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REVIEW

Roles of NKT cells in cancer immunotherapy

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Abstract Cancer immunotherapy has emerged as an effective therapeutic strategy to treat cancer. Among diverse immune populations, invariant natural killer T (iNKT) cells have shown potent antitumor activity by linking innate and adaptive immune systems. Upon activation by lipid antigens on CD1d molecules, iNKT cells rapidly produce various cytokines and trigger antitumor immunity directly or indirectly by activating other antitumor immune cells. Administration of a representative iNKT cell ligand alpha-galactosylceramide (α-GalCer) or α-GalCer-pulsed APCs effectively stimulates iNKT cells and thereby induces antitumor effects. In this review, we will introduce the biology and importance of NKT cells in antitumor immunity. Previous studies have demonstrated that iNKT cells not only activate various immune cells but also reinvigorate exhausted immune cells in the tumor microenvironment. Furthermore, we will summarize the major clinical trials utilizing iNKT-based immunotherapies.

Keywords Invariant natural killer T (iNKT) cell · Cancer immunotherapy · Alpha-galactosylceramide (α-GalCer) · CD1d · Tumor immunology

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Introduction

Recent clinical trials using cancer immunotherapy have shown promising outcomes, and results are still evolving through continuous studies (Pardoll 2012; Mahoney et al. 2015; Sharma and Allison 2015). It is now generally thought that immune cells such as T cells and NK cells recognize and eliminate cancerous cells. However, many studies have also shown that these killer cells have limited potency at the advanced stage of tumors because their activity is braked by immune suppressive environmental factors, including PD-1, Tim-3 and LAG-3, and these cells became hyporesponsive exhausted cells via continuous antigenic stimulation (Wherry 2011; Cho 2017). Thus, overcoming this dysfunctional state of immune cells in tumor microenvironments is challenging. Immune checkpoint blockades such as anti-PD-1 and anti-CTLA4 antibodies rescue the dysfunction of immune systems to fight against tumors, but the clinical efficacy is only experienced in a portion of patients (Wolchok et al. 2013; Pauken and Wherry 2015). Although NKT cells comprise a small portion of immune cells, they can eradicate tumors, and we have recently found that iNKT cell activation reinvigorates exhausted CD8 T cells and NK cells (Seo et al. 2017; Bae et al. 2018). Here, we review the biology and function of NKT cells in the antitumor immunity and propose a strategy to overcome immune exhaustion via iNKT cell activation.

NKT cell biology

It is known that NKT cells are a distinct subset of immune cells co-expressing T cell receptor (TCR) and NK lineage markers (Kawano et al. 1997; Benlagha et al. 2002). The

NKT cell receptor generally consists of an invariant TCRα and semi-variant TCRβ chain and recognizes lipid antigens presented by the non-classical MHC class I molecule, CD1d, which is expressed on various immune cells including monocytes, macrophages, dendritic cells (DCs), and B cells (Kawano et al. 1997; Exley et al. 2000; Benlagha et al. 2002; Godfrey and Berzins 2007).

There are 3 types of NKT cells: type I NKT, type II NKT, and NKT-like cells. Type I NKT cells are the most prevalent type of NKT cells and have a restricted TCR recombinant, the so-called invariant NKT (iNKT) cells (Godfrey et al. 2004). In mice, iNKT cells express semi-invariant TCRs with a limited Vβ repertoire, including Vβ2, Vβ7, and Vβ8.2 (Gapin et al. 2001). In humans, iNKT cells are characterized by the expression of the invariant Vα24-Jα18 TCRα chain paired with the Vβ11 TCRβ chain (Zhou et al. 2004). The representative iNKT cell ligand is α-GalCer (also known as KRN 7000) (Fig. 1), a synthetic glycosphingolipid originally isolated from a marine sponge *Agelas mauritianus* (Kobayashi et al. 1995).

In contrast to iNKT cells, type II NKT cells express variant TCRs and are called non-classical NKT cells (Godfrey et al. 2004; Terabe et al. 2005). Despite the diverse recombination of TCRs, type II NKT cells are also found to recognize antigens in a CD1d-dependent manner (Terabe et al. 2005). Among the 3 types of NKT cells, iNKT cells are known to have superior antitumor activity than any other type of NKT cells (Cui et al. 1997; Smyth and Godfrey 2000). Thus, we will hereafter focus on iNKT cells and their roles in cancer immunotherapy.

Antitumor mechanisms of iNKT cells

iNKT cells are known to exert antitumor activity in direct or indirect manners (Cui et al. 1997; Smyth and Godfrey 2000). iNKT cells can rapidly produce various and large quantities of cytokines in response to stimuli, which link innate and adaptive immunity (Smyth and Godfrey 2000). Tumors expressing CD1d molecules can be directly killed by these iNKT cells through the Fas–FasL interaction, perforin, granzyme B, and tumor necrosis factor α-related apoptosis-inducing ligand (TRAIL) (Kawano et al. 1998).

As mentioned above, iNKT cells secrete various cytokines upon activation and indirectly activate antitumor mechanisms (Coquet et al. 2007, 2008). iNKT cells produce IFNγ, IL-2, -4, -5, -6, -10, -13, -17, -21, -22, TNF-α, TGF-β, and GM-CSF, which affect a broad spectrum of immune cells, including dendritic cells, macrophages, neutrophils, NK cells, and T and B cells (Coquet et al. 2007, 2008). In addition, activated iNKT cells express CD40L and induce the maturation of DCs through CD40–CD40L interaction (Kitamura et al. 1999). Mature DCs then express higher costimulatory molecules such as CD40, CD80 and CD86 and produce larger quantities of IL-12, which in turn activate IFNγ secretion from iNKT cells, NK cells, and CD8 T cells, and accelerate this positive feedback loop (Cui et al. 1997; Kitamura et al. 1999; Taraban et al. 2008). Moreover, DCs upregulate the expression of NKG2D ligands and CD70, a ligand for CD27, and contribute to killer cell activation (Cui et al. 1997; Kawano et al. 1997; Taraban et al. 2008). Consequently, this action of iNKT cells turns on antitumor mechanisms to eliminate tumor cells. Furthermore, $CD8\alpha^+$ DCs cross-primed by iNKT cells contribute to antitumor immunity via secretion of the chemokine CCL17, which attracts and primes CD8 T cells through CCL17-CCR4 (Semmling et al. 2010). B cells are also known to play a role in iNKT-induced antitumor immunity via upregulated IgG production for antibody-dependent cellular cytotoxicity (ADCC) (Moreno et al. 2008).

Immune exhaustion in tumor microenvironments and reinvigoration via activation of iNKT cells

In the tumor environment, T and NK cells are frequently exhausted, which is characterized by high expression of co-inhibitory receptors such as PD-1, Tim-3, LAG3, and TIGIT (Wherry 2011; Mognol et al. 2017). These

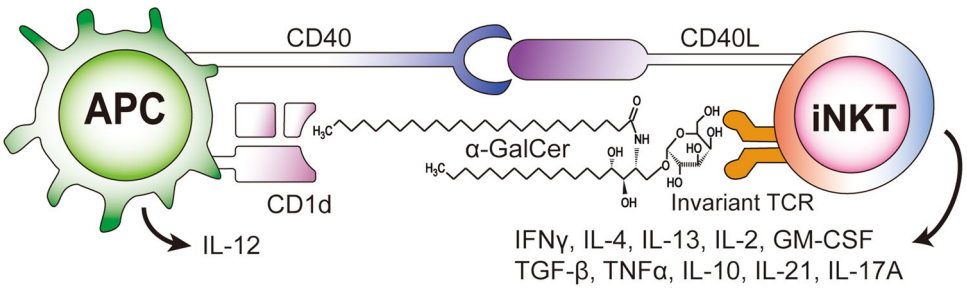

Fig. 1 Mode of iNKT cell activation by α-GalCer. α-GalCer loaded on CD1d molecules in antigen presenting cells (APCs) can be recognized by invariant T cell receptors (TCRs) on iNKT cells. Activated iNKT cells can initiate the production of cytokines such as IL-4 and IFNγ. Upregulated CD40L on activated iNKT cells induces activation signals on APCs via CD40-CD40L

exhausted T and NK cells are defective in proliferation and effector functions. However, our group has recently found that iNKT cell activation by α-GalCer efficiently reverses the function of exhausted tumor NK cells via IL-21 (Seo et al. 2017, 2018) (Fig. 2). Further studies have shown that activation of iNKT cells by α-GalCer reinvigorates not only NK cells but also exhausted CD8 T cells in tumors via IL-2 and IL-12 (Bae et al. 2018). These results revealed that iNKT cell activation plays a crucial role in overcoming immune exhaustion in the tumor microenvironment, suggesting that a combination of iNKT cell agonists is an excellent strategy for current cancer immunotherapy.

Despite the potent antitumor activity of α-GalCer, we need to optimize the dose and schedule of this therapy because repetitive injection of α-GalCer was shown to induce NKT cell anergy (Parekh et al. 2005; Sullivan and Kronenberg 2005). We and other groups have found that the administration of α-GalCer-loaded APCs showed prolonged and enhanced NKT cell responses compared to the injection of free α-GalCer (Chang et al. 2005; Chung et al. 2006; Kim et al. 2008, 2014a, b) and IL-2 has enough potency to break anergic NKT states (Parekh et al. 2005). In addition, PD-1 is highly induced by α-GalCer stimulation, supporting the idea that the combination of anti-PD-1 with α-GalCer can be an efficient way to treat advanced tumors (Chang et al. 2008; Parekh et al. 2009; Bae et al. 2018).

Clinical trials harnessing iNKT cells

Numerous clinical attempts utilizing NKT cells have been made and are on-going in cancer patients. A representative iNKT cell ligand, α-Galcer, was used to activate the antitumor effects of iNKT cells in cancer patients. A phase 1 clinical study was conducted by slow i.v. administration of various doses of α-GalCer in patients with solid tumors and 7 out of 24 patients showed stable disease progression without serious adverse effects (Table 1) (Giaccone et al. 2002). Nieda et al. conducted a phase 1 clinical study using α-GalCer-pulsed, monocyte derived immature DCs in patients with metastatic malignant tumors and

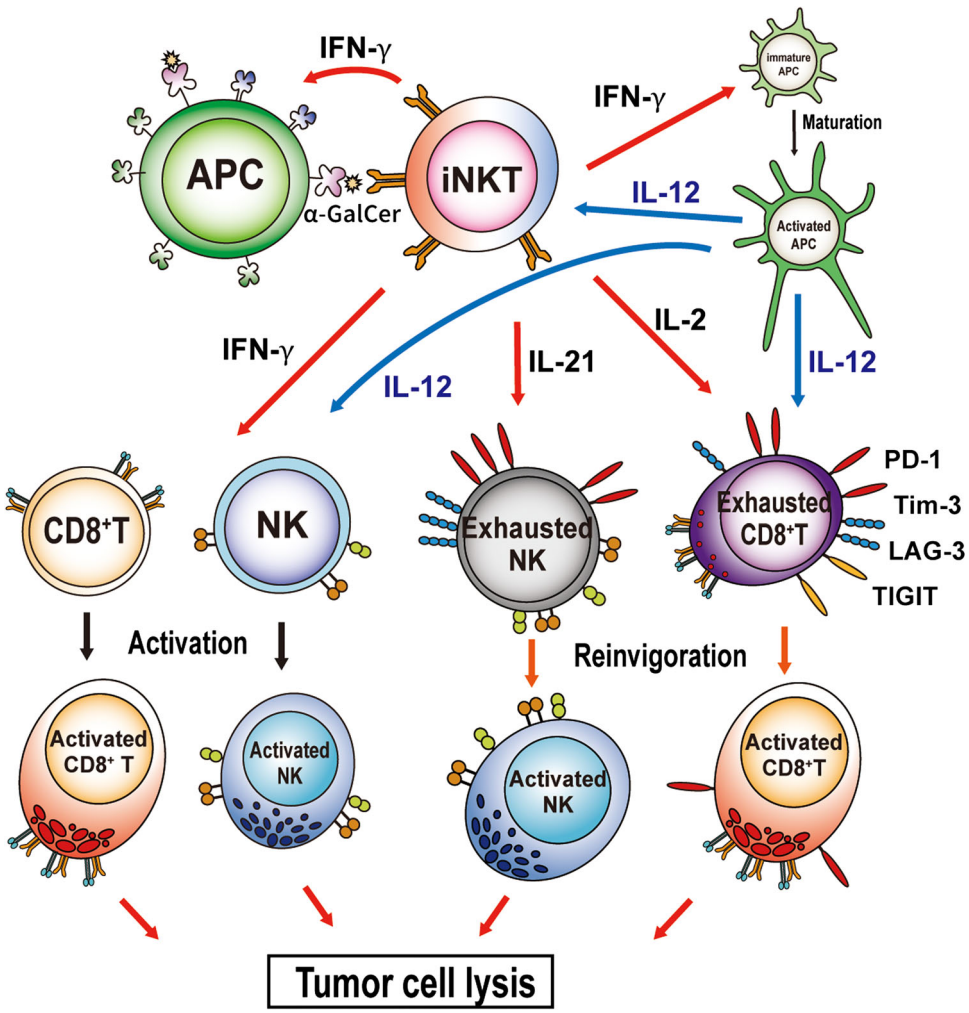

Fig. 2 The effect of activated iNKT cells on anti-tumor immunity. Upon activation of iNKT cells by α-GalCer, iNKT cells secrete IFNγ rapidly. Matured APCs, by costimulatory signals, including CD40-CD40L, start to produce IL-12. IL-12 triggers IFNγ secretion by NKT cells as well as NK cells. IFNγ stimulates the antitumor activities of both CD8 T cells and NK cells. The exhaustion of NK cells in advanced tumors could be reversed by IL-21 secreted by activated NKT cells. Furthermore, IL-2 and IL-12 could reinvigorate exhausted CD8 T cells in the tumor microenvironment. Not only iNKT cells but also activated CD8 T and NK cells participate in antitumor immunity

Table 1 Summary of clinical trials utilizing iNKT-based therapies

Cancer type	Number of patients (completed/ enrolled)	Phase	Applied treatment	Immunological responses	Clinical outcomes	References
Solid tumors	24/24	I	α-GalCer (i.v.)	Increase in serum cytokine (TNFα)	SD (7)	Giaccone et al. (2002)
Solid tumors with metastatic malignancy	12/12	I	α-GalCer-pulsed immature MoDC (i.v.)	Increase in IFNγ in serum	Reduction of serum tumor markers (2) Necrosis of tumor (1)	Nieda et al. (2004)
Solid tumors and myeloma	5/6	(−)	α-GalCer-pulsed mature DC (i.v.)	Increase in IL-12p40 and IP-10 in serum Expansion in NKT cells (> 100 fold)	Reduction of M protein (3) SD (1)	Chang et al. (2005)
Advanced and recurrent NSCLC	17/23	I–II	α-GalCer-pulsed APCs (i.v.)	Increase in IFNγ producing cells in PBMC Increase in the circulating NKT cells	SD (5)	Motohashi et al. (2009)
Stage IIb or IIIa NSCLC	4/4	(−)	α-GalCer-pulsed APCs (i.v.)	Increase in infiltration and activation of iNKT cells in tumor		Nagato et al. (2012)
Advanced or recurrent cervical cancer	8/10	I	α-GalCer-loaded B cells and monocytes infected with HPV16/18 E6/E7 expressing Adenovirus (i.v.)	Activation of NK, NKT, HPV E6/E7 specific CD4 and CD8 T cells	PR (1) SD (5)	Choi et al.(2018)
Stage IIIB–IV melanoma	9/9	I	Expanded iNKT transfer (i.v.)	Increase in iNKT cells and IFNγ production	SD (3)	Exley et al. (2017)
Recurrent HNSCC	10/10	II	α-GalCer-pulsed APCs (nasal submucosal administration) + ex vivo-expanded iNKT cells (intra-arterial infusion)	Increase in NKT cells and IFNγ production in cancer tissue	SD (5) PR (5)	Yamasaki et al. (2011)

SD – Stable Disease; PR – Partial Response; NSCLC – Non Small Cell Lung Cancer; HNSCC – Head and Neck Squamous Cell Carcinoma

demonstrated that α-GalCer-pulsed DCs increased the activation of T cells, the number and cytotoxicity of NK cells, and the levels of IFNγ and IL-12 in sera (Nieda et al. 2004). Chang et al. used α-GalCer-loaded mature DCs in the clinical trials of advanced cancer patients. They clearly showed more than 100-fold expansion of iNKT cells after injecting patients with α-GalCer-loaded mature DCs compared to unloaded DCs. Interleukin-12 p40 and IFNγ inducible protein-10 (IP-10) in sera were also increased in α-GalCer-loaded mature DC-treated groups (Chang et al. 2005). Motohashi et al. performed phase 1 and -2 clinical trials in patients with advanced non-small cell lung cancer using this α-GalCer-pulsed APCs, from total PBMCs with GM-CSF and IL-2 for 7 days. This trial also observed higher numbers of NK and NKT cells and increased levels of IFNγ in the peripheral blood (Motohashi et al. 2009). Nagato et al. also conducted a clinical study using α-GalCer-loaded APCs and showed a significant increase in iNKT cell numbers among tumor-infiltrating lymphocytes (TILs) and increased IFNγ production in TILs (Nagato et al. 2012).

Autologous B cells and monocytes from PBMCs can be alternatively chosen for the APC compartment. Choi et al. showed that B cells and monocytes (B/Mo) pulsed with α-GalCer and transfected with recombinant HPV E6/E7 gene by a 1-day process efficiently activated NK and NKT cells as well as HPV E6/E7 specific CD4 and CD8 T cells in HPV type 16 or 18 positive recurrent cervical carcinoma patients (Choi et al. 2018).

The number of iNKT cells is significantly reduced in cancer patients (Giaccone et al. 2002). To supplement NKT cells in cancer patients, clinical trials using in vitro-expanded NKT cells were conducted in patients with advanced or non-small cell lung cancer. Exley et al. used expanded autologous NKT cells from PBMCs with IL-2 and CD3 mAb and observed significant type 1 responses in iNKT cell recipients with grade 1–2 toxicity (Exley et al. 2017). Yamasaki et al. performed a phase 2 clinical study

using ex vivo expanded NKT cells with IL-2 and α-GalCer and APCs pulsed with α-GalCer in patients with head and neck squamous cell carcinoma. Fifty percent of the patients showed stable disease progression (Yamasaki et al. 2011).

Conclusion

Cancer immunotherapy is one of the most powerful tools for the treatment of tumors. However, the current immunotherapy shows a limited response rate in cancer patients (Ribas and Wolchok 2018). Activation of iNKT cells has been shown to quickly and persistently potentiate antitumor responses by not only priming various immune cells but also reinvigorating exhausted CD8 T and NK cells. To date, clinical trials using this method have shown that they induce promising results in diverse cancer patients without severe adverse effects. Thus, the combination of iNKT cell-based immunotherapy is a good option for cancer patients who are resistant to current immunotherapies.

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Compliance with ethical standards

Conflict of interest All authors declare no potential conflicts of interest.

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