

Regulatory NK-Cell Functions in Inflammation and Autoimmunity

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Natural killer (NK) cells were viewed traditionally as cytotoxic effector cells whose rapid killing of infected and transformed cells without preactivation provides a first line of defense prior to the initiation of an adaptive immune response against infection and tumor development. However, it has become clear that NK cells interact with various components of the immune system, and therefore have the potential to function as regulatory cells. While NK cells can assist in dendritic cell (DC) maturation and T-cell polarization, increasing evidence indicates that NK cells can also prevent and limit adaptive (auto) immune responses via killing of autologous myeloid and lymphoid cells. Investigating immunoregulatory NK-cell functions might generate exciting insights into the reciprocal regulation between NK-cell-mediated innate immunity and adaptive immune responses, improve our capacity to monitor these cells as surrogate markers for disease activity and treatment responses in autoimmune diseases, and, perhaps, provide new prospects for NK cell-directed therapies.

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Online address: <http://www.molmed.org>

doi: 10.2119/molmed.2009.00035

PHENOTYPES AND FUNCTIONS OF NK CELLS IN HUMANS

Although NK cells were described originally as a homogenous population of innate lymphocytes, there is increasing evidence that NK cells include distinct subsets with disparate functions, locations, and developmental origins. Human NK cells in peripheral blood can be divided into at least two functional subsets based on the expression of CD56 and CD16 (Figure 1). CD56^{dim}CD16⁺ NK cells constitute about 90% of total blood NK cells, efficiently kill target cells, and secrete only low levels of cytokines. In contrast, CD56^{bright}CD16⁻ NK cells constitute <10% of total blood NK cells, but are enriched in secondary lymphoid tissues (1). In contrast to the CD56^{dim}CD16⁺ NK-cell subset, activated CD56^{bright}CD16⁻ cells produce many cytokines, including

IFN- γ , TNF, and GM-CSF, but acquire cytotoxicity only after prolonged activation (2). Therefore, cytokine secretion and cytotoxic effector functions are separated in human NK-cell subpopulations.

CD56^{bright}CD16⁻ and CD56^{dim}CD16⁺ NK cells also differ from each other in the expression of inhibitory and activating NK-cell receptors, as well in the expression of adhesion molecules and chemokine receptors which facilitate homing to lymphoid tissues and sites of inflammation. NK-cell activation during target cell recognition is controlled by germ line encoded activating and inhibitory receptors on these innate lymphocytes. Among these, triggering of killer immunoglobulin-like receptors (KIRs) as well as of the CD94/NKG2A receptor on NK cells by classical and nonclassical MHC class I molecules de-

livers negative signals that prevent target cell killing (3). In contrast, engagement of activating receptors such as CD16 (Fc γ RIII), NK cell protein 30 (NKp30), NKp44, NKp46, DNAM-1, and NKG2D by antibody opsonization or ligands whose expression is upregulated following infection, transformation, or cellular stress, provides an NK-cell activating signal (4,5). Of the above-mentioned inhibitory receptors, cytokine-secreting CD56^{bright}CD16⁻ NK cells express high levels of the inhibitory CD94/NKG2A complex recognizing HLA-E, but lack MHC class Ia allele-specific killer cell Ig-like receptors, which are, in contrast, expressed by CD56^{dim}CD16⁺ NK cells. Both NK-cell subsets express the activating receptors NKG2D as well as NKp30 and NKp46, but expression of the antibody-dependent cellular cytotoxicity mediating receptor CD16 (Fc γ RIII) is confined to the CD56^{dim}CD16⁺ subset (6). Therefore, cytokine secreting CD56^{bright}CD16⁻ NK cells express a more rudimentary repertoire of inhibitory NK-cell receptors than cytotoxic CD56^{dim}CD16⁺ NK cells.

CD56^{bright}CD16⁻ NK cells constitutively express CD62L (L-selectin) and

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Submitted May 6, 2009; Accepted for publication May 11, 2009; Epub (www.molmed.org) ahead of print May 14, 2009.

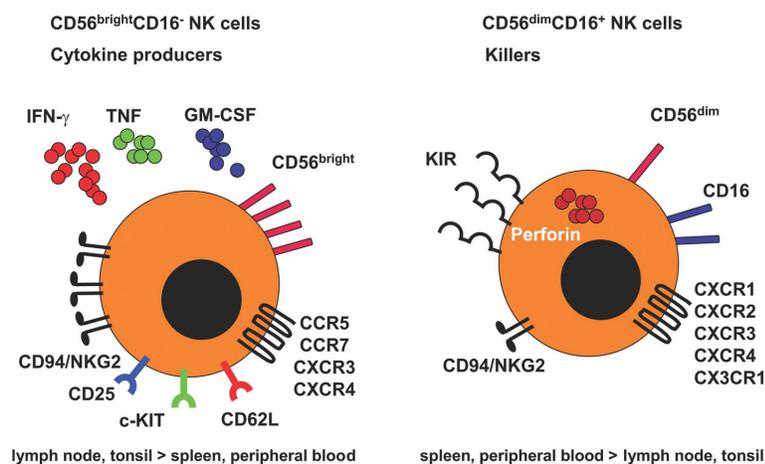


Figure 1. Human NK cells in peripheral blood can be divided into at least two subsets based on the expression of CD56 and CD16. The major subset of CD56^{dim}CD16⁺ NK cells constitutes ~90% of total blood NK cells, kills target cells upon proper recognition, and secretes only low levels of cytokines. CD56^{bright}CD16⁻ NK cells (<10% of total blood NK cells, but 75% of NK cells in secondary lymphoid tissues), in contrast, produce many cytokines, including IFN- γ , TNF, and GM-CSF, upon stimulation by proinflammatory cytokines, but acquire cytotoxicity only after prolonged activation. In addition, both subsets differ from each other with respect to expression of inhibitory and activating receptors. Although CD56^{bright}CD16⁻ NK cells express high levels of the inhibitory CD94/NKG2A complex recognizing HLA-E, they do not express MHC class I allele-specific killer cell Ig-like receptors that are, in contrast, expressed by CD56^{dim}CD16⁺ NK cells. Moreover, only CD56^{bright}CD16⁻ NK cells express homing markers for secondary lymphoid organ (SLO), such as CCR7 and CD62L, and immature lymphocyte markers, such as c-KIT.

CCR7, which allows their recruitment from the blood into lymphoid tissues and sites of inflammation (7,8). In fact, the CD56^{bright}CD16⁻ subset is markedly enriched in secondary lymphoid tissues, constituting up to 75% of NK cells in lymph nodes and 50% in the spleen (9). Even so, only 5% of lymph node mononuclear cells are NK cells, as lymph nodes are suggested to harbor 40% of all human lymphocytes; whereas probably only 2% of all lymphocytes circulate through peripheral blood at any given moment, CD56^{bright}CD16⁻ NK cells in secondary lymphoid organs constitute a significant pool of innate effector cells in humans. It is also noteworthy that the infiltrating NK cells in a number of human inflammatory lesions were found to be mainly CD56^{bright}CD16⁻ NK cells, although the CD56^{dim}CD16⁺ subset expresses chemokine receptors that could also guide them to these sites (10–13). The homing cells were negative for per-

forin and had an increased capability to produce IFN- γ upon stimulation with a combination of IL-12 and IL-18, suggesting a prominent role for CD56^{bright}CD16⁻ NK cells both in secondary lymphoid tissues and at sites of infection and inflammation.

IMMUNOREGULATORY NK-CELL FUNCTIONS

Dendritic cells (DCs) are potent antigen-presenting cells that initiate and regulate immune responses. They are potent stimulators of naïve T cells, key inducers of primary immune responses, and play a central role in the development and maintenance of T-cell tolerance. NK cells are found in close association with DCs in both secondary lymphoid tissues and at inflammatory sites (14–17). DCs can activate resting NK cells directly, by cell-to-cell contact; and indirectly, via the secretion of cytokines such as type I IFNs, IL-12, IL-15,

and IL-18. Among the soluble factors, IL-12 has been observed to induce IFN- γ secretion and proliferation repeatedly, and was thought to be the most pivotal signal-enhancing factor for NK-cell effector functions in humans and in mice (15,18–21). IL-15 appears to determine NK cell differentiation and survival, thereby possibly promoting NK-cell expansion (15,22,23). In addition, type I IFNs were suggested primarily to augment NK-cell cytotoxicity (24), but IL-12 can also contribute to enhancing this NK-cell function (21). Thus, different DC cytokines trigger different NK-cell-effector functions, enabling DC subsets or differently matured DCs to elicit a spectrum of NK-cell responses.

After *in vivo* stimulation with TLR ligands or bacterial and viral infection, it was shown that myeloid CD11c^{high} DCs need to prime NK cells via presentation of IL-15 to produce IFN- γ and become cytotoxic against an MHC class I low cell line expressing NKG2D ligands. In humans, we have shown recently that IL-15 receptor α colocalizes at the synapse between DCs and NK cells and contributes to NK-cell survival (22). While cytokines play a dominant role in human NK activation by DCs, IFN- α treatment of DCs additionally upregulates the NKG2D ligands, which seem to activate resting NK cells in a cell-contact-dependent manner (25), suggesting that cell contact might contribute additionally to NK activation by human DCs under certain inflammatory conditions.

DC-NK cell interactions are bidirectional. Activated NK cells also can mature DCs, via TNF and IFN- γ production and additional cell-to-cell contact-dependent signals (26,27), which promote priming and expansion of CD8⁺ T cells (28). On the other hand, activated NK cells can kill autologous immature myeloid DCs via Nkp30-, Nkp46-, and DNAM-1-mediated recognition (29–31). Resistance to NK lysis was achieved via upregulation of MHC class I molecules upon DC maturation, in particular, upregulation of HLA-E (32), suggesting that NK cells expressing the inhibitory recep-

tor for HLA-E recognition, that is, CD94/NKG2A, are particularly important in editing nonimmunogenic DCs. In addition to DCs, other myeloid cells also have been found to be susceptible to NK-cell cytotoxicity. Along these lines, activated macrophages have been found to be susceptible to NKG2D-dependent cytotoxicity by NK cells (33), and we have shown recently that human microglial cells, resident macrophage-like antigen presenting cells (APCs) of the central nervous system (CNS), are lysed by activated NK cells via NKG2D- and NKp46-mediated recognition (34). Similar to immature DCs, resting microglia are susceptible to NK-cell-mediated cytotoxicity while microglial activation and upregulation of MHC class I molecules protected these CNS-resident APCs from being killed by NK cells (34). We suggest that this mechanism reduces the pool of immature DCs and resting microglial cells during immune activation, but allows fully activated APCs to present antigens to infiltrating T cells and to initiate a limited immune response. In contrast to DCs and microglia, monocyte-derived macrophages are resistant to autologous NK-cell cytotoxicity, unless they become activated by high doses of lipopolysaccharide (LPS), and express NKG2D ligands (NKG2DL) (33). This indicates that the stimulatory signal resulting from NKG2D–NKG2DL interactions overcomes the inhibitory signal provided by MHC class I ligands during recognition of activated macrophages by NK cells. The latter study also indicates fundamental differences between different subsets of myeloid cells in their susceptibility toward NK-cell-mediated killing. Although all of the above mentioned studies were performed *in vitro*, and definite evidence that these mechanisms are also operative *in vivo* is still lacking, the results obtained suggest that activated NK cells might play an important regulatory role by selectively editing APCs during the course of immune responses.

In addition to regulation of myeloid cells by NK cells, several studies also have shown the importance of NK cells

for promoting Th1 polarization of CD4⁺ T cells through production of IFN- γ , a cytokine that not only initiates, but also reinforces Th1 differentiation. During experimental *Leishmania major* infection, NK cells are recruited rapidly to lymph nodes where they are found in close contact to the same DCs as antigen-specific CD4⁺ T cells providing the IFN- γ required for the induction of Th1 polarization (17). A similar effect was observed in allogeneic immune responses during which NK cells produce high levels of IFN- γ that are sufficient to mediate T-cell polarization via acting on naïve T cells directly, and by enhancing DC maturation (35–37). In addition to their function in T-cell polarization, NK cells expressing OX40 ligand and CD86 upon ligation of the activating Fc γ RIII (CD16) are capable of inducing IFN- γ production and proliferation of autologous T cells (38). Moreover, a supportive role of NK cells in B-cell activation and the promotion of isotype class switching has also been documented (39–41). These studies indicate that NK cells, particularly the cytokine secreting CD56^{bright}CD16⁻ subset (37), can influence T-cell polarization during primary immune responses.

In addition to shaping T-cell responses, NK cells can, however, also dampen these. Following T-cell activation, T cells upregulate NKG2D ligands and become susceptible to autologous NK-cell-mediated cell lysis *in vitro* (42–44). In this context, Lu *et al.* (45) demonstrated that the interaction between the mouse homologue of the human MHC class Ib molecule HLA-E, Qa-1-Qdm, on activated T cells and CD94/NKG2A inhibitory NK-cell receptors, protects activated CD4⁺ T cells from perforin-mediated NK-cell cytotoxicity. Ab-dependent blockade of this Qa-1-NKG2A interaction resulted in potent NK-dependent elimination of activated autoreactive T cells and amelioration of experimental autoimmune encephalomyelitis (EAE) in myelin oligodendrocyte glycoprotein (MOG) 35–55 immunized C57BL/6 mice (45). Thus, NK cells contribute to the resolution of adaptive immune responses via deletion of activated

T cells *in vivo*. The latter study provided a mechanistic insight into the finding that NK-cell depletion profoundly influences the outcome of T-cell-mediated autoimmune disease models as outlined below.

NK-CELL FUNCTION IN EXPERIMENTAL AUTOIMMUNE DISEASES

Because of the lack of mouse strains that are selectively deficient in NK cells, the study of NK-cell function *in vivo* has been challenging in the past (46). Animal models of autoimmune diseases provide evidence for both disease-accelerating and disease-protective effects of NK cells (Figure 2). The contradictory results achieved by NK-cell depletion are best illustrated in EAE, the animal model of multiple sclerosis (MS). It has been suggested that NK cells could be pathogenic by shaping Th1-polarized adaptive immune responses and by activating CNS-infiltrating DCs (47). Indeed, several mouse strains which have defective NK-cell functions, such as IL-18 deficient mice, or that are devoid of NK cells, such as T-bet deficient mice, are resistant to EAE induction (48,49). Surprisingly, most studies in the EAE model reported that NK cells protect from autoimmune-mediated tissue damage, presumably by editing initiator and effector cell populations (45,50–52). Antibody-mediated depletion of NK cells exacerbated EAE pathology in Lewis rats, SJL mice, and C57BL/6 mice (50,51,53), whereas adoptive transfer of *in vitro*-generated NK cells from the bone marrow decreased the severity of EAE in DA rats (54). Furthermore, it was observed that NK-cell depletion resulted in increased proliferation and IFN- γ production of T cells specific for the antigen that was used to induce EAE (50). Interestingly, opposite findings were observed in a different study using the same mouse strain immunized with the same myelin antigen (47). Contradictory findings on the effects of NK-cell depletion also were reported in animal models of type 1 diabetes (T1D). Whereas antibody-mediated NK-cell depletion was protective in one study (55), another report suggested that

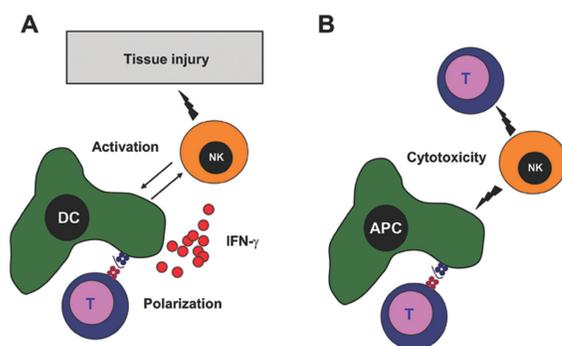


Figure 2. Immunoregulatory Functions of NK cells. Depending on the model system, NK cells were found to either accelerate or inhibit the development of autoimmune diseases. (A) NK cells could contribute to autoimmune inflammation by shaping Th1-polarized adaptive immune responses, by activating DCs, and by causing tissue destruction directly. (B) On the other hand, NK cells could be protective by editing initiator and effector cell populations such as antigen-presenting cells (APC)—including DCs, macrophages, and microglia, and autoreactive T cells via their cytotoxicity.

NK cells protect from T1D through secretion of perforin, IFN- γ , or immunoregulatory cytokines (56,57). Such apparently controversial findings might be explained, at least in part, by differences in the model system used to determine NK-cell function. For EAE induction, timing of myelin immunization and NK-cell activation/depletion could be critical for the outcome; NK cells could modulate and suppress T-cell polarization and effector function during the initiation of autoimmune responses against autoantigens, but might contribute to immunopathology by directly causing tissue damage during progression of the established disease. In addition, using different tools and protocols to achieve NK-cell depletion could explain different outcomes. Unfortunately, no antibody targets NK cells specifically. The most frequently used antibodies for NK-cell depletion target NK1.1 and asialo-GM1, which also are expressed on natural killer T cells (NKT cells) and a subset of cytotoxic T cells, respectively. Moreover, antibody-mediated NK-cell depletion could be preceded by NK-cell activation and IFN- γ production, or might preferentially target distinct subsets of NK cells that mediate divergent effects on EAE initiation and progression. Studies in mice which allow selective *in vivo* abla-

tion of NK cells (46) might be helpful in better characterizing the functional impact of NK cells on the initiation and progression of experimental autoimmune diseases in the future.

NK-CELL (DYS)FUNCTION IN HUMAN AUTOIMMUNE DISEASES

Several studies reported that individuals with autoimmune diseases such as MS and systemic lupus erythematosus (SLE), have fewer blood NK cells compared with healthy subjects. Moreover, NK cells isolated from patients with MS were found not only to be decreased in frequency, but also to be impaired in effector function (58–68). Notably, patients with hemophagocytic lymphohistiocytosis (HLH), a rare condition characterized by impaired or absent function of the perforin/granzyme system in NK cells and cytotoxic T-cells, demonstrated decreased NK-cell activity. This resulted in increased T-cell and sustained-macrophage activation, and in the production of large quantities of the lymphokines IFN- γ , TNF- α , and GM-CSF, as well as of IL-1 and IL-6 (69). The macrophage activation syndrome (MAS), now considered a special form of HLH, occurs in children and adults with autoimmune diseases, especially systemic juvenile rheumatoid arthritis (sJRA) (70). Interestingly, patients with

sJRA show decreased NK-cell frequencies and impaired NK-cell functions compared with children with other forms of juvenile rheumatoid arthritis such as pauciarticular and polyarticular JRA, even in the absence of MAS (71,72), which can, however, be triggered by environmental insults such as viral infections (73). Thus, patients with HLH and sJRA represent an example for an association of NK-cell dysfunction and excessive immune activation, which could contribute, potentially, to the initiation and maintenance of autoimmune responses.

On the other hand, there are many studies which found no differences in NK-cell frequencies and functions in patients with common autoimmune diseases compared with healthy controls (74–77). These contradictory findings are difficult to interpret since all of the aforementioned studies differed widely in their criteria used to classify NK cells. Some of the older reports did not distinguish between NK cells and NKT cells and none of the above studies differentiated between CD56^{bright}CD16⁻ and CD56^{dim}CD16⁺ NK cells. Moreover, the assays and protocols used to study NK cell frequencies and functions, as well as the patient populations studied, varied significantly (78). With these caveats in mind, genetic predisposition for autoimmune diseases has been linked to NK cells, and successful therapies of autoimmune diseases correlated with changes in the NK-cell compartment.

The genetic analysis of NK cells has focused mainly on KIR allele typing. KIRs are expressed on NK cells and subsets of T cells. The KIR genes are extremely polymorphic, probably more than the HLA loci, and the KIR gene complex is polygenic with varying numbers of inhibitory and activating receptors (79). HLA class I molecules serve as ligands for the KIR. Interactions of the independently segregating KIR and HLA loci are important for recognition of targets by NK cells. Several studies correlated incidence and progression of infectious and autoimmune diseases with the expression of particu-

lar KIRs, as well as with HLA–KIR combinations. For example, in patients with psoriasis and psoriatic arthritis, conditions that have long been associated with HLA-C, specifically with the C2 allotype gene *HLA-Cw*06*, it has been reported that activating KIR genes (usually KIR2DS1 and/or KIR2DS2) are at a higher frequency in patients than in healthy control individuals (80,81). These studies suggest that the overall balance of activating and inhibitory composite KIR–HLA genotypes contributes to the susceptibility toward autoimmune diseases. However, it remains to be defined whether these genotypes also translate into functional differences (82).

Stronger evidence for a regulatory role of NK cells in MS stems from immunomonitoring of a phase II therapy trial in MS. The rationale for the use of a humanized IgG1 monoclonal antibody targeting the interleukin-2 receptor α chain (daclizumab) in patients with autoimmune diseases such as MS was to block the proliferation of antigen-activated autoreactive T cells. Indeed, results of four open-label studies of intravenous daclizumab in patients with active forms of either RRMS or secondary progressive MS (SPMS) have suggested beneficial effects of daclizumab for both add-on and monotherapy protocols as measured by magnetic resonance imaging (MRI) and clinical outcomes (83). Surprisingly, CD4⁺ and CD8⁺ T-cell counts were decreased only moderately in patients responding to therapy. In stark contrast, CD56^{bright}CD16⁻ NK cells increased in frequency in the blood of treated patients and the suppression of disease activity, as quantified by MRI, correlated with the expansion of blood NK cells (84). Notably, NK cells isolated from patients during, but not before, therapy killed autologous-activated T cells even without the need for NK-cell activation *in vitro* (84). Similar observations were made in patients who received the identical monoclonal antibody for the treatment of autoimmune uveitis (85). In addition, patients with MS receiving IFN- β therapy

also show an increase in the frequency of CD56^{bright}CD16⁻ NK cells within 3 months of treatment (86). Altogether, these human studies suggest that NK cells exert beneficial functions in autoimmune diseases. The mechanisms that could mediate such immunoregulatory NK-cell functions remain, however, poorly understood.

Nevertheless, both genetic and immunotherapeutic observations point to an involvement of NK cells in autoimmune disease and therefore their role in these pathologies needs to be better understood.

CONCLUSION

NK cells are multicompetent lymphocytes with the ability to regulate innate and adaptive immune responses through their reciprocal interaction with antigen-presenting cells as well as T cells and B cells. Antibody-mediated NK-cell depletion profoundly affects the outcome of many experimental autoimmune diseases. The observation that NK cells are decreased in frequency or impaired in function in patients with autoimmune diseases are reminiscent of defective functions noted for regulatory T-cell populations such as CD4⁺CD25⁺ regulatory T (Treg) cells and CD1d-restricted NKT cells, in patients with autoimmune diseases (87–90).

NK cells include distinct subsets with disparate repertoires, location, function, and developmental origin. In analogy to regulatory T-cell subsets, NK-cell subpopulations that have yet to be characterized might be particularly important in regulating autoimmune inflammation. We suggest that investigating immunoregulatory NK-cell functions in healthy individuals and patients with autoimmune diseases will generate exciting insights into the reciprocal regulation between NK-cell-mediated innate immunity and adaptive immune responses, improve our capacity to monitor these cells as surrogate markers for disease activity and treatment response, and, perhaps, provide new prospects for NK-cell-directed therapies.

ACKNOWLEDGMENTS

The authors are supported by the Dana Foundation's Neuroimmunology program, the Burroughs Wellcome Fund, the Starr Foundation, the National Cancer Institute (R01CA108609 and R01CA101741), the National Institute of Allergy and Infectious Diseases (RFP-NIH-NIAID-DAIDS-BAA-06-19), the Foundation for the National Institutes of Health (Grand Challenges in Global Health), and an Institutional Clinical and Translational Science Award (to the Rockefeller University Hospital) to C Münz; by a Dana Foundation and Irvington Institute's Human Immunology Fellowship and an Institutional Clinical and Translational Science Pilot and Collaborative Project Grant (to the Rockefeller University Hospital) to JD Lünemann.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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