocking) glycolipds or reduce their own surface CD1d which reduces circulating NKT cells. Understanding those mechanisms will reveal potential targets for novel therapeutic paradigms using the CD1d/NKT cell axis.

Conclusions

In this review, we briefly discussed the ways in which a variety of viruses, bacteria and tumors can impair the CD1d/NKT cell axis. This can be by affecting the antigen presenting cells, by either down regulating CD1d itself or disrupting cell signaling pathways. Alternatively, impacts on NKT cell numbers and function can also prevent a significant anti-microbial pathogen or anti-tumor immune response in a host. That being said, understanding the ways in which microbial pathogens and tumors can evade host defense, will provide insight into the identification of new targets one could use in novel treatment paradigms--in each of these disease states.

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Highlights

- Viruses, bacteria and tumors can impair the CD1d/NKT cell axis
- CD1d can be downregulated or cell signaling pathways disrupted
- NKT cells can be directly infected and/or unable to recognize CD1d
- Immune evasion strategies might be used to develop new treatments paradigms

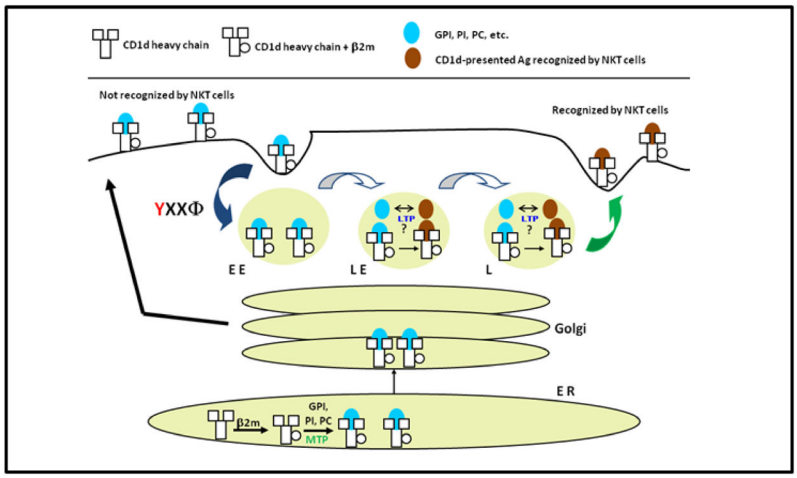

Figure 1. Intracellular trafficking of CD1d molecules

CD1d molecules are synthesized in the endoplasmic reticulum (ER) and form a complex with β_2m. It is within this compartment that CD1d is loaded with an endogenous glycolipid (GPI, PI, PC, etc.), facilitated by the microsomal triglyceride transfer protein (**MTP**). The complex then traverses through the Golgi complex and onto the cell surface. These lipid-loaded molecules cannot be recognized by NKT cells. A Tyr-based endosomal targeting sequence (YXXΦ) causes the CD1d1-β_2m-lipid complex to reenter the cell and traffic to intracellular vesicular compartments in the endocytic pathway. It is there that the first lipid can be replaced by the appropriate endogenous Ag(s) by a lipid transfer protein (LTP); it then returns to the cell surface, where it can now be recognized by NKT cells. EE, early endosomes; LE, late endosomes or early lysosomes; L, lysosomes. Modified from Roberts et al., Recycling CD1d1 molecules present endogenous antigens processed in an endocytic compartment to NKT cells, *J. Immunol.* 168:5409 – 5414, 2002. ***Copyright 2002. The American Association of Immunologists, Inc.***

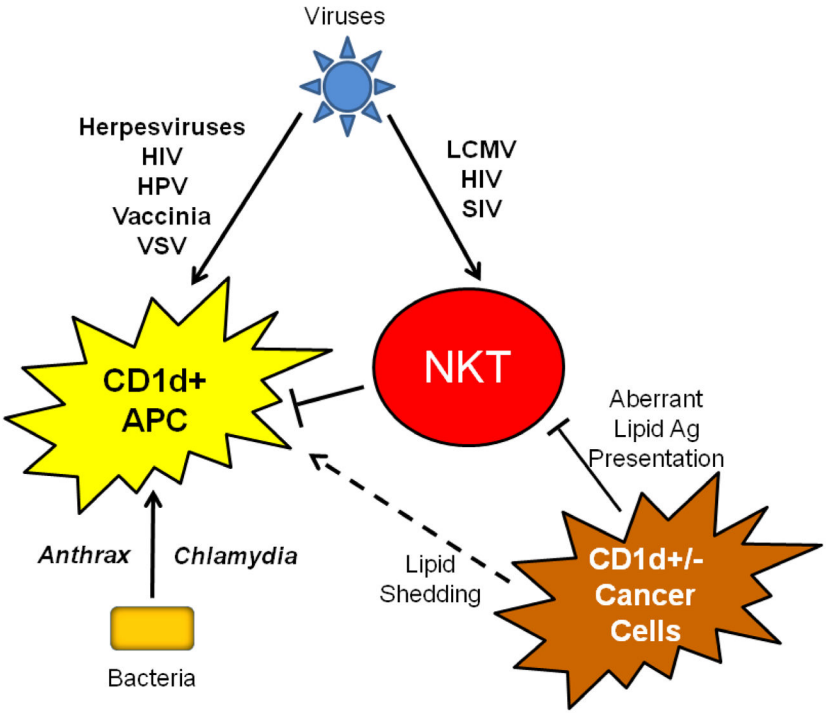

Figure 2. Immune evasion targets

Viruses, bacteria and tumor cells have various means to evade the CD1d/NKT cell axis. Various viruses can target APCs and/or NKT cells, either directly or indirectly. Bacteria can infect APCs and impair the functional expression of CD1d. Lastly, can tumor cells can present aberrant lipids to NKT cells, effectively preventing their activation; alternatively, tumor cells can shed glycolipids from their membranes, binding to CD1d on normal APCs and preventing their recognition by NKT cells.