# Dendritic cell maturation by innate lymphocytes: coordinated stimulation of innate and adaptive immunity

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**Pathogen recognition by Toll-like receptors (TLRs) on dendritic cells (DCs) leads to DC maturation and the initiation of adaptive immunity. Recent studies have shown that innate lymphocytes—natural killer (NK), natural killer T (NKT), and γδ T cells—also trigger DC maturation. This interaction in turn expands and activates innate lymphocytes and initiates adaptive T cell immunity. Here, we comment on the evidence that these pathways are TLR independent and have the potential to respond to infection, malignancy, and immunotherapy.**

DC maturation, first proposed as a critical step in immunogenicity 20 years ago, is now accepted as a crucial component of the induction of most adaptive immune responses. The term maturation refers to an intricate differentiation process whereby DCs respond rapidly to an environmental stimulus and become capable of eliciting adaptive immunity. The type of stimulus determines the program of DC differentiation and the subsequent host immune response. DCs can directly sense pathogen components via TLRs, and respond to this recognition by up-regulating surface costimulatory molecules, secreting cytokines and chemokines, enhancing antigen presentation, and migrating to secondary lymphoid tissues (1). Some features of DC maturation, such as the up-regulation of CD86, can be induced by proinflammatory cytokines, but cytokines alone seem insufficient for the induction of adaptive immunity in vivo (2, 3). Additional changes can be imparted to the DCs by CD40 ligation, which contributes to the generation of both CD4 and CD8 T cell immunity (2).

Innate immune cells also sense infections and cellular transformation via receptors other than TLRs. We will first summarize recently identified molecular mechanisms used by NK cells, NKT cells, and γδ T cells to detect infected and transformed cells, then release cytokines such as interferon (IFN)-γ and exert cytolytic activity. These recognition mechanisms are now being placed into the context of DC biology. We will consider how innate lymphocytes induce DC maturation, which in turn expands the numbers and function of both innate and adaptive lymphocytes. We propose that the interaction of DCs with innate lymphocytes represents a major control mechanism for immunity that is independent of TLR ligands.

## Detection of viruses and tumors by NK cells

NK cells, originally defined by their ability to lyse tumor cells without prior activation, recognize their targets via activating and inhibitory receptors (4). The balance of signals transmitted by these receptors determines whether NK cells are inhibited or activated. Activating NK cell receptors include Ly49H, the natural cytotoxicity receptors (NCRs), and NKG2D (4). Ly49H in mice and the NCRs NKp46 and NKp44 in humans directly recognize viral proteins on the surface of infected cells. Ly49H detects the m157 protein of murine cytomegalovirus (MCMV) and is essential for the resistance to MCMV infection in mice (4). The sialylated forms of NKp44 and NKp46 recognize hemaglutinins of para- and orthomyxoviridae, such as influenza, on the surface of infected cells (5). The nature of NCR ligands on transformed cells remains unclear, although heparan sulfate proteoglycans have been implicated in the NKp30- and NKp46-mediated NK cell recognition of adenocarcinoma cell lines (6). Furthermore, it has been established that NCRs are the main activating receptors for NK cell recognition of melanoma and B cell lymphomas (7).

Much more is known about the tumor-associated ligands of NKG2D (4). Both in humans and mice, NKG2D recognizes self-molecules expressed on the cell surface upon transformation or infection. In humans, these include the MHC class I chain-related proteins A and B (MICA and MICB) and UL16 binding proteins (ULBP1-4) and, in mice, the retinoic acid early inducible 1 protein family (Rae1α-ε), H60, and murine ULBP-like transcript 1 (MULT1) (4). These NKG2D ligands are found on some melanomas, carcinomas, and T cell lymphomas (7). In sum, activating NK cell receptors can recognize virus-infected or transformed cells by binding to virus surface proteins or to up-regulated self-proteins that are ligands for NKG2D.

NK cell activation is further enhanced by the absence of NK cell inhibition. The inhibitory NK receptors of the CD94/NKG2, Ly49, and killer cell immunoglobulin-like receptor (KIR) families recognize classical and nonclassical MHC class I molecules (4). Multiple viral proteins, especially of the herpes-

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viridae family, down-regulate the expression of MHC class I molecules or antigen processing (4). As a result of the loss of MHC class I molecules, or "missing self," inhibitory NK cell receptors are not engaged, which results in enhanced NK cell activation and destruction of transformed and infected cells.

### Detection of glycolipids on CD1d by NKT cells

Invariant NKT cells, which express both NK cell markers and T cell receptors (TCRs) that use a single Vα chain, recognize foreign and self-glycolipids presented by the nonclassical MHC class I molecule CD1d (8). Natural CD1d ligands are currently being identified. One example is lipophosphoglycan from *Leishmania donovani*, a constituent of the parasitic surface glycocalyx, which stimulates IFN-γ secretion by a subset of hepatic mouse NKT cells (9). Glycosylceramides from the gram-negative bacteria *Ehrlichia muris* and certain *Sphingomonas* species, and phosphatidylinositol mannoside from mycobacterial membranes, are also recognized by human and mouse NKT cells (10–12). There is also evidence that glycolipids, possibly glycosylphosphatidylinositol from *Plasmodium* and *Trypanosoma* parasites, are detected by NKT cells (8). NKT cell stimulation by other pathogens such as *Salmonella typhimurium*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* has also been reported (8), but specific CD1d ligands from these organisms have not been identified. These findings suggest that NKT cells are primarily involved in the detection of bacterial and parasitic pathogens, whereas NK cell activity is focused on recognition of viral infections.

Similar to NK cells, NKT cells are able to detect altered self-ligands. The ganglioside GD3, which is overexpressed on human melanoma cells, can be cross-presented on CD1d to mouse NKT cells (13). Most recently, the lysosomal glycosphingolipid isoglobotrihexosylceramide was shown to be a potent CD1d-restricted self-ligand that stimulates mouse NKT cells (14). In fact, a lack of isoglobotrihexosylceramide results in severe NKT cell deficiency. DCs can be induced to present isoglobotrihexosylceramide upon TLR ligation by gram-positive bacteria like *Salmonella typhimurium* (10). Therefore, both self and microbial glycolipids presented on CD1d can elicit NKT cell activation.

### Detection of microbial antigens and tumors by γδ T cells

γδ T cells, which express γδ TCRs instead of the αβ TCRs found on classical T cells, recognize microbial and tumor antigens, typically small pyrophosphomonoesters and alkylamines (15). Similar to NK and NKT cells, γδ T cells can also recognize microbial products and self-molecules on infected or tumor cells, including small organic molecules, chaperone proteins, or nonclassical MHC class I molecules. Pyrophosphomonoesters, including isopentenyl pyrophosphate, are natural antigens from Mycobacteria such as *M. tuberculosis* (15) or accumulate as mevalonate metabolites in tumor cells such as breast carcinoma, facilitating recognition of tumors by invariant γδ T cells (16). The same invariant γδ T cell population detects bacterial alkylamines (15) and aminobiphosphonates, which are synthetic compounds used in cancer therapy (17). Other γδ T cell populations recognize mycobacterial and tumor-derived HSP60 molecules (15). In addition, some murine γδ T cells seem to directly recognize viral surface proteins such as herpes simplex virus glycoprotein I (15). Finally, nonclassical MHC class I molecules stimulate distinct γδ T cells. MICA and MICB are recognized by human intestinal γδ T cells (18), and the MHC class Ib T10/T22 antigens bind to murine γδ T cell receptors (19). As is the case for NK cell recognition, these nonclassical MHC class I molecules are thought to be upregulated upon cell transformation and infection. Moreover, in humans a subpopulation of peripheral blood γδ T cells is also restricted by the nonclassical MHC class I molecule CD1c, which presents microbial glycolipids (15). In sum, γδ T cells recognize infected and transformed cells via a diverse set of ligands that range from small organic compounds to pathogen-derived antigens and stress-induced self-molecules.

### Dendritic cell maturation by NK, NKT, and γδ T cells

DC maturation has been documented in vitro and in vivo after NK cell recognition of MHC class $I^{low}$ tumor cells (20), NKT cell stimulation by the synthetic invertebrate glycolipid α-galactosylceramide (α-GalCer) presented on DC CD1d molecules (21, 22), and activation of phosphoantigen-specific and CD1c-restricted γδ T cell subsets (23, 24). After activation, all three innate lymphocyte populations were able to induce DC maturation as evidenced by increased expression of CD86, IL-12 production, and priming of T cell responses (2, 20, 22–25). TNF has been identified as a crucial inducer of DC maturation in these studies (2, 23–26). In addition, CD40–CD40L interactions induced by NKT cells allowed for priming of adaptive immune responses by DCs (2). Thus, NK, NKT, and γδ T cells mature DCs by a combination of cytokine- and cell contact–dependent signals.

In turn, matured DCs also stimulate NK, NKT, and γδ T cells for sustained innate immune responses (21, 24, 26–28). IL-12, IL-15, IL-2, and IFNα/β, which are all produced by maturing DCs, contribute to the activation of different NK cell functions (29–31). This interaction likely takes place at sites of infection and in secondary lymphoid organs (27).

An important component of DC maturation is the ability of the DC to mediate lymphocyte differentiation. The interaction of NK cells with DCs in vivo assists in the T helper type 1 (Th1) cell polarization of primary immune responses, most likely via secretion of the Th1 cell–promoting cytokine IFN-γ by the NK cells (32). The interaction of NKT cells with antigen-capturing DCs likewise allows for the induction of antigen-specific, IFN-γ–producing $CD4^+$ and $CD8^+$ T cells (2). Thus, when DCs are matured by NK, NKT, and γδ T cells, the DCs both augment innate responses and prime adaptive immunity.

### Comparing DC maturation induced by TLRs or innate lymphocytes

DC maturation is a sensor that links innate immune responses to adaptive ones. During TLR-mediated DC maturation, distinct TLR ligands likely evoke distinct responses in DCs (1). This signaling complexity is further increased by the expression of distinct TLRs on different DC subsets, as well as by the differences in adaptor molecules used by different TLRs (1). One difference between TLR-induced versus innate lymphocyte-induced DC maturation is the nature of the ligands. TLRs bind microbial constituents (protein, DNA, and RNA) or autoantigens that erroneously mimic these pathogen components (33). NK, NKT, and γδ T cells can also be activated by self-molecules, but these serve as desirable molecular beacons to signal infection or transformation of cells that display these molecules (4, 10, 15). This altered self-recognition by innate lymphocytes allows DC maturation in response to tumors or other stresses, which may not express TLR ligands. In addition, TLR ligands stimulate many cell types, including epithelial cells, and lead to systemic responses, whereas DC maturation in response to innate lymphocytes is potentially a much more local and very early event that is restricted to the site of innate lymphocyte activation. In sum, NK, NKT, and γδ T cells have considerable potential to induce protective DC maturation after both local expression of stress-induced molecules and systemic spreading of pathogen-derived constituents.

Innate lymphocytes can also provide antigenic material for DCs. Fragments of infected or tumor cells, generated during the destruction of target cells by innate lymphocytes, are taken up by DCs and displayed on MHC molecules, thus eliciting an adaptive T cell response in vivo (20) (Fig. 1).

### DC activation by innate lymphocytes in immunotherapy

It should prove fruitful to harness innate lymphocyte-mediated DC maturation for immunotherapy, because the innate lymphocytes themselves have direct antitumor functions and they can mobilize an adaptive immune response via DCs. In other words, they act as adjuvants. A recent study showed that NKT cell activation induced by α-GalCer–pulsed immature DCs also provoked NK and T cell expansion in patients with metastatic malignancies (34). This study suggested that DCs activated by one population of innate lymphocytes, such as NKT cells, can activate another group of innate lymphocytes, such as NK cells, to induce antitumor effects. In another recent study (28), mature α-GalCer–pulsed DCs induced a >100-fold expansion of NKT cells, which was sustained for up to 6 months after vaccination. This treatment also boosted memory T cell responses against a persistent human cytomegalovirus antigen, but not against influenza antigens, except in one patient, likely due to the reintroduction of influenza antigens from a recent vaccination. These data suggest that NKT cell–mediated immune activation can lead to enhanced T cell responses against antigens present in the patient, possibly as a result of NKT cell–mediated maturation of DCs that can present antigenic peptides. Another study showed that γδ T cells could be stimulated with the aminobiphosphonate pamidronate plus low-dose IL-2 in relapsed non-Hodgkin lymphoma and multiple myeloma patients (17). In patients whose γδ T cells expanded in response to pamidronate and IL-2 in vitro, the treatment led to increased numbers of γδ T cells in the peripheral blood in 55% of patients and to clinical improvement in 33% of the patients. However, the induction of adaptive T cell immunity was not analyzed in this patient cohort. Finally, allogeneic hematopoetic stem cell transplantation mediates a graft-versus-leukemia effect, which has been ascribed to detection of mismatched HLA molecules by NK cells (35). This would suggest a major role for suitably activated NK cells in direct resistance to human leukemia. The effect on adaptive antileukemia immune responses has yet to be evaluated. With these initial results on innate lymphocyte activation in immunotherapy, NK, NKT, and γδ T cell stimuli should be considered in addition to TLR stimuli as adjuvants for DC-based vaccines as a way to enhance both in-

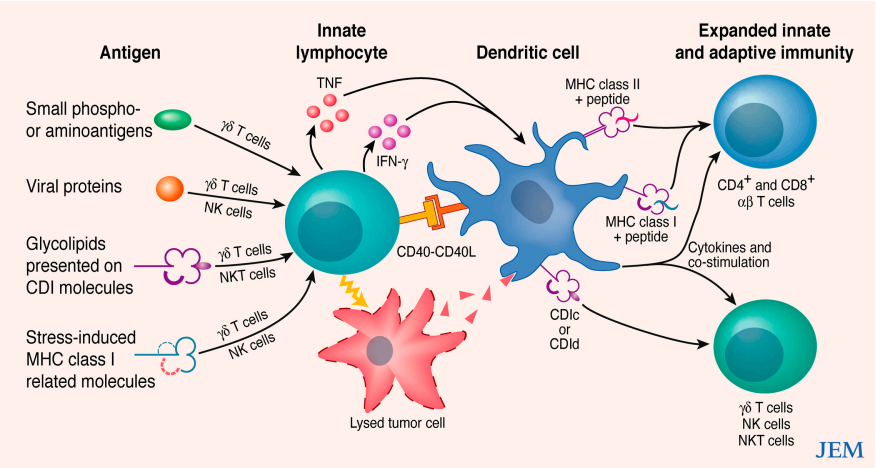


**Figure 1. Innate lymphocytes mature DCs.** Innate lymphocytes, including γδ T, NKT, and NK cells recognize pathogen-derived and self-antigens on infected cells, tumors, and stressed self-tissues (left). Their activation leads to DC maturation, presumably under conditions where the DCs are also presenting ligands recognized by innate lymphocytes. The DCs thus expand the innate response (bottom right) and also elicit adaptive immunity to processed antigens (top right), including those derived from cells lysed by innate lymphocytes. Cytokines and cell contact–dependent molecules mediate DC activation by different types of innate lymphocytes, whereas DCs produce cytokines that expand and differentiate additional innate and adaptive lymphocytes.

nate and adaptive immune responses against infectious diseases and tumors.

## Conclusions

Molecular mechanisms are being identified to explain how innate NK, NKT, and γδ T cells detect infected and transformed cells, and directly provide resistance at the level of cytolysis and cytokine production. Another new area relates to the consequences of innate lymphocyte interactions with DCs. First, the innate cells induce DC maturation through cell contact mechanisms that remain to be unraveled. Second, the DCs expand the number and enhance the function of the innate lymphocytes. Finally, maturing DCs process antigens, particularly from cells lysed by innate lymphocytes, and elicit adaptive Th1-type immunity. This newly recognized cross talk between DCs and innate lymphocytes, which seems to occur largely in the secondary lymphoid organs, is starting to be exploited for therapeutic purposes, because innate lymphocytes serve as attractive adjuncts for tumor resistance and also as adjuvants for initiating antigen-specific, cell-mediated immunity. Major goals for the future are to identify mechanisms by which DCs expand and activate innate lymphocytes, to understand the role of lymphoid organs as sites where DCs and innate cells interact to initiate adaptive immunity, and to harness these pathways in therapy and perhaps vaccination.

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