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CD1d is a nonpolymorphic, MHC class I–like molecule that presents phospholipid and glycosphingolipid Ags to a subset of CD1d-restricted T cells called invariant NKT (iNKT) cells. This CD1d–iNKT cell axis regulates nearly all aspects of both the innate and adaptive immune responses. Expression of CD1d on B cells is suggestive of the ability of these cells to present Ag to, and form cognate interactions with, iNKT cells. In this article, we summarize key evidence regarding the role and regulation of CD1d in normal B cells and in humoral immunity. We then extend the discussion to B cell disorders, with emphasis on autoimmune disease, viral infection, and neoplastic transformation of B lineage cells, in which CD1d expression can be altered as a mechanism of immune evasion and can have both diagnostic and prognostic importance. Finally, we highlight current and future therapeutic strategies that aim to target the CD1d–iNKT cell axis in B cells. The Journal of Immunology, 2014, 193: 4761–4768.

CD1d is a nonpolymorphic, MHC class I–like, β2-microglobulin-associated molecule that presents phospholipid and glycosphingolipid Ags to a subset of immunoregulatory T cells called type I (or invariant) and type II NKT (iNKT) cells (1). Although CD1d is the only lipid-presenting molecule in rodents, there are four other CD1 molecules (CD1a, b, c, and e) in humans that interact with lipid-specific T cell subsets distinct to iNKT cells.

A hallmark of invariant NKT (iNKT) cells is their use of a semi-invariant αβ TCR. In humans, it comprises an invariant TCRVα24–Jβ18 chain paired nearly always with a noninvariant TCRVβ11 chain; in mice, the homologous invariant TCRVα14–Jβ18 chain pairs with a limited set of TCRVβ-chains (TCRVβ2, 7, and 8). iNKT cells are the best-studied subset of CD1d-restricted T cells and can be described as a type of innate-like lymphocyte that can bridge the innate and adaptive arms of the immune system (2). Following activation, iNKT cells assume a Th1, Th2, or Th17 functional immune profile and can exhibit direct cytotoxicity. This diverse range of functions underpins the ability of the CD1d–iNKT cell axis to play a key role in antimicrobial, antitumor, and autoimmune responses (3). iNKT cells are activated in response to a range of endogenous and exogenous lipids, with the glycosphingolipid α-galactosylceramide (α-GalCer) being the prototypical and one of the most powerful, although not physiological (i.e., not synthesized in mammalian tissues), stimulating agonists (4).

Transcriptional regulation of CD1d

CD1d is expressed on cells of both myeloid (monocytes, macrophages, dendritic cells) and lymphoid (B lymphocytes, thymocytes but not mature T cells) lineage (5, 6); it is also expressed outside of the hematopoietic system (e.g., on epithelial and vascular smooth muscle cells) (7). Expression of CD1d on B cells, the focus of this review, points to the potential of these cells to present lipid Ag to, and engage in cross-talk with, iNKT cells.

Expression of CD1d is regulated by multiple transcription factors (TFs). In humans, the ubiquitous TF SP1 activates transcription by binding to the proximal promoter (8, 9), whereas LEF-1 represses CD1d transcription by binding to the distal promoter (10). In mice, a minimal proximal promoter region has been identified, which is regulated by various members of the ETS family of TFs, including Elf-1 in murine B cells and PU.1 in cells of myeloid lineage (11). Human and murine CD1d genes share a retinoic acid response element in the distal promoter (≈1.5 kb from ATG) (12), and retinoic acid was shown to increase CD1d expression in myeloid and B cells in vitro (13–15). It is of interest that single nucleotide polymorphisms in the proximal promoter of PWD inbred mice drastically reduce CD1d expression, with a consequent severe reduction in iNKT cell frequency (16).

Lipid presentation by CD1d

Central to its ability to function as an Ag-presenting molecule, surface CD1d undergoes internalization and trafficking from the cell surface to endosomal and lysosomal compartments in the cytosol. In these compartments, CD1d exchanges its ligands with glycolipids, either endogenous to the cell or acquired from exogenous sources, before returning to the cell surface to present these lipids (6).

Specifically, B cells may capture and internalize foreign lipid Ag directly through the BCR, a concept that may be used in the
design of novel lipid-bound immunogens (17–19). Alternatively, B cells may, like dendritic cells, be able to capture and present ApoE/lipid complexes via the low-density lipoprotein receptor in a BCR-independent manner (20).

In the ensuing discussion, we highlight key studies that have helped to elucidate the potential role and regulation of CD1d expression on B cells in health and in disease. We aim to show the importance of CD1d expression on B cells for efficient humoral immune responses against pathogens and in response to vaccines. In addition, we examine how CD1d, by marking the development of mature B cells, might provide novel insights into the biology of autoimmune disease, EBV infection of B cells, and B lineage malignancies. We suggest that a greater understanding of these processes will allow their exploitation for diagnostic, prognostic, and therapeutic benefit.

**CD1d in normal B cells**

CD1d is expressed in mature, naive, and memory B cells, plasma cells, and B regulatory cells (14, 21). The last are a subset of immunoregulatory, IL-10–secreting B cells, which immunophenotypically correspond to recent bone marrow emigrants called transitional B cells, and are implicated in the pathogenesis of autoimmune disorders. Their role in immune regulation was reviewed recently (21) and will not be discussed further.

**The humoral immune response**

The B cell immune response can be categorized as T cell independent (TI) or T cell dependent (TD). TI responses do not require direct interaction with Th cells. They can be further classified as type 1, in which the B cell is stimulated by activating ligands (e.g., CPG) that do not engage the BCR, or type 2, in which the BCR is engaged by multivalent epitopes, such as polysaccharides. TI responses generally lead to extrafollicular Ab-producing cells rather than germinal center (GC) formation, do not generate high-affinity Abs, and produce few plasma cells and atypical memory cells (22). The result is a rapid, yet transient, innate-like response that does not lead to enhanced recall responses.

TD responses occur through BCR activation in the presence of cognate help from a specialized subset of CD4+ Th cells, termed T follicular helper (T_FH) cells (23). T_FH cells are regulated by the transcriptional repressor Bcl-6, use the chemokine receptor CXCR5 to home toward the B cell follicles, and express key molecules important for T cell–B cell interactions, including IL-21, PD-1, signaling lymphocyte activation molecule–associated protein (SAP), ICOS, and CD40L (24). B cells consequently differentiate within the follicles, giving rise to GCs, the hallmark of the TD response. Within GCs, class-switch recombination, somatic hypermutation, and affinity maturation lead to generation of high-affinity Ig-secreting, long-lived plasma cells and memory cells, thus ensuring a strong anamnestic response (25).

**Regulation of the humoral immune response by CD1d and iNKT cells**

Similar to conventional T cells, iNKT cells also can regulate, enhance, and sustain humoral immune responses. Early studies revealed that administration of α-GalCer to mice induced iNKT cell activation, led to an IL-4–dependent activation of B cells, and, in some cases, resulted in an increase in total serum IgE levels (26). Using iNKT cell–deficient TCRα18−/− mice, the dependency of IgE responses on iNKT cells subsequently was shown in models of allergy, such as OVA-induced asthma (27). Similarly, the use of CD1d−/− mice revealed impaired Ab responses to bacteria, including *Borrelia* species and *Streptococcus pneumoniae* polysaccharides (28, 29). More recently, it was shown that NKT cells play a critical role in the production of Abs against the blood group A Ag (30). In comparison with wild-type mice, NKT cell–deficient mice did not develop increased anti-A levels (IgM and IgG) on immunization with blood group A RBCs. Furthermore, CD1d blockade by administration of a mAb prior to immunization also abrogated the anti-A response in both wild-type and humanized mice.

The precise nature of the interaction between iNKT and B cells can vary and does not always depend on CD1d expression specifically by B cells. To further elucidate this interaction, investigators took advantage of the adjuvant function of lipid Ags, primarily α-GalCer.

**Cognate and noncognate interactions between iNKT cells and B cells.** The help provided by iNKT cells to B cells may occur indirectly through noncognate mechanisms. This principle was demonstrated by the generation of a series of murine bone marrow radiation chimeras lacking CD1d or CD40 on B lymphocytes or expressing CD1d or MHC class II disjointly on APCs (31). These experiments showed that B cell responses against nominal protein Ags could be enhanced by α-GalCer. This could occur in the absence of CD1d, but not CD40, on B cells; furthermore, it required coexpression of CD1d and MHC class II on APCs. Taken together, the findings suggested a noncognate mechanism for iNKT cell help to B cells through licensing of APCs, increased T_FH cell activation, and, thus, improved conventional T cell–B cell interactions. In this role, α-GalCer is acting as a classical immunological adjuvant, stimulating early immune responses to aid the establishment of protective adaptive responses. This is underlined by preclinical studies in which vaccines containing α-GalCer mixed with protein Ags induced more effective humoral and memory responses against several viral, parasitic, and bacterial pathogens (32).

However, there is now firm evidence that B cells, through CD1d expression, are indeed also able to form cognate interactions with iNKT cells, driving a novel form of humoral immune response. First, it was demonstrated that iNKT cells in vitro promoted proliferation of autologous B lymphocytes and induced Ig production in a CD1d-dependent manner (33). iNKT cell help to B cells could occur both in the presence and absence of α-GalCer, suggesting that B cells expressing CD1d can present exogenous or endogenous lipid to iNKT cells. Further work in MHC class II−/− mice (which lack all class II–restricted T cells) provided support for this concept in vivo. Coadministration of α-GalCer with TD Ag was able to induce a limited Ab response in mice lacking Th cells, implying that iNKT cells could act as an alternative, albeit less efficient, cognate partner for B cells (34, 35). The CD1d–restricted nature of these cognate iNKT cell–B cell interactions also was shown to occur in vivo. Specifically, in B cell–deficient μMT mice reconstituted with B cells from wild-type or CD1d−/− donors, α-GalCer enhanced Ab responses against NP–keyhole limpet hemocyanin, dependent on CD1d expression by the reconstituting B cells (36).
As a caveat, several of the studies up to this point had used a similar immunization strategy, using a combination of protein Ags mixed with uncoupled α-GalCer. Such a combination is well suited to demonstrating the adjuvant properties of α-GalCer but does not ensure efficient delivery to individual B cells of both the nominal Ag and the adjuvant lipid.

This was addressed by novel immunization methodologies that aimed to target glycolipid to the BCR and generate lipid-specific B cell responses, either by using NP hapten directly conjugated to α-GalCer (18) or protein Ag (hen egg lysozyme) and α-GalCer both linked to bead particles (19). In both cases, B cells activated by Ag can internalize both the Ag and the physically linked α-GalCer molecule through the BCR. Lipid can then bind to CD1d and subsequently be presented by the B cells to iNKT cells. Immunization of mice in this way was shown to produce rapid increases in the titers of hapten- or protein-specific IgM and IgG (18, 19). These immunogenic formulations are not able to generate MHC class II–restricted epitopes, ruling out a role for a cognate Th cell effect. However, humoral responses were shown to be dependent on the presence of iNKT cells, CD1d expression by B cells, CD40–CD40L signaling, CD80/CD86 costimulation, and IFN-γ production, strongly supporting a role for a cognate iNKT cell–B cell interaction.

This work was followed up by studies using the same immunization techniques to establish the longer-term outcome for B cells that have received cognate help from iNKT cells. When NP-α-GalCer was used to ensure lipid delivery specifically to B cells, the response was characterized by extrafollicular plasmablasts, GC formation, affinity maturation, and a strong primary IgG response that were dependent on IL-21 production by iNKT cells (37). However, there was impaired development of long-lived plasma cells and memory B cells, commensurate with a lack of an enhanced humoral memory response. Similar work involving the use of hen egg lysozyme–α-GalCer to induce stable iNKT cell–B cell cognate interactions also found evidence of IL-21–dependent GC reactions but a lack of long-lived plasma cells, memory B cells, and enhanced recall responses (38). Finally, the outcomes of B cells in MHC class II–mice immunized with protein Ag and α-GalCer were explored (39). In this different immunization model, entailing the use of mixed radiation chimeras and B cell–transfer experiments, Ag-specific Ab responses occurred in a CD1d- and CD40-dependent manner, suggestive of a cognate iNKT cell–B cell interaction. Furthermore, this again was accompanied by rapid, but short-lived, GC formation and transient, rather than long-lived, Ab responses. Taken together, these studies suggest that the cognate interactions between CD1d-expressing B cells and iNKT cells generate a hybrid immune signature, termed the type 2 TD immune response, encompassing features of both the classic TD and TI responses.

Intriguingly, these studies revealed a subset of iNKT cells recapitulating features of TFH cells, including expression of CXCR5, IL-21, PD-1, and CD28, all under control of the Bcl-6 transcriptional program (38, 39). Using inducible knockout mice, it was further shown that SAP, which is essential for iNKT cell development (see below), is also critical for this cognate B cell interaction (40). Termed iNKT_FH cells, these are the specialized NKT cells, which, like their T cell counterparts, are responsible for interacting with the Ag-presenting B cells and driving the immune response.

Recent in situ imaging studies revealed that activated iNKT cells preferentially localize in the marginal zone (MZ) of the spleen, a specialized region in continuous contact with blood-borne Ags (41, 42). The MZ contains several innate and innate-like lymphocytes, including MZ B cells, which may play a prominent role in responding rapidly to TI Ags (43). It is of note that MZ B cells express high amounts of CD1d and primarily secrete IgM and IgG3, the main Ab isotypes produced in response to lipid-conjugated Ag (44). Thus, it is plausible that these MZ B cells may be one of the predominant recipients of cognate iNKT_FH help.

The physiological role of this type 2 TD response is not clear, because it may appear counterintuitive that there is a rapid immune response with affinity maturation and, yet, this does not persist. It is possible that exposure in real life to pathogen lipid ligands may be more prolonged than that of soluble α-GalCer and, thereby, could sustain the presence of iNKT_FH cell–dependent immune responses. Alternatively, pathogens may simultaneously stimulate both lipid and peptide B cell responses. Therefore, the role of iNKT_FH cell–dependent GC formation may be to provide a rapid response by lipid-specific B cells, which, although deliberately abrogated, can provide a platform of primed GCs that can be reused by newly activated peptide-specific B cells. A more recent study added further complexity to this issue (45). By immunizing mice with liposomal nanoparticles containing both S. pneumoniae polysaccharides and α-GalCer, the investigators demonstrated extrafollicular B cell proliferation, leading to a prolonged, high affinity, class-switched Ab response and a strong anamnestic response. This was dependent on CD1d expression by dendritic cells and B cells, indicating a two-step cognate process. This outcome, incongruous with the previous studies, may be explained by the use of a different antigenic formulation, because polysaccharides are able to act as type 2 TI Ags; nevertheless, it demonstrates the potential to target cognate iNKT cell help to B cells in vaccination strategies.

Downregulation of CD1d in GC B cells: mechanisms and purpose. In light of the concept that the help provided by iNKT_FH cells may be purposely halted, it is notable that CD1d expression is lost from the surface of GC B cells (5). However, the in vivo biological mechanism and significance of this phenomenon remain to be determined. It is of interest that, in EBV-infected lymphoblasts, ENCODE analysis reveals that CD1d transcriptional downregulation (see below) is associated with binding of the Polycomb component EZH2 and bivalent chromatin status (i.e., coexistence of H3K4me3 and H3K27me3 marks) at the promoter of CD1d, suggestive of Polycomb-mediated transcriptional repression of CD1d in proliferating B cells (M.S. Chaudhry and A. Karadimitris, unpublished observations).

Indeed, transcriptional downregulation of CD1d can be induced in proliferating B cells activated in vitro (14). CD1d downregulation was found to occur at both the cell surface and the mRNA level in response to various activating ligands, including CD40L. Mechanistically, CD1d downregulation was associated with a decrease in RARx signaling, and could be reversed by agonists of this pathway, including all-trans retinoic acid and the specific RARx agonist AM580. Following in vitro
activation, CD1d downregulation occurred at 24 h, reaching maximum effect at 5 d.

Upregulation of CD1d by AM580 predictably re-enabled lipid presentation. Following CD1d upregulation, lower doses of α-GalCer presented by B cells led to increased stimulation by iNKT cells and B cell proliferation. In contrast, higher doses of α-GalCer induced an iNKT cell–cytotoxic effect, leading to decreased numbers of B cells (14). It is tempting to speculate that these findings can be extended to the in vivo setting. A B cell CD1d–iNKT cell interaction in the GC, if too persistent, may similarly have the potential to induce iNKT cell cytotoxicity toward B cells. If appropriately timed, the downregulation of CD1d observed in the GC may indeed exist to terminate such an interaction before it becomes disadvantageous. Given this temporal change in the pattern of CD1d expression during mature B cell ontogeny, it would be of great interest to analyze the endogenous lipid repertoire generated by naive, GC, and memory B cells and presented by CD1d in the context of a T cell response. Further insights on the significance of CD1d downregulation selectively in GC B cells would require a genetic approach that would ensure persistence of CD1d expression during the GC reaction.

**CD1d in pathological B cells**

Mature B cells are implicated in the pathogenesis of autoimmune disease, such as systemic lupus erythematosus (SLE). In addition, they are targets for viral infection, especially by B cell–tropic viruses, such as EBV, and for malignant transformation, leading to a variety of B lineage malignancies, including B cell lymphomas and multiple myeloma (MM). Accumulating evidence, reviewed below, suggests an important role for the CD1d–iNKT cell axis in these processes, with potential therapeutic repercussions.

**CD1d and B cells in SLE.** B cell dysfunction is central to the pathogenesis of SLE, a systemic autoimmune disorder. This is highlighted by the ability of the anti-CD20 mAb rituximab to induce clinical remissions in a substantial fraction of patients (46).

Recent work demonstrated a critical intersection of the CD1d–iNKT cell axis with B cells in healthy subjects and in patients with SLE (47). Specifically, the presence of CD1d-expressing B cells and their direct interaction with peripheral blood (PB) iNKT cells appears to be indispensable for the α-GalCer–dependent in vitro expansion of iNKT cells. Much of this effect is mediated by transitional B cells (i.e., CD19+ CD38hiCD24hi), which express the highest levels of CD1d among PB B cell subsets.

Compared with healthy controls, patients with SLE have a significantly lower frequency of PB iNKT cells, which secrete abnormally low levels of IFN-γ but high levels of IL-10. This finding correlates with considerably lower surface CD1d expression in patient versus control B cells (but not monocytes) and, in particular, in B regulatory cells. Like GC B cells, loss of CD1d surface expression in SLE B cells is due, at least in part, to BCR signaling, which is increased in the disease in combination with other inflammatory stimuli, such as IFN-α. However, unlike the transcriptional loss observed in GC B cells, loss of CD1d expression in SLE is the result of an enhanced rate of CD1d internalization in patient B cells. In patients who had a clinical response to rituximab, restoration of the PB B cell pool following their initial depletion was associated with restoration of the frequency and function of iNKT cells and expression of CD1d on B cells.

Although these findings provide important insights into the mechanisms that underpin the quantitative and qualitative iNKT cell defects in SLE, the role of dysfunctional iNKT cells in the pathogenesis of SLE and, indeed, of autoimmune disease, in general, remains unclear. In preclinical models, activation of the CD1d–iNKT cell axis can prevent or ameliorate established autoimmune disease (48), providing impetus for development of clinical protocols that will aim to restore iNKT cell frequency and function in patients with autoimmune disorders, including SLE.

**CD1d and virally infected B cells.** Immune evasion through downregulation of classical MHC molecules is a recognized strategy used by viruses to withstand elimination by host defense mechanisms and to help ensure their propagation (49). Highlighting the importance of CD1d in antiviral immune responses, several viruses, including herpes viruses, were shown to downregulate expression of CD1d in APCs through post-transcriptional mechanisms (50, 51). This raised the prospect that EBV, a ubiquitous human herpes virus that targets B cells (52), could use a similar strategy.

EBV has initial tropism for pharyngeal epithelial cells but then spreads to local naive B cells (via surface CD21 and HLA class II molecules) within tonsillar lymphoid tissue. Currently accepted models of chronic EBV infection propose that, to persist in the host, it infects naive B cells and drives B cell maturation through a GC-type reaction to produce memory B cells in which the virus can reside latently long term (52). EBV achieves this through the expression of different genetic latency programs (0–III) in different B cell subsets, which is associated with the transcription of different viral proteins, notably LMP1 and LMP2a (53, 54).

It is possible that the imitation of the process of GC formation, as well as the consequent drastic downregulation of CD1d in EBV-infected cells, confers protection to the virus-propagating B cells from iNKT cell attack. Indeed, evidence from the study of patients with X-linked lymphoproliferative disorder, which is caused by mutations in SH2D1A/SAP or XLP, further suggests that the CD1d–iNKT cell axis might be important in restraining EBV into a latent state. Individuals with X-linked lymphoproliferative disorder, in addition to other immune function defects, have profound defects in iNKT cell development associated with active EBV replication and EBV-associated lymphoproliferation (55, 56).

Following on from these observations, the nature of the interaction between EBV-infected B cells and NKT cells was examined in vitro (15). It was demonstrated that EBV infection of resting B cells can be mitigated by the presence of iNKT cells, indicating that EBV-infected B cells are indeed a target for NKT cells. However, in a parallel to the physiological activation of B cells, EBV infection of B cells rapidly leads to loss of expression of CD1d, abrogating further interaction with NKT cells and, thus, providing a form of immune evasion. Similarly, like their physiologically activated counterparts, CD1d expression in EBV-infected B cells in vitro could be restored by an RARα agonist, re-enabling the stimulation and cytotoxic effects of NKT cells, even in the absence of exogenous Ag (15).

Downregulation of CD1d expression by EBV occurs at the transcriptional level as opposed to the posttranscriptional
mechanisms that are used by other viruses. Using chromatin immunoprecipitation, it was shown that transcriptional repression of CD1d in B cells occurs through binding of the LEF-1/β-catenin complex (members of the Wnt pathway) to the CD1d distal promoter upon EBV infection and that treatment with AM580 restores CD1d expression by inhibiting binding of LEF-1 in this region.

**CD1d and malignant B cells.** Numerous preclinical studies demonstrated the power of the CD1d-iNKT cell axis to enhance (or in some cases inhibit) antitumor immunity (57). iNKT cells can target CD1d-expressing tumors (mostly of hematological, including lymphoid origin) directly (58, 59) or indirectly, by activating adaptive and innate immune responses that can secondarily target CD1d+ tumors (mostly of epithelial origin). We restrict our discussion to the evidence linking the CD1d–iNKT cell axis to the biology and clinical behavior of mature B lineage malignancies, in particular MM and chronic lymphocytic leukemia (CLL), two of the most common hematological malignancies.

**Multiple myeloma.** MM is a malignant monoclonal plasma cell disorder characterized by end-organ damage, including anemia, hypercalcemia, renal insufficiency, and bone lesions (60). CD1d is dynamically downregulated on myeloma plasma cells during disease progression (61). Specifically, in primary myeloma samples, CD1d was highly expressed in premalignant and early-stage disease, but it was decreased, and subsequently lost, in advanced-stage MM. Similarly, loss of CD1d expression was observed in most myeloma cell lines, in terms of both surface and mRNA expression, thus implicating this molecule as an important antisurvival factor in MM. These observations suggest that loss of CD1d is advantageous for the propagation of the malignant clone and permits evasion of myeloma cells

![Figure 1](http://www.jimmunol.org/)

**FIGURE 1.** Dynamic expression and role of CD1d on B cells in health and disease. Expression of CD1d on normal naive B cells permits their cognate interaction with iNKT cells. This leads to the development of the type 2 TD immune response, followed by CD1d downregulation in the GC. Pathological B cells in SLE, EBV infection, or B lineage malignancy display abnormal CD1d expression. Transcriptional regulation of CD1d in these cells also may involve use of physiological transcriptional pathways. Yellow highlighted boxes describe areas that warrant further research, and blue highlighted boxes describe potential therapeutic strategies.
from iNKT cell–mediated immune surveillance, a process that would be further undermined by the defective (but reversible) production of IFN-γ by iNKT cells in patients with progressive disease (62).

However, in addition to immune escape, CD1d may act as a signaling conduit in myeloma cells. In myeloma cell lines with restored expression of CD1d, ligation of surface CD1d by mAb induced caspase-independent apoptosis (an effect dependent on the cytoplasmic tail of CD1d but not the Tyr residue required for endosomal trafficking of CD1d) (61, 63). Thus, loss of CD1d also may be important because it allows myeloma cells to avoid the triggering of CD1d-dependent, downstream antisurvival signaling pathways.

The therapeutic potential of the CD1d–iNKT cell axis was explored in a phase I trial in which autologous myeloid myeloma cells to avoid the triggering of CD1d-dependent, downstream antisurvival signaling pathways.

The reversible nature of CD1d expression regulation may appear counter to the postulated role of CD1d as an adaptive immune pathway. Although current experimental evidence suggests an important role for CD1d and iNKT cells in the development of protective humoral immunity against pathogens, more work is required to better define their role in this context. By contrast, the preclinical data demonstrating B cells as the direct or indirect effectors of the potent adjuvant activity of the CD1d–iNKT cell axis are sufficiently convincing to justify development of protocols aiming to enhance vaccine efficacy in the clinical setting.

High levels of CD1d expression by certain types of B lineage malignancies make them suitable targets for iNKT cell–based immunotherapeutic approaches, including adoptive transfer of in vitro–expanded autologous iNKT cells or even chimeric AgR-modified iNKT cells targeting the B cell–specific CD19 Ag. Furthermore, the emerging evidence suggests that regulation of CD1d expression during viral infection and malignant transformation reflects its regulation during late B cell development. The reversible nature of CD1d expression regulated by the differential activity of the retinoic acid pathway points to therapeutic approaches in B lineage malignancies (including those driven by EBV) that could combine iNKT cell–based cellular therapies with biological agents, such as all-trans retinoic acid.

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**Disclosures**

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**References**

dna synthesis in developing human dendritic cells. J. Exp. Med. 203:
duction. J. Immunol. 4767
Innate immunity of EBV-infected B cells by invariant natural killer T cells. Blood
22. MacLennan, I. C., K.-M. Toellner, A. F. Cunningham, K. Serre, D. M. Sze,
8. 22–33.
histone deacetylase inhibitor through inhibition of HDAC1/2 and activation of Sp1.
Epigenetics 7: 390–399.
10. Chen, Q.-Y., T. Zhang, S. H. Pincus, S. Wu, D. Ricks, D. Liu, Z. Sun,
5: 835–842.
27. Lisbonne, M., S. Diem, A. de Castro Keller, J. Lefort, L. M. Araujo, P. Hachem, J.-
159: 1526–1532.
35. Rastelli, J., C. Ho¨mig-Ho¨lzel, J. Seagal, W. M
174: 8–19.
9. Li, J., W. Sun, P. B. Subrahmanyam, C. Page, K. M. Younger, I. V. Tiper,
54. Mancao, C., and W. Hammerschmidt. 2007. Epstein-Barr virus latent membrane
184: 5047–5054.
113: 370–376.
2007. BCR targeting of biotin-alpha-galactosylceramide leads to enhanced presen-
51. Yuan, W., A. Dasgupta, and P. Cresswell. 2006. Herpes simplex virus evades natural
39. Unutmaz, D., M. A. Davis, M. C. Link, M. T. Hiley, D. J. H. Green, A. J.
113: 2498–2507.
34. Mancao, C., and W. Hammerschmidt. 2007. Epstein-Barr virus latent membrane
112: 1659–1664.
13. Szatmari, I., A. Pap, R. R.
4. 2–3.
8. 22–33.
2005. BCR targeting of biotin-alpha-galactosylceramide leads to enhanced presen-

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