FIGURE 1 Structures of synthetic glycolipid ligands for iNKT cells. KRN7000, α -galactosylceramide (α-GalCer), is the most commonly used lipid ligand in experimental studies. Arrows indicate the modified portions of KRN7000.

shown to be a potent stimulator of both murine and human iNKT cells [29–31]. α-GalCer is different from mammalian glycolipids in which sugar moieties are usually linked in the β-anomeric position. Therefore, activation of iNKT cells with α-GalCer might differ from the physiologic activation by natural ligands, particularly endogenous ligands. Consistent with the preactivation status, iNKT cells release large amounts of cytokines including IL-2, 4, 5, 10, 13, IFN-γ, and TNF-α within several hours after α-GalCer administration. In fact, iNKT cells have been shown to be a predominant source of IL-4 production after injection of anti-CD3 mAb into mice [32]. The ability of iNKT cells to produce significantly higher amounts of these cytokines compared with conventional T cells is also observed on a per cell basis *in vitro*. The preexisting transcripts of IL-4 and IFN-γ present in iNKT cells possibly due to hyperacetylation of histone genes at the IL-4 and IFN-γ promoters supported by the expression of T-bet and GATA-3 may explain the mechanisms underlying their rapid and abundant cytokine production [33–35]. It is well-known that dynamic changes in histone hyperacetylation of cytokine gene and expression of lineage-specific transcription factors such as T-bet and GATA-3 are a hallmark of T helper cell differentiation, which ensures persistent and abundant expression of IL-4 and IFN-γ by these cells. These preactivated phenotypes of activated iNKT cells are possibly

accomplished by the recognition of putative endogenous self-antigen(s). Shortly after activation of iNKT cells with α-GalCer, TCR and NK1.1 were downmodulated, which makes the detection of iNKT cells difficult [36–38]. Although downregulation of TCR is relatively transient, downregulation of NK1.1 is rather sustained. iNKT cell numbers expand by day 2–3 after administration of α-GalCer then return back to homeostatic levels.

Although most iNKT cell–derived cytokines exert their functions as transient intercellular mediators, iNKT cells once activated by glycolipid antigens can affect the functions of bystander cells such as T cells, NK cells, B cells, and dendritic cells (DCs) in a direct or indirect manner, resulting in possible secondary modification of the whole immune network [39–43]. IFN-γ production was induced both in iNKT cells and NK cells sequentially after glycolipid administration. IFN-γ production by iNKT cells was dominant at earlier time points after glycolipid administration, and IFN-γ production by NK cells was higher at later time points [39]. Interestingly, activated NK cell–derived IFN-γ seems to be partly responsible for α-GalCer–induced IFN-γ production by iNKT cells. DCs are also activated by α-GalCer injection [40,41], and then maturation markers such as the CD80, CD86, and MHC class II molecules are upregulated on DCs. The interaction of CD40 on DCs and CD40 ligand on iNKT cells results in the production of IL-12 by DCs, leading to induction of IFN-γ from NK cells.

SYNTHETIC α-GalCer ANALOGUES

α-GalCer has been used most frequently in experimental studies and is a strong agonist from a therapeutic viewpoint inducing both Th1 and Th2 cytokines nonselectively. Therefore, it would be preferable if an agent with a more selective than global activation effect was available. OCH, a sphingosine truncated analogue of α-GalCer, was first described as a Th2 cytokine selective inducer [44]. OCH is a less potent stimulator for iNKT cells in terms of proliferative response. *In vivo* injection of OCH into mice induced comparable levels of IL-4 production by iNKT cells, but the systemic induction of IFN-γ was significantly lower compared with the injection of α-GalCer. There was a good correlation between the lipid tail length of α-GalCer analogues and the ability to induce IFN-γ by iNKT cells; that is, a higher amount of IFN-γ was produced when stimulated with a glycolipid possessing a longer sphingosine chain [45]. In contrast, IL-4 production differed less than that observed for IFN-γ induction. Regarding the mechanism of selective induction of Th2 cytokines, a Th2-bias in iNKT cells

themselves and the subsequent effect of downstream activation of bystander cells has been demonstrated. Crystal structure analyses revealed that the two lipid tails of the glycolipids associated with the highly hydrophobic binding grooves of CD1d [46], suggesting that the binding of a glycolipid with a shorter lipid length to CD1d is less stable. In fact, a glycolipid with a shorter sphingosine chain was revealed to have a shorter half-life in terms of iNKT cell stimulation compared with α-GalCer [45]. Intriguingly, TCR stimulation of iNKT cells for a shorter period could induce a detectable amount of IL-4 *in vitro*. In contrast, IFN-γ production by iNKT cells required longer TCR stimulation. Taken together, the structural difference between OCH and α-GalCer reflects their stability of binding to the CD1d molecule, which in turn exerts a differential duration of TCR stimulation to iNKT cells.

How is the expression of IFN-γ and IL-4 regulated in the context of the duration of TCR stimulation? One possibility is that the expression of these two cytokines may have different cellular requirements. The notion is supported by studies conducted with the protein synthesis inhibitor cyclohexamide (CHX). Interestingly, production of IL-4 or IFN-γ depends on an intrinsic difference in their *de novo* level of protein synthesis. Further analyses revealed that transcription of IL-2 and Granulocyte macrophage colony stimulating factor (GM-CSF) were cyclohexamide (CHX)-sensitive and that transcription of TNF-α was CHX-resistant, implying that cytokines produced by iNKT cells may be divided into two groups based on their dependency on *de novo* protein synthesis. Comparative microarray analysis between α-GalCer–stimulated iNKT cells and OCH-stimulated iNKT cells identified the protooncogene c-Rel, a member of the NFκB family of transcription factors, as a candidate molecule for α-GalCer–induced transcription of the IFN-γ gene [45]. Functional involvement of c-Rel for the transcription of IFN-γ gene in iNKT cells has been demonstrated by transducing c-Rel and its loss-of-function mutant into iNKT cells. Overexpression of wild-type c-Rel showed slightly augmented IFN-γ production, and loss-of-function mutant-expressing cells barely secreted IFN-γ after TCR stimulation, suggesting an important functional role of c-Rel for the effective production of IFN-γ in activated iNKT cells [45]. Studies of c-Rel–deficient mice have revealed a crucial role for c-Rel in IFN-γ production by activated T cells and consequent Th1 development by affecting the function of both T cells and antigen-presenting cells (APCs) [47,48]. In addition, the c-Rel inhibitor pentoxyfylline selectively suppressed Th1 cytokine production and EAE induction [49,50]. Primary calcium influx and subsequent nuclear factor of activated T cells (NF-AT) activation is essential for IFN-γ

production by activated iNKT cells, and c-Rel plays a crucial role in this pathway as well [45]. NF-AT shows a quick and sensitive nucleocytoplasmic shuttling upon TCR activation. Furthermore, the pattern of cytokine production by T cells was determined by the duration of nuclear residence of NF-AT [51]. Sustained NF-AT signaling promoted IFN-γ expression in CD4$^+$ T cells [52]. Considering the structural differences between α-GalCer and OCH, sustained stimulation by α-GalCer induces long-lasting Ca influx, resulting in a sustained nuclear residence of NF-AT, and c-Rel protein synthesis that enables iNKT cells to produce IFN-γ. In contrast, the rather sporadic stimulation by OCH induces a short-lived nuclear residence of NF-AT followed by marginal c-Rel expression, which renders iNKT cells unable to produce IFN-γ efficiently (Fig. 2).

The effect of downstream activation of bystander cells by OCH differs from that of α-GalCer [53]. The fact that α-GalCer induced a much larger population of IFN-γ–producing NK cells than OCH suggests the relative lack of IFN-γ secretion after OCH stimulation occurs not only by a direct effect on iNKT cells but also by an indirect effect on NK cells. Although the β-anomeric galactosylceramide can reduce the number of iNKT cells without inducing a typical NK cell–mediated response, the differential effect of α-GalCer and OCH is more typical in which a functional outcome such as cytokine production can be

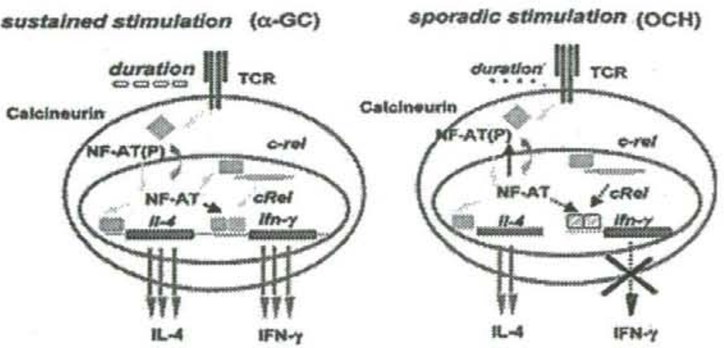

FIGURE 2 A model for the differential expression of IFN-γ and IL-4 by glycolipid-stimulated iNKT cells. There is a good correlation between the lipid tail length of α-GalCer analogues and the ability to induce IFN-γ by iNKT cells. A glycolipid with a shorter sphingosine chain compared with α-GalCer has a shorter half-life in terms of iNKT cell stimulation. Stimulation by α-GalCer induces a long-lasting Ca^{+2} influx, leading to a sustained nuclear residence of NF-AT and c-Rel protein synthesis that enables iNKT cells to produce IFN-γ. In contrast, stimulation by OCH induces a short-lived nuclear residence of NF-AT followed by marginal c-Rel expression, which renders iNKT cells unable to produce IFN-γ efficiently.

observed [54,55]. The different effect of α-GalCer and OCH on NK cells may be explained by the different effect on DCs. After *in vivo* administration of α-GalCer, DCs produce large amounts of IL-12 in a MyD88-independent manner [41,56,57]. IL-12 is one of the most potent inducers of IFN-γ. OCH injection induced one-tenth the amount of serum IL-12 compared with α-GalCer *in vivo* [53]. In addition, freshly isolated liver iNKT cells cocultured with Flt3L-induced DCs produced a significantly higher amount of IL-12 in the presence of α-GalCer compared with OCH, suggesting that OCH administration does not induce effective IL-12 production *in vivo*. Activated iNKT cells stimulated DCs to produce IL-12 through the engagement of CD40 on DCs with CD40L inducibly expressed on activated iNKT cells [57]. Accordingly, CD40-deficient mice have a defect in their production of IFN-γ after treatment with α-GalCer. The reduced induction of CD40L on iNKT cells by OCH was shown at both the level of transcription and surface expression. Thus, the diverse effect of α-GalCer and OCH on IL-12 production by DCs is possibly due to their differential induction of CD40L on iNKT cells.

Although the CD40 pathway plays an important role under physiologic conditions in eliciting IL-12 production, the effective production of bioactive IL-12 by DCs requires another signal elicited by microbial stimuli or IFN-γ [58]. IFN-γ is also required for uncommitted immature DCs to develop the capacity to produce high levels of IL-12 upon subsequent contact with naïve T cells [59]. Furthermore, IFN-γ enhances the transcription of genes encoding both the p40 and p35 components of IL-12, leading to a particularly marked production of heterodimeric IL-12 [60,61]. Interestingly, concomitant administration of IFN-γ and stimulatory anti-CD40 mAb with OCH induced augmented IL-12 production, indicating that the lower level of expression of CD40L and IFN-γ by OCH-stimulated iNKT cells leads to a small amount of IL-12 production from DCs. Moreover, coadministration of IL-12 with OCH significantly induces IFN-γ *in vitro* and *in vivo*. Taken together, the overall effect of OCH *in vivo* may be summarized as follows. OCH induces less IFN-γ upon direct stimulation of iNKT cells. This results from both the short duration of iNKT cell activation and an indirect effect on NK cells, the latter being due to ineffective IL-12 production by DCs by insufficient induction of CD40L and IFN-γ by iNKT cells (Fig. 3).

This Th2-biased response seems to be a general consequence of truncation in the acyl or sphingosine chains of α-GalCer [62]. Apart from lipid chain truncation of α-GalCer, unsaturation of the fatty acid portion of α-GalCer, C20:2 also has been reported to be a Th2 skewing ligand [63]. C20:2 contains a C20 fatty acid with *cis*-unsaturations

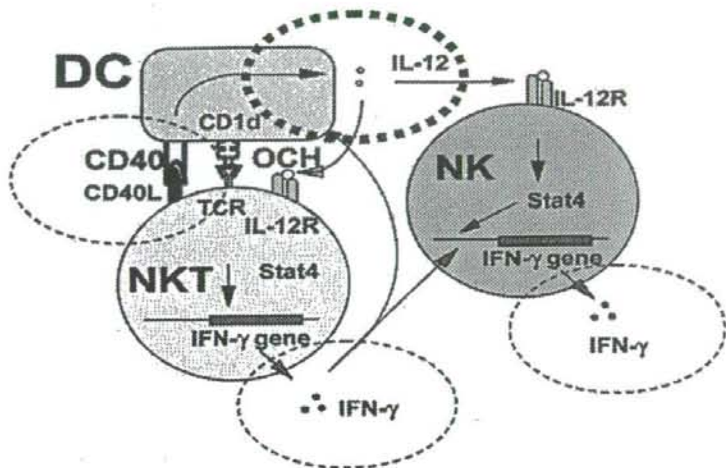

FIGURE 3 Differential effects of α-GC and OCH on activation of bystander cells. OCH induces less IFN-γ production upon direct stimulation of iNKT cells due to a short duration of iNKT cell activation. This also results from an indirect effect on NK cells, due to ineffective IL-12 production by DCs resulting from insufficient induction of CD40L and IFN-γ by iNKT cells.

at positions 11 and 14 (Fig. 1). Although C20:2 elicits Th2-biased responses similar to those obtained with OCH, the mechanism of induction of preferential Th2 cytokines appears different from OCH and remains to be determined.

Conversely, α-C-GalCer, a C-glycoside analogue of α-GalCer, activates iNKT cells at very low concentrations, elicits a Th1-biased response *in vivo*, and exhibits a stronger antitumor effect than α-GalCer (Fig. 1) [64]. Although induction of systemic IFN-γ is sustained for several days, the mechanism underlying this Th1-biased response remains unclear.

GLYCOLIPID THERAPY FOR AUTOIMMUNE DISEASE MODELS

Experimental Autoimmune Encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE) is a prototypical model for multiple sclerosis (MS) mediated by Th1 autoimmune cells, which can be induced by immunization with central nervous system (CNS) antigens in *Mycobacterium*-containing adjuvant. The possible involvement of iNKT cells in the regulation of EAE investigated by using genetically engineered mice is controversial. In TCR Vα14-Jα18

transgenic NOD mice that bear an increased number of iNKT cells, myelin oligodendrocyte glycoprotein (MOG)-induced EAE was significantly suppressed in association with the inhibition of antigen-specific IFN-γ production in the spleen [65]. Consistent with this result, another study showed that CD1d$^{-/-}$ mice developed a more severe EAE compared with C57BL/6 mice [66]. However, other groups did not observe any difference in the disease course between wild-type and iNKT cell–deficient CD1d$^{-/-}$or Jα18$^{-/-}$mice [67,68] or any amelioration of disease in C57BL/6. CD1d$^{-/-}$ and B10.PL.CD1d$^{-/-}$ mice [69].

The results obtained from α-GalCer treatment of EAE mice were also complicated. Intraperitoneal injection of α-GalCer before immunization led to suppression of EAE in B10.PL mice induced with a peptide from MBP [69]. Co-immunization of α-GalCer with antigen ameliorated MOG-induced EAE in C57BL/6 mice and MBP-induced PL/J mice [67,68] but exacerbated MBP-induced EAE in B10.PL and SJL/L mice [67,68]. The protective effect of α-GalCer appears to correlate with the abilities of the mouse strains to produce IL-4 by iNKT cells stimulated with α-GalCer. Moreover, the protective effect of α-GalCer in EAE was not observed in IL-4– or IL-10–deficient mice [67], whereas disease was ameliorated in IFN-γ–deficient mice [55,69]. These studies suggest that EAE protection by α-GalCer is mediated by Th2 cytokines produced by iNKT cells, with the exception of one study that demonstrated that IFN-γ but not IL-4 is critical for the disease protection by α-GalCer in C57BL/6 mice [69]. However, injection of α-GalCer after immunization is not effective for suppression of EAE probably because both Th1 and Th2 cytokines were induced. In contrast, administration of OCH, a Th2-skewing ligand, can suppress EAE and exhibit some efficacy even when treatment is initiated several days after EAE induction [44]. OCH was also effective when administrated orally, which is the favored treatment route for humans. *In vivo* injection of α-GalCer–pulsed APCs with CD86 blockade polarized iNKT cells toward a Th2-like phenotype and suppressed EAE, further providing an alternative strategy for suppressing disease by targeting iNKT cells [56].

iNKT Cells in Autoimmune Type 1 Diabetes

Non-obese diabetic (NOD) mice develop a form of spontaneous autoimmune diabetes similar to insulin-dependent type 1 diabetes mellitus (T1D) in humans. Early studies have indicated a deficit in the number and function of iNKT cells in NOD mice [70–73]. Accelerated disease onset and increased incidence of diabetes have been demonstrated in iNKT cell–deficient CD1d knockout mice [74–76]. Conversely, mice

are protected against diabetes in transgenic NOD mice overexpressing CD1d molecules within the pancreatic islets [77]. Moreover, NOD mice were also protected against diabetes by increasing the number of iNKT cells either by infusion of iNKT cell–enriched thymocyte preparations [78] or by the introduction of the Vα14Jα18 gene into NOD mice [79]. Consistent with these studies, activation of iNKT cells with synthetic glycolipid ligands such as α-GalCer or OCH have been shown to prevent the development of diabetes in NOD mice [75,76,80–82]. In many studies, protection from diabetes by iNKT cells is associated with the induction of Th2 response to islet autoantigens [75,76, 80–83]. However, Th2-independent mechanisms underlying iNKT cell–mediated suppression have been reported in a different system using TCR transgenic mice. Increased number or activation of iNKT cells with α-GalCer protected mice against diabetes induced by transfer of diabetogenic CD4 T cells from BDC2.5 NOD mice [84,85] or diabetogenic transgenic CD8 AI4 T cells [86]. In both cases, transferred diabetogenic cells were rendered anergic.

iNKT Cells in Arthritis

Collagen-induced arthritis (CIA) is an animal model for human rheumatoid arthritis induced by immunization of susceptible mouse strains with type II collagen (CII) in an adjuvant. The protective effect of a blocking anti-CD1 monoclonal antibody on CIA and the amelioration of arthritis induced in iNKT cells–deficient CD1d$^{-/-}$ or Jα18$^{-/-}$ mice have revealed an important role of iNKT cells in the development of arthritis [16–18]. The reduction of disease severity in Jα18$^{-/-}$ mice was associated with an increase of IL-10 or a decrease of IL-1β production in response to antigen stimulation [17,18].

Recent advances in the development of anti-inflammatory drugs such as anti-TNF reagents prompted us to recognize the importance of the late inflammatory phase in the pathogenesis and control of arthritis. Antibody-induced arthritis, such as K/BxN serum transfer model or CII antibody-induced arthritis, is suitable to investigate the inflammatory phase of arthritis [87,88]. Even though antibody-induced arthritis does not require lymphocytes in the development of disease, arthritis induced either by injection of K/BxN serum or CII antibody was ameliorated in iNKT-deficient mice [17,19]. Regarding the mechanisms by which iNKT cells contribute to the development of arthritis in the K/BxN serum transfer model, production of IFN-γ and IL-4 by iNKT cells has been implicated in the suppression of TGF-β1 [19]. Although iNKT cells appear to contribute to the pathogenesis of arthritis, activation of iNKT cells by synthetic glycolipid

ligands protected mice against CIA [16]. In particular, repeated injections of OCH inhibited the clinical and pathologic course of CIA, whereas α-GalCer administration exhibited a mild suppression of disease. Interestingly, OCH treatment suppressed CIA in SJL mice that are deficient in their numbers and function of iNKT cells. Moreover, OCH treatment ameliorated disease even after arthritis had developed. Suppression of arthritis was associated with the elevation of IgG1:IgG2a ratio suggesting a Th2 bias of CII-reactive T cells. Furthermore, neutralization of IL-10 or IL-4 reversed the beneficial effect of OCH treatment. In contrast with CIA, the treatment of α-GalCer has been shown to exacerbate disease in K/BxN serum transfer arthtitis [19]. In our study, however, administration of α-GalCer efficiently inhibited K/BxN serum transfer arthritis by a Th2-independent mechanism (S. Kaieda, unpublished data). The protective effect of arthritis by synthetic glycolipid ligands in arthritis models seems inconsistent with the reduction of disease severity in iNKT-deficient mice. It is possible that activation of iNKT cells by a synthetic glycolipid differs from the physiologic activation of iNKT cells by endogeneous ligands under pathogenic conditions such as those that mediate arthritis.

iNKT Cells in Systemic Lupus Erythematosus

Although the effect of α-GalCer on lupus-like disease differs depending on the mouse strain used, the effect of iNKT cells on disease is consistent with the results observed in iNKT cell deficient–mice. CD1d deficiency accelerates skin disease in MRL lpr/lpr mice without significant differences in the incidence of nephritis and production of autoantibodies to nuclear antigens [89]. Moreover, stimulation of iNKT cells with α-GalCer ameliorates dermatitis in MRL lpr/lpr mice in association with the expansion of iNKT cells and increased Th2 responses, while treatment with α-GalCer has no effect on kidney disease and serum anti-DNA antibody levels [89]. In contrast, however, it has also been observed that CD1d deficiency neither exacerbates skin disease nor ameliorates kidney disease in MRL/lpr mice [90]. In pristine-induced nephritis models, the effect of α-GalCer varies depending on the mouse strain used. In Balb/c mice, treatment with α-GalCer promotes Th2 responses and protects mice against nephritis consistent with the exacerbation of disease in Balb/c.CD1d$^{-/-}$mice [91]. Conversely, treatment with α-GalCer promotes Th1 responses and exacerbates disease in SJL/J mice [92]. The differences noted in the effects of α-GalCer correlates with the relative amounts of Th2 cytokines produced by activated iNKT cells, similar to that observed in mouse models of EAE.

In another model of lupus in (NZB × NZW) F1 mice, iNKT cells increase in number after the onset of disease [93,94], and the transfer of NK1.1^{+} T cells from diseased mice to young F1 mice (before the onset of renal failure) induces proteinuria and swelling of the glomeruli [95]. Moreover, treatment with an anti-CD1d monoclonal antibody augments Th2-type responses, increases serum levels of IgE, decreases levels of total IgG2a and anti-double-stranded DNA (dsDNA) specific IgG2a antibodies, and ameliorates lupus [95]. In agreement with these results, α-GalCer activation of iNKT cells accelerates nephritis and correlates with an enhanced Th1 response [95]. Despite different outcomes of disease treatment in various strains of mice after iNKT cell activation, a consistent observation is that iNKT cell–driven Th1 responses lead to disease exacerbation, whereas iNKT cell–driven Th2 responses lead to disease amelioration. Further elucidation of the strain-dependent factors that promote iNKT cell–induced Th1 or Th2 responses will likely be valuable for the selection of patients suitable for iNKT cell–targeted immunotherapy.

iNKT Cells in Experimental Inflammatory Bowel Disease

Dextran sodium sulfate (DSS)-induced colitis is an experimental model for Crohn disease mediated by Th1 cells. The protective effect of α-GalCer or OCH has been demonstrated in DSS-induced colitis [96,97]. Administration of OCH has been shown to be more effective in this model and correlates with higher IL-10 production in the supernatants of colon organ cultures than that seen in similar cultures from α-GalCer–treated mices [97]. Conversely, iNKT cells have been proposed to act as effector cells in oxazalone-induced colitis [98], an experimental colitis model of human ulcerative colitis. This model of colitis was effectively blocked by neutralizing IL-13 or depleting iNKT cells. Moreover, colitis did not develop in mice deficient in iNKT cells, indicating the crucial pathologic role of iNKT cells in this model. The effect of α-GalCer on oxazalone-induced colitis remains to be determined.

PROSPECTS FOR TARGETING INKT CELLS FOR THE THERAPY OF HUMAN AUTOIMMUNE DISEASES

The promising results of glycolipid therapy achieved in autoimmune disease models raises the possibility of developing iNKT cell–targeted immunotherapies for human autoimmune diseases. Preclinical studies, however, have also raised several concerns about the efficacy and safety of treatment of humans with glycolipid ligands. In most

studies, treatment with glycolipid ligands needs to be initiated early during the disease course to be effective, although some studies have demonstrated the therapeutic effect even after disease has developed. Therefore, the inhibitory effects of glycolipid treatment may be preferable for the prevention of relapse during the remission phases of disease, such as that observed in multiple sclerosis, rather than being curative. Treatment with α-GalCer can also exacerbate disease (e.g., in experimental EAE and lupus induced in certain mouse strains), likely as result of a α-GalCer–induced Th1 response rather than Th2 response. This problem might be overcome by using α-GalCer analogues such as OCH, which can promote selective Th2 responses, even in situations where treatment with α-GalCer results in disease acceleration. The identification of those diseases that may be treated by iNKT cell–targeted therapies is also important. Recent data from animal models of disease suggest that T1D, MS, and Crohne disease might be suitable for iNKT cell–targeted therapy. In contrast, because α-GalCer therapy in SLE is variable, more detailed studies are required.

The potential adverse effects of glycolipid therapy predicted by animal models are liver injury, abortion, and exacerbation of allergic reactions such as allergic airway inflammation. Preliminary data suggest that α-GalCer treatment in patients with solid tumors or administration of α-GalCer–pulsed DCs in patients with advanced and recurrent non–small cell lung cancer is well tolerated [99,100], probably because the proportion of liver iNKT cells is significantly lower in humans than in mice. Longitudinal analyses are required to determine whether other adverse effects result, such as the onset of atherosclerosis or an increase in malignant tumorgenesis.

Another concern is the effect of repeated administration of glycolipid ligands on the responsiveness of iNKT cells, as repeated injection of synthetic glycolipid ligand can induce the hyporesponsiveness of iNKT cells [101]. It is prudent to use an appropriate stimulation protocol to avoid the induction of iNKT cell hyporesponsiveness.

CONCLUSION

Manipulation of regulatory T cells is a novel strategy for immunotherapy. iNKT cells are one of the most suitable cells to stimulate *in vivo* due to the availability of specific ligands. The lack of polymorphism in the antigen-presenting molecule encourages the global application of the ligand for all individuals, unlike MHC-restricted antigens. Because the function of different iNKT cells is very divergent, it may be useful to determine the clinical parameters that yield the

required effect of these glycolipid ligands. To develop the proper treatment protocol for a wide variety of diseases, it is of particular importance to further understand how the different potential activities of iNKT cells are controlled.

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Review article

Understanding the behavior of invariant NKT cells in autoimmune diseases

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Abstract

Invariant NKT (iNKT) cells are a unique subset of lymphocytes that recognize glycolipid antigens presented by a monomorphic glycoprotein CD1d. Numerous works have shown that iNKT cells may serve as regulatory cells in autoimmune diseases including multiple sclerosis (MS). However, recent studies have revealed that the presence of iNKT cells accelerates some inflammatory conditions, implying that their protective role against autoimmunity is not predetermined. Here we review recent information concerning the mechanism of how iNKT cells intervene or promote autoimmune inflammation. Although iNKT cells are thought to be specific for a limited set of glycolipids, they may cross-react to self and non-self ligands. Regarding the response to non-self, it is now known that iNKT cells produce enormous amounts of proinflammatory cytokines during the course of infectious diseases, which is triggered by TCR ligation by microbial lipids, cytokines produced from APCs or both. Whereas the strongly activated iNKT cells play a beneficial role in combating environmental pathogens, they could play a deleterious role in autoimmunity by producing disease-promoting cytokines. However, iNKT cells in the steady state would retain an ability to produce anti-inflammatory cytokines, which is needed for terminating the ongoing inflammation. Though an initial trigger for their regulatory responses remains elusive, our recent work indicates that iNKT cells may start regulating inflammation after sensing the presence of IL-2 in addition to recognizing a ubiquitous endogenous ligand. Understanding of how iNKT cells regulate autoimmunity should lead to a more sophisticated strategy for controlling autoimmune diseases.
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