

Chapter 2

The Role of NKT Cells in the Immune Regulation of Neoplastic Disease

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1 Definition of NKT Cells

Natural killer T (NKT) cells are a subset of T cells that have phenotypic and functional characteristics of both T cells and NK cells, expressing both a T cell receptor and NK lineage markers (Godfrey et al. 2004). NKT cells are defined by their ability to recognize lipid antigens presented by the non-classical MHC class Ib molecule CD1d (Godfrey et al. 2004; Bendelac et al. 2007; Tupin et al. 2007). Although NKT cells make up only a small percentage of lymphocytes (1–2% of mouse spleen and 0.01–2% of human peripheral blood mononuclear cells), they play very important roles in many aspects of the immune system because they can regulate many other cell types such as macrophages, dendritic cells (DCs), CD8⁺T, and NK cells and are uniquely equipped to link innate and adaptive immune responses (Taniguchi et al. 2003; Kronenberg 2005; Bendelac et al. 2007).

Upon activation, NKT cells can rapidly release many cytokines, such as IFN- γ , IL-4, IL-13, and IL-17, and also stimulate other cells to produce cytokines, such as IL-12 from CD1d-expressing APCs (Matsuda et al. 2003; Stetson et al. 2003; Michel et al. 2007; Rachitskaya et al. 2008). NKT cells express IFN- γ and IL-4 mRNA, even in the absence of TCR stimulation, suggesting that they are poised to quickly respond once stimulated (Matsuda et al. 2003; Stetson et al. 2003). The balance of cytokines determines which downstream immune cells are activated, and thus NKT cells help to steer the adaptive immune system in the desired direction.

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1.1 Type I NKT Cells

NKT cells are a heterogeneous population which can be further subdivided into two groups, type I and type II. Type I NKT cells express an invariant TCR receptor α chain (V α 14J α 18 in mice and V α 24J α 18 in humans) which pairs with V β 2, 7, and 8.2 in mice and V β 11 in humans (Imai et al. 1986; Koseki et al. 1989; Porcelli et al. 1993; Dellabona et al. 1994; Lantz and Bendelac 1994; Makino et al. 1995; Godfrey et al. 2004). Type I NKT cells often express other markers such as NK1.1, CD44, and CD69; however none of these are expressed on all type I NKT cells and cannot be used to define this population (Chiu et al. 1999; Kronenberg 2005; McNab et al. 2007). Both CD4⁺ and CD4⁺CD8⁻ double negative (DN) populations of type I NKT cells exist in mice, and some express CD8 α or CD8 $\alpha\beta$ in humans (Bendelac et al. 1994; Gadola et al. 2002). In humans, CD4⁺ type I NKT cells were found to express both Th1 and Th2 cytokines, while DN type I NKT cells mainly expressed Th1 cytokines (Gumperz et al. 2002; Lee et al. 2002). Tissue distribution has also been implicated in the function of type I NKT cells. NKT cells derived from the liver could stimulate tumor rejection, while those from the thymus or spleen could not (Crowe et al. 2005). The role of type I NKT cells is often investigated in J α 18^{-/-} mice which lack only type I NKT cells. CD1d^{-/-} mice are also useful tools since they lack all NKT cells. There are no known markers specific for type II NKT cells, and a knockout mouse expressing only type I NKT cells and not type II does not exist. NKT cells are often defined by staining with CD1d-tetramers loaded with α -galactosylceramide (α -GalCer) for type I NKT cells or sulfatide for type II cells (Benlagha et al. 2000; Matsuda et al. 2000; Karadimitris et al. 2001; Jahng et al. 2004).

Despite being very limited in their TCR β repertoire with an invariant TCR α chain, type I NKT cells recognize a range of lipid antigens (Brutkiewicz 2006; Behar and Porcelli 2007; Tupin et al. 2007). Recently discovered NKT cell recognition of a variety of microbial lipids from *Sphingomonas*, *Ehrlichia*, and *Borrelia* organisms suggests that type I NKT cells play a role in host defense (Kinjo et al. 2005; Mattner et al. 2005; Wu et al. 2005; Brutkiewicz 2006; Tupin et al. 2007). Only a few endogenous glycolipid antigens have been discovered to stimulate NKT cells including phosphatidylinositol, isoglobotrihexosylceramide, and disialoganglioside GD3 (Gumperz et al. 2000; De Silva et al. 2002; Wu et al. 2003; Zhou et al. 2004). The most widely investigated antigen for type I NKT cells is α -GalCer, a glycolipid derived from a marine sponge (Kobayashi et al. 1995; Morita et al. 1995; Kawano et al. 1997; Taniguchi et al. 2003). Upon stimulation with α -GalCer, type I NKT cells rapidly release large amounts of both Th1 (IFN- γ) and Th2 (IL-4, IL-13) cytokines and promote anti-tumor immunity. The mechanism of α -GalCer-mediated tumor protection was shown to require IFN- γ and IL-12 (Cui et al. 1997; Fuji et al. 2000; Chiodoni et al. 2001; Hayakawa et al. 2002; Smyth et al. 2002) and involved IFN- γ -activated NK cells (Hayakawa et al. 2001; Smyth et al. 2001; 2002) as well as activated CD4⁺ and CD8⁺ T cells (Nakagawa et al. 2004; Osada et al. 2004; Hong et al. 2006).

Distinct from conventional T cells, for which different cytokine profiles can be induced against the same peptide-MHC complex, the structure of antigens seems to

play a critical role in determining the cytokine profile induced in type I NKT cells. Modifications of the length and saturation of the lipid chains of α -GalCer can lead to different binding affinities to CD1d as well as altered TCR signaling (McCarthy et al. 2007). Truncation of the lipid chains has been associated with more Th2-skewed immune responses using glycolipids such as OCH (Miyamoto et al. 2001; Oki et al. 2004). More recently, it has been shown that glycolipids modified to include an aromatic ring in their acyl or sphingosine tail were more potent than α -GalCer in activating and expanding human NKT cells (Fujio et al. 2006; Chang et al. 2007).

Although the majority of structure function studies are focusing more on alterations of the lipid portion of α -GalCer, the sugar moiety, as well as its linkage to the ceramide tails, also influences the response of the NKT cells, as this is the portion of the antigen which the TCR interacts with. For example, while α -GalCer is a potent stimulator of cytokine production, α -glucosylceramide can also stimulate type I NKT cells, while β -galactosylceramide has been found to downregulate TCR expression without causing cytokine release or activation of effector cells (Ortaldo et al. 2004). A subsequent study attributed differences in the activity of these glycolipids to their affinity for the TCR (Sidobre et al. 2002). A C-glycosidic analog of α -GalCer induces more IFN- γ production and is a more potent inhibitor of tumor growth (Schmieg et al. 2003). β -linked glycosylceramides have been shown not to induce significant anti-tumor immune responses, compared with α -linked glycosylceramides (Ortaldo et al. 2004; Parekh et al. 2004). Although IFN- γ has been found to be the key mediator for type I NKT-mediate anti-tumor immunity together with α -GalCer and other type I NKT agonists (Smyth and Godfrey 2000; Berzofsky and Terabe 2008), we have recently discovered that β -mannosylceramide is just as potent in eliciting an anti-tumor immune response similar to α -GalCer, despite failing to induce significant IFN- γ production (O'Konek et al. 2011).

Recently, nonglycosidic lipid antigens, such as threitolceramide, were found to be type I NKT cell agonists (Silk et al. 2008). While these lipid/CD1d complexes were found to have weaker binding affinities for the TCR compare to α -GalCer/CD1d, they could stimulate type I NKT cells to promote DC maturation and activation of antigen-specific T cells. Interestingly, the decreased affinity for TCR resulted in less activation-induced anergy and decreased lysis of DCs presenting the antigen. Thus despite limited TCR usage, NKT cells can discriminate a wide variety of antigen structures to initiate the proper immune response.

As mentioned above, α -GalCer was originally discovered for its anti-tumor properties, as it promotes type I NKT-dependent tumor rejection in a wide variety of mouse models (Kawano et al. 1998; Fuji et al. 2000; Chiodoni et al. 2001; Hayakawa et al. 2001, 2002, 2003; Miyagi et al. 2003; Nakagawa et al. 2004; Osada et al. 2004; Ambrosino et al. 2007). α -GalCer can induce protection against chemical or oncogene-driven tumor formation (Hayakawa et al. 2003). Loading tumor cells with α -GalCer induce antitumor immunity (Chung et al. 2007; Shimizu et al. 2007). Because α -GalCer is such a potent stimulator, it also causes type I NKT cells to become anergic (Wilson et al. 2003; Harada et al. 2004; Parekh et al. 2005). Blockade of the interaction between PD-1 and PD-L during α -GalCer treatment prevented this

anergy, and in mice which lacked PD-1, repeated injection of α -GalCer did not induce anergy of type I NKT cells (Parekh et al. 2009). Thus PD-1/PD-L blockade could be a potential therapeutic target to enhance the antitumor effect of α -GalCer, allowing it to be administered repeatedly.

Even in the absence of exogenous stimulation by α -GalCer, type I NKT cells can prevent tumor formation (Cui et al. 1997). Mice lacking type I NKT cells are more susceptible to methylcholanthrene-induced carcinogenesis (Smyth et al. 2000, 2001; Crowe et al. 2002; Nishikawa et al. 2003). Both $J\alpha 18^{-/-}$ and $CD1d^{-/-}$ $p53^{+/-}$ mice exhibit a faster onset of tumorigenesis and decreased survival compared to $p53^{+/-}$ mice, suggesting that type I NKT cells can suppress spontaneous tumorigenesis (Swann et al. 2009).

Although it has been reported that type I NKT cells can kill tumor cells in vitro (Kawano et al. 1998), the immune response initiated by stimulation of type I NKT cells relies on activation of other effector mechanisms to ultimately kill tumor cells (Smyth et al. 2000). Type I NKT cells have been shown to activate NK and $CD8^{+}$ T cells (Carnaud et al. 1999; Toura et al. 1999; Eberl and MacDonald 2000; Smyth et al. 2002; Fujii et al. 2003b). NKT cells also promote maturation and production of IL-12 by DCs through interaction of CD40L on NKT cells with CD40 on DCs, and α -GalCer can induce DC maturation by mimicking the effect of Toll-like receptor agonists (Fujii et al. 2004). This NKT-mediated anti-tumor response is likely initiated by the production of IFN- γ by activated type I NKT cells, leading to the recruitment of NK and $CD8^{+}$ T cells which directly lead to tumor cell lysis. The sequential production of IFN- γ by NKT cells followed by NK cells recruitment has been shown to be necessary for tumor protection induced by α -GalCer (Smyth et al. 2002). Additionally, type I NKT cells have been shown to activate B cells, resulting in increased Ig secretion and generation of better antibody responses (Galli et al. 2003). NKT-mediated cytotoxic activity has also been demonstrated to occur through several mechanisms including perforin/granzyme, Fas ligand, and TNF-related apoptosis-inducing ligand (TRAIL) (Kawano et al. 1999; Nieda et al. 2001; Gumperz et al. 2002).

A role for type I NKT cells has also been demonstrated in humans. In vitro it was shown that stimulating human NKT cells with α -GalCer induced NK-mediated lysis of human tumor cells (Ishihara et al. 2000). Studies have reported a decreased type I NKT cell number in the blood of patients with advanced cancer (Tahir et al. 2001; Giaccone et al. 2002; Dhodapkar et al. 2003), and levels of circulating type I NKT cells inversely correlated with survival in patients with head and neck squamous cell carcinoma (Molling et al. 2007). It was also reported that type I NKT cells from cancer patients have decreased capacity to make IFN- γ , proliferate, and respond to α -GalCer when compared to healthy controls (Tahir et al. 2001; Yanagisawa et al. 2002; Dhodapkar et al. 2003; Fujii et al. 2003a; Crough et al. 2004). In colon carcinoma, a correlation was observed between the number of type I NKT cells infiltrating the tumor and survival (Tachibana et al. 2005). It is also important to note that in humans expression of V α 24 alone cannot be used to define type I NKT cells as a population of V α 24-negative cells was found to bind and respond to α -GalCer, possibly suggesting a new subset of NKT cells (Gadola et al. 2002). Both in humans and mice, type I NKT cells are being defined more commonly by staining

with CD1d-tetramers loaded with α -GalCer or an analog (Benlagha et al. 2000; Matsuda et al. 2000; Karadimitris et al. 2001).

1.2 Type II NKT Cells

In contrast to type I NKT cells, type II NKT cells express a diverse TCR repertoire (Cardell et al. 1995; Godfrey et al. 2004). Type II NKT cells also are CD1d restricted; however these cells are much less characterized than type I NKT cells, and there are no good markers to define these cells. Type II NKT cells recognize a distinct set of lipid antigens from type I NKT cells. While sulfatide is the prototypical antigen for type II NKT cells (Jahng et al. 2004; Zajonc et al. 2005), some type II NKT cell hybridomas have been reported not to recognize sulfatide (Park et al. 2001; Jahng et al. 2004), suggesting that type II NKT cells may be further subdivided on the basis of antigen recognition. Recently, it was reported that alterations of the fatty acid chain of sulfatide alter the degree to which it can stimulate a type II NKT cell hybridoma (Roy et al. 2008; Blomqvist et al. 2009). This suggests that alternating the structure of sulfatide may influence its action, as has been observed with type I NKT stimulation and modifications of the structure of α -GalCer.

Unlike type I NKT cells, which can be characterized by specific markers (V α 14J α 18 TCR, recognition of α -GalCer), type II NKT cells are far less defined. It has been reported that a subset of type II NKT cells may be stained using CD1d-sulfatide tetramers (Jahng et al. 2004); however, this has not yet seen as widespread use as CD1d- α -GalCer tetramers. Further characterization of type II NKT cells will depend upon future discovery of markers specifically expressed on these cells.

Type II NKT cells have been implicated in suppressing immune responses which result in the development of autoimmune diseases. For example, in the NOD mouse model of type I diabetes, overexpression of type II NKT cells prevented disease onset (Duarte et al. 2004), and similarly type II NKT cells have been found to suppress experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis (Jahng et al. 2004) and concanavalin A-induced hepatitis (Halder et al. 2007). In contrast to the protective role of type I NKT cells in tumor models, type II NKT cells have been shown to suppress anti-tumor immunity and enhance tumor growth (Moodycliffe et al. 2000; Terabe et al. 2000, 2003a). For example, it has been demonstrated that 15-12RM fibrosarcoma, 4T1 mammary tumors, CT26-L5 subcutaneous tumors, and CT26 lung metastases, which grow well in wild-type and J α 18KO mice, are rejected in CD1d^{-/-} mice (Terabe et al. 2005). Blockade of CD1d with monoclonal antibodies inhibited tumor growth, presumably by inhibiting type II NKT cells (Terabe et al. 2005; Teng et al. 2009a, b). Stimulation of type II NKT cells with the glycolipid sulfatide suppressed immunosurveillance (Ambrosino et al. 2007). In humans, a subset of type II NKT cells which recognize lysophosphatidylcholine has been identified in the blood of patients with multiple myeloma (Chang et al. 2008). In human bone marrow, type II NKT cells have been shown to suppress autoimmune T cell responses by releasing Th2 cytokines (Exley et al. 2001). In a similar manner, type II NKT cells may also suppress anti-tumor immune responses in humans.

1.3 Interaction Between Type I and Type II NKT Cells

A new immunoregulatory axis was discovered in tumor immunity where type I and type II NKT cells not only have opposite roles but also counterregulate each other (Ambrosino et al. 2007; Terabe and Berzofsky 2007, 2008; Ambrosino et al. 2008; Berzofsky and Terabe 2008). When type II NKT cells are activated in vitro with sulfatide, they are able to suppress the proliferation of activated type I NKT cells (Ambrosino et al. 2007). This result was verified in vivo, as sulfatide suppressed α -GalCer induced protection against 15-12RM subcutaneous tumors and CT26 lung metastases (Ambrosino et al. 2007). From these studies, a new immunoregulatory axis was defined in which the interaction between type I and type II NKT cells may be analogous to that of Th1 and Th2 cells. Understanding of the interaction between type I and type II NKT cells is critical, as the success of immunotherapies may depend on which way the balance of this axis is shifted. One goal of future anti-tumor therapies should be to enhance the activity of type I NKT cells while simultaneously blocking type II NKT cells.

1.4 Interaction Between NKT Cells and Other Cell Types

NKT cells have been shown to interact with other immune components (Terabe and Berzofsky 2008). As described above, type I NKT cells can also induce maturation of DCs and activation of NK cells.

CD4⁺CD25⁺ T regulatory (Treg) cells have been well characterized for their ability to suppress other cells of the immune system (Sakaguchi 2004). The interaction between NKT cells and Tregs has not been well-characterized; however, evidence suggests that such crosstalk does exist. In a mouse lung metastasis model, it was reported that Tregs reduced the number of type I NKT cells in tumor-bearing mice, resulting in increased tumor burden (Nishikawa et al. 2003). Human Tregs can suppress proliferation and function of type I NKT cells activated by α -GalCer-loaded DCs (Azuma et al. 2003). Increased number of Tregs and decreased type I NKT cells in cancer correlate with worse prognosis or more advanced cancer (Tahir et al. 2001; Dhodapkar et al. 2003; Curiel et al. 2004; Tachibana et al. 2005; Molling et al. 2007). Interestingly, in the setting of autoimmune disease, type I NKT cells and Tregs cooperate with one another (Roelofs-Haarhuis et al. 2003). Also in autoimmune disease, type I NKT cells appeared to increase Treg cell numbers through IL-2 production (Liu et al. 2005; La Cava et al. 2006). Further characterization of how type I NKT cells as well as type II NKT cells interact with Tregs is needed.

Myeloid-derived suppressor cells (MDSC), which are defined as CD11b⁺Gr-1⁺ cells, are immature myeloid lineage cells capable of producing arginase, nitric oxide, and TGF- β to suppress other immune cells (Gabrilovich 2004; Bronte and Zanovello 2005). Accumulation of MDSCs has been well characterized in many mouse tumor models as well as in human cancer patients (Pak et al. 1995; Almand et al. 2001; Schmielau and Finn 2001; Gabrilovich 2004; Bronte and Zanovello

2005). Type II NKT cells produce IL-13 which, along with TNF- α , stimulates MDSCs to produce TGF- β , resulting in the inhibition of CD8⁺ T cell-mediated tumor lysis in multiple mouse tumor models (Terabe et al. 2003a, b; Fichtner-Feigl et al. 2005, 2008; Renukaradhya et al. 2008). IL-13, which can be made by type II NKT cells, can also induce arginase expression in MDSCs (Gallina et al. 2006). MDSCs can in turn suppress the function of type I NKT cells. In a B16 melanoma model where MDSCs suppress type I NKT cells, α -GalCer is a poor inducer of anti-tumor immunity; however, if the number of MDSCs was reduced using retinoic acid, α -GalCer was able to protect against tumor formation (Yanagisawa et al. 2006). It has also been reported in a model of influenza that activated type I NKT cells can reduce the suppressive activity of MDSCs in both mice and humans (De Santo et al. 2008). Recently, it was reported that type I NKT cells from human tumors can kill tumor-associated macrophages which are considered to be a subset of MDSCs (Song et al. 2009). Conversely, IL-13 from type II NKT cells can activate tumor-associated macrophages (Sinha et al. 2005). These studies support a role for type I NKT cells in suppressing and type II NKT cells in activating MDSCs.

2 Clinical Trials/Therapeutics

Activation of type I NKT cells using α -GalCer and other glycolipid antigens has generated much preclinical success in mice, leading to several clinical trials in humans (reviewed in (Motohashi and Nakayama 2009)). To date, all of the trials have used α -GalCer to manipulate NKT cells, but preclinical success achieved with other glycolipids suggests that these may progress into the clinic trials. Phase I clinical trials have used soluble α -GalCer (Giaccone et al. 2002), α -GalCer-pulsed autologous DCs (Chang et al. 2005; Ishikawa et al. 2005; Kunii et al. 2009), or adoptive transfer of NKT cells expanded ex vivo with α -GalCer (Motohashi et al. 2006) in patients with melanoma, glioma, lung, breast, colorectal, liver, kidney, prostate, and head and neck cancers. These trials have demonstrated that α -GalCer is well-tolerated with no dose-limiting toxicity (Giaccone et al. 2002; Ishikawa et al. 2005). In some patients, this treatment induced expansion of type I NKT cells as well as an increase in IFN- γ -producing PBMCs and memory CD8⁺ T cells, suggesting that this may have the potential to induce an anti-tumor immune response.

However, α -GalCer has had limited success so far in patients. A few possible explanations have been suggested. The frequency of type I NKT cells is much lower in humans than in mice (Kronenberg 2005), and as noted above, cancer in advanced stages often correlates with reduced number of type I NKT cells. Patients in these trials also had much more advanced disease than the mice in which α -GalCer showed significant greater therapeutic effect. This therapy may also be hindered by the anergy induced by α -GalCer, since in mice it has been demonstrated that following injection of α -GalCer, type I NKT cells can not be restimulated for at least 1 month (Fujii et al. 2002). The lack of success with α -GalCer in humans compared with mice also may be due in part to the presence of anti- α -linked sugar antibodies in humans which the mouse lacks (Galili et al. 1987, 1988; Yoshimura et al. 2001).

More success has been observed with the adoptive transfer of α -GalCer-pulsed DCs. In contrast to the administration of soluble glycolipid, adoptive transfer of DCs loaded with α -GalCer resulted in prolonged NKT activation in mice without the induction of anergy (Fujii et al. 2002). Several clinical trials have studied the effects of injecting monocyte-derived immature DCs loaded with α -GalCer (Nieda et al. 2004; Chang et al. 2005; Ishikawa et al. 2005). This therapy was also shown to be well-tolerated and gave more promising results compared with soluble α -GalCer. A similar trial using mature DCs showed better NKT expansion in vivo, although these cells displayed diminished ability to secrete IFN- γ (Chang et al. 2005). Because many patients with advanced cancers have defects in NKT cell number or function, an adoptive transfer study was carried out in which in vitro expanded NKT cells were administered to patients with lung cancer (Motohashi et al. 2006). Two out of three patients who received the higher dose of NKT cells showed increased numbers of IFN- γ -producing cells and had stable disease. A recent Phase I/II study of adoptive transfer of whole PBMCs cultured with IL-2 and GM-CSF and subsequently pulsed with α -GalCer for the treatment of non-small cell lung cancer reported that 10 of 17 patients displayed an increased number of IFN- γ producing cells following treatment (Motohashi et al. 2009). The patients who showed increased IFN- γ producing cells had significantly longer median survival. This suggests that IFN- γ production following α -GalCer administration can be a predictive marker of success and may be a useful screening tool for selecting patients who may benefit from this treatment.

Manipulating NKT cells alone may not be sufficient to eradicate tumors in patients, and combinatorial approaches may prove to be more successful. For example, α -GalCer can function as a vaccine adjuvant by promoting the generation of antigen-specific T cells (Gonzalez-Aseguinolaza et al. 2002; Silk et al. 2004) and overcoming oral tolerance by inducing the upregulation of costimulatory molecules on dendritic cells (Chung et al. 2004). Recently, α -GalCer has been shown to be an effective mucosal adjuvant for inducing antigen-specific immune responses following administration of HIV peptides (Courtney et al. 2009) and for inducing protective immunity against sexually transmitted HSV-2 infection in mice (Lindqvist et al. 2009). Because α -GalCer-pulsed DCs can stimulate cytokine production without inducing anergy, they may also be attractive candidates in the adjuvant setting. Combining α -GalCer with monoclonal antibodies against TRAIL and 4-1BB, which induce apoptosis of tumor cells and activation of T cells, respectively, induced regression and complete rejection of established tumors in mice (Teng et al. 2007). Taken together, data from these preclinical mouse models suggest that clinical approaches combining multiple agents which take advantage of the interactions of NKT cells with other immune cells may work better than stimulating NKT cells with α -GalCer alone.

3 Conclusion

NKT cells act as pivotal regulatory as well as effector cells bridging the gap between the innate and adaptive immune systems. The balance along the immunoregulatory axis between type I and type II NKT cells may play a key role in many immune

responses, and manipulating this balance may be an important component of immunotherapy for autoimmune, infectious, and neoplastic diseases.

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