

Natural killer cells in patients with allergic diseases

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Natural killer (NK) cells not only exert cytotoxic activity against tumor cells or infected cells but also act to regulate the function of other immune cells through secretion of cytokines and chemokines or cell contact-dependent mechanisms. NK cells are able to polarize *in vitro* into 2 functional distinct subsets, NK1 or NK2 cells, which are analogous to the T-cell subsets T_H1 or T_H2. In addition, a regulatory NK cell subset has been described that secretes IL-10, shows antigen-specific T-cell suppression, and suppresses IgE production. Although it has been demonstrated that NK cells play important roles in autoimmunity, cancer, transplantation, and pregnancy, the role of NK cells in allergy has not been extensively discussed. This review aims to discuss our understanding of NK cells and NK cell subsets in allergic inflammation and IgE regulation. (J Allergy Clin Immunol 2013;132:527-35.)

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Natural killer (NK) cells comprise a heterogeneous subpopulation of lymphocytes with important roles in innate and adaptive immune responses. They are present in healthy skin and the gut, liver, lungs, and uterus during pregnancy.¹ At steady state, many NK cells reside in lymphoid organs, such as the bone

Abbreviations used

AD: Atopic dermatitis
AR: Activating receptor
ILC: Innate lymphoid cell
IR: Inhibitory receptor
KIR: Killer cell immunoglobulin-like receptor
NK: Natural killer
ROR: Retinoic acid-related orphan receptor
T-bet: T-box transcription factor

marrow, spleen, and lymph nodes. In human subjects NK cells constitute approximately 10% of peripheral blood lymphocytes and include distinct subsets with disparate repertoires, location, function, and developmental origin.^{2,3} NK cells are present at a high frequency in the circulation and are ready to extravasate to tissues under inflammatory conditions. They respond to several chemoattractants, such as CXCL12-CXCR4 chemokine signaling,⁴ which regulate the maintenance of resting NK cells in the circulation or sites of maturation or function or the recruitment of activated NK cells into the sites of disease and inflammation.⁵

On the basis of the relative densities of **CD56** surface expression, NK cells can be split into 2 major subsets: CD56^{dim} and CD56^{bright} NK cells. CD56^{dim} NK cells comprise 90% of peripheral blood NK cells, have a high cytolytic capacity, and secrete low levels of cytokines, whereas CD56^{bright} NK cells secrete a great number of cytokines but acquire cytotoxicity only after prolonged activation.⁶ The CD56^{bright} **CD16**[−] cell subset is found at low frequencies in secondary lymphoid organs, such as the lymph nodes and tonsils, and these cells respond vigorously to locally produced **IL-2**.¹

Compared with T and B cells, NK cell development is self-limited, and NK cell maturation depends on myeloid cells, such as dendritic cells (DCs), monocytes, and neutrophils.⁷ NK cells exert cell-mediated cytotoxicity against nonself eukaryotic cells, tumor cells, or virus-infected cells, and they also regulate the function of other immune cells through secretion of cytokines and chemokines.⁸

PHENOTYPIC CHARACTERIZATION OF NK CELLS

Human NK cells can be distinguished from other lymphocytes by lack of T-cell receptor and its associated CD3 complex. Although NK cells do not rearrange T-cell receptor subunits, they share a number of features with T cells, including expression of surface molecules and secretion of the same cytokines. The relative expression of the NK cell markers CD16 (the low-affinity receptor for the **Fc** portion of IgG [FcγRIIIA]) or CD56 (neural cell adhesion molecule) allows definition of several different

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Terms in boldface and italics are defined in the glossary on page 528.

NK cell subsets.^{9,10} The majority of human NK cells have low-density expression of CD56 (CD56^{dim}) and express high levels of CD16 (CD16^{bright}), whereas the remaining cells are CD56^{bright} and can be further subdivided into CD16⁻ and CD16⁺ fractions.¹¹ These 2 subsets of NK cells differ in cytotoxic activity, cytokine production, and migratory capacity. Freshly isolated CD56^{bright} cells are the major subset present in the secondary lymphoid organs and are capable of producing large amounts of IFN- γ and TGF- β on activation. CD56^{dim} NK cells can produce very rapid IFN- γ within 2 to 4 hours after triggering through Nkp46 and Nkp30 activating receptors (ARs).^{12,13} CD94^{high}CD56^{dim} NK cells express higher levels of granzyme B and *perforin*. Their CD94-mediated redirected killing is higher than that of CD56^{bright} NK cells but lower than that of CD94^{low}CD56^{dim} NK cells. The density of CD94 surface expression on CD56^{dim} NK cells might identify an intermediary developmental stage between CD56^{bright} and CD94^{low}CD56^{dim} NK cells.¹⁴ Furthermore, CD56^{dim} NK cells carry homing markers for inflamed peripheral sites. CD56^{bright} NK cells home to sites of chronic inflammation, whereas CD56^{dim} NK cells preferentially migrate to acute inflammatory sites. It has been shown that in the mouse CD27 is a key marker of the NK cell lineage, dissecting the mature Mac-1^{high} NK cells into 2 functionally distinct subsets (CD27^{high} and CD27^{low}). Similar to human CD56^{bright} NK cells, mouse CD27^{high} NK cells are effective

producers of IFN- γ ; however, they are poorly cytotoxic.¹⁵ CD27^{high} and CD27^{low} NK cell subsets with distinct cell-surface phenotypes also exist in human subjects, and therefore CD27 is also a novel subset marker in the human lineage. CD27^{high} cells have many features similar to CD56^{bright} human NK cells, such as predominating in the lymph nodes. In contrast, CD27^{low} NK cells were comparatively excluded from the lymph nodes, whereas this subset was the main NK cell population in the lungs and blood. In another study the authors have demonstrated that CD57 characterizes a functionally different population of mature NK cells in the human CD56^{dim}CD16⁺ NK cell subset.¹⁶ *In vitro* evidence indicates that CD56^{bright} NK cells are precursors of CD56^{dim} NK cells, and recently, a human immunodeficiency-like condition was described that was characterized by a reduced frequency of CD3⁻CD56^{dim} cells with lower percentages of terminally differentiated NK cells and accumulation of CD3⁻CD56^{bright} cells in peripheral blood, supporting the idea that *in vivo* CD56^{bright} NK cells differentiate into CD56^{dim} NK cells.¹⁷

Activated NK cells lose CD16 (Fc γ RIII) and CD62 ligand through a metalloprotease called a disintegrin and metalloprotease 17, and inhibition of a disintegrin and metalloprotease 17 enhances CD16-mediated NK cell function by preserving CD16 on the human NK cell surface.¹⁸ Cytokine stimulation also downregulates CD16 expression and upregulates CD56 and

GLOSSARY

B CELL-ACTIVATING FACTOR OF THE TNF FAMILY (BAFF): This protein in the spleen aids in B-cell activation. The BAFF receptor, BAFF-R, is located on B cells. Binding of BAFF to its receptor enhances expression of Bcl-2 (a survival factor). BAFF is also capable of inducing isotype switching in naive B cells.

CD16: CD16 (Fc γ RIII) has been described as a receptor expressed on natural killer cells that facilitates antibody-dependent cellular cytotoxicity by binding to the Fc portion of various antibodies.

CD40 LIGAND: A cell-surface molecule also found on CD4⁺ T lymphocytes. It binds to CD40 on B cells and dendritic cells, macrophages, endothelial cells, and some epithelial cells. CD40 ligand interactions with CD40 are important for germinal center formation, terminal differentiation of B lymphocytes, and effective defense against intracellular pathogens. CD40 ligand mutations are responsible for X-linked hyper-IgM syndrome.

CD56: A cell-surface adhesion molecule expressed in greater than 95% of adult NK cells.

CXCL8: An important chemokine in neutrophil accumulation in response to infectious and noninfectious stimuli. The presence of CXCL8 has been associated with multiple inflammatory conditions, including psoriasis, rheumatoid arthritis, and acute respiratory disease syndrome.

EXOSOMES: Small phospholipid-enclosed vesicles released by cells. These vesicles might be a way for cells to exchange molecules and genetic information but could also pose a threat because evidence also exists that exosomes can provide a surface for coagulation.

FC: A portion of the heavy chains in an immunoglobulin molecule that is responsible for the effector function of a given class of immunoglobulin. The Fc portion of an antibody is completely encoded for by the constant region of the heavy chain genes.

$\gamma\delta$ T CELLS: A subpopulation of T cells located at epithelial barriers and sites of inflammation. $\gamma\delta$ T cells are capable of binding to antigens directly without MHC presentation. They can also react to MHC molecules without an associated peptide. In addition to playing a role in

defense against multiple types of bacteria, they can accumulate at inflammatory sites in patients with autoimmune disease.

IL-2: A cytokine that regulates the activities of leukocytes and induces the differentiation and proliferation of natural killer cells.

IL-15: A cytokine with structural similarity to IL-2 that regulates T and natural killer cell activation and proliferation.

IL-27: A cytokine secreted mostly by macrophages and dendritic cells. It promotes T_H1 differentiation, inhibits T_H17 differentiation, and enhances IL-10 production.

IMMUNORECEPTOR TYROSINE-BASED INHIBITORY MOTIF (ITIM): Located in the cytoplasmic tails of inhibitory receptors, ITIMs are essential for the signaling functions of these molecules. ITIMs recruit phosphatase enzymes that counteract the effect of kinases in the signaling cascades initiated by activating receptors.

ISOTOPE SWITCHING: The process of changing the class (isotype) of antibody production. Isotype switching occurs in the germinal center of the lymph node in mature B cells during B-cell proliferation after antigen exposure. Isotype switching allows an antibody-producing cell to alter the biological effects of its secreted product without affecting its specificity.

PERFORIN: A membrane-disrupting protein (either plasma or lysosomal membranes) found in lytic granules. After membrane disruption and internalization of lytic granules into the target cell inside the immunologic synapse, granzymes work to incite cell death.

T_H17 CELLS: A T_H family induced by IL-23 and IL-6 that is involved in defense against extracellular bacteria.

T_H22 CELLS: T_H22 cells are a CD4⁺ cell subset dedicated to the production of IL-22. Maturation of T_H22 cells requires TNF- α and IL-6. T_H22 cells appear to provide a protective role in regulating wound repair and healing in the skin, gut, and lungs. T_H22 cells might also play a pathogenic role in many inflammatory diseases, such as asthma, atopic dermatitis, psoriasis, rheumatoid arthritis, scleroderma, Crohn disease, and uveitis.

CCR7 expression on CD16⁺CD56^{low} NK cells *in vitro*.^{19,20} Moreover, certain cytokines can greatly enhance the cytotoxicity and cytokine production of the CD16⁺CD56^{high} and CD16⁺CD56^{low} NK cell subsets, respectively.¹⁰ For example, *IL-27* treatment induces *IL-10* and *IFN-γ* production, increased viability, and decreased proliferation in both CD56^{bright} and CD56^{dim} NK cell subsets in human subjects.²¹ On the other hand, *IL-12/IL-15/IL-18*–preactivated NK cells accumulated in the tumor tissue and persisted at high cell numbers, with potent effector function that required the presence of CD4⁺ T cells.²²

Recently, a subset of innate lymphoid cells (ILCs) called lymphoid tissue inducer cells, which share some characteristics with conventional NK cells and can populate the same compartments, was discovered. Although NK cells and lymphoid tissue inducer cells have different functions, they are developmentally related because both cell types require the common cytokine receptor γ -chain (γ_c , also known as *IL-2* receptor γ) and the transcriptional repressor inhibitor of DNA binding 2 for their development. It could be suggested that NK cells and *IFN-γ*–producing noncytotoxic ILC1s should be classified as group 1 ILCs. CD3⁺NKp46⁺ NK cells comprise one of the classical innate lymphocyte populations.²³ In tissues it is difficult to discriminate NK cells from other NKp46⁺ ILCs, such as NKp46⁺ retinoic acid–related orphan receptor (ROR) γ t⁺ cells. The latter ILCs, both in human subjects and mice, are functionally distinct from conventional NK cells and have been referred to as NK22 cells. NKp46⁺ROR γ t⁺ ILCs produce *IL-22*, are noncytotoxic, and are represented in mucosal tissues.²⁴ Another group has also identified a novel subset of CD56^{dim}NKp46^{low} cells that includes ROR γ t⁺ ILCs with a lineage[−]CD94[−]CD117^{bright}CD127^{bright} phenotype in lymphoid and nonlymphoid tissues of healthy human subjects.²⁵

WHAT DO NK CELLS DO?

The major functional properties of NK cells are cytotoxicity and cytokine production. NK cell–mediated lysis of target cells is mainly achieved through the release of the cytotoxic molecules perforin and granzymes A and B. Cytotoxicity can be subdivided into natural cytotoxic activity predominantly directed toward tumor cells and virally infected cells in the absence of prior stimulation or immunization and antibody-dependent cellular cytotoxicity directed against IgG-coated target cells. In the latter situation the Fc portion of IgG triggers the Fc γ receptor CD16. Experiments in mouse models of bone marrow graft rejection led to the proposal that NK cells would kill any target that lacked self-MHC class I molecules (the “missing self” hypothesis).²⁶ However, it is now clear that NK cells directly engage MHC class I molecules, MHC class I-like molecules, and molecules unrelated to MHC.²⁷

NK cells express a wide range of ARs, as well as inhibitory receptors (IRs), that regulate NK cell activation and tolerance,²⁸ and their functions are governed by a balance between activating messages transmitted by their ARs and inhibitory signals transmitted by their IRs. The IRs are characterized by an **immunoreceptor tyrosine-based inhibitory motif** in their cytoplasmic domains. NK cell activation transduces signals by interacting with small transmembrane adaptor proteins that contain the immunoreceptor tyrosine-based activator motif. The ligands to ARs are self-proteins, which are usually rare on normal

TABLE I. Main NK cell-surface receptors and their ligands

Receptors	Ligands
Activating receptors	
CD16 (Fc γ RIIIA)	IgG
CD2	CD58 (LFA-3)
LFA-1 (CD11a/CD18)	ICAM-1
2B4 (CD244)	CD48
CD69	Unknown
DNAM-1 (CD226)	CD112, CD155
NKp80	AICL
CD96 (Tactile)	CD155, CD111
NKp46 (NCR1)	Viral hemagglutinin
NKp44 (NCR2)	Viral hemagglutinin
NKp30 (NCR3)	B7h6, HCMV–pp56
NGK2D	MICA, MICB, ULBP-1, ULBP-2, ULBP-3, ULBP-4, ULBP-5, ULBP-6
CRTAM	TSLC1
CD94/NGK2C	HLA-E
Inhibitory receptors	
TIGIT	CD112, CD113, CD155
KIR2DL1 (CD158a)	HLA-C
KIR2DL2/3 (CD158b)	HLA-C
KIR3DL1	HLA-B
KIR3DL2	HLA-A
NGK2A (CD94/CD159a)	HLA-E
NKR-P1A (CD161)	LLT1

AICL, Activation-induced C-type lectin; CRTAM, class I–restricted T cell–associated molecule; DNAM-1, DNAX Accessory molecule-1; ICAM-1, intercellular cell adhesion molecule; LFA, lymphocyte function–associated antigen; NCR, natural cytotoxicity receptors; MIC, MHC class I related chain; Tactile, T-cell activation, increased late expression; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains; TSLC1, tumor suppressor in lung cancer 1; ULBP, UL16 binding proteins.

cells but are upregulated at the cell surface during either infection or malignant transformation. The most potent ARs of NK cells are CD16, NGK2D, and the natural cytotoxicity receptors NKp30, NKp44, and NKp46. It was shown that NKp46 and NKp30 are constitutively expressed by all peripheral blood NK cells and not found on other immune cells (Table I).^{29–32} NKp44 is not expressed by resting NK cells but is upregulated on NK cells after *IL-2* stimulation and might be important for the cytotoxicity of *IL-2*–activated NK cells. Killer cell immunoglobulin-like receptors (KIRs) are a family of cell-surface receptors that are expressed on NK cells and some subpopulations of T lymphocytes and therefore might influence the activation of both cell types. KIRs bind to classical MHC class I ligands (HLA-A, HLA-B, and HLA-C) and the inhibitory CD94-NGK2A heterodimeric receptors that bind the nonclassical MHC class I (HLA-E).^{33,34} In this system every NK cell with killing capacity must have an IR that recognizes at least 1 of the MHC class I gene products on the cell’s surface. Once engaged with classical MHC class I, the inhibitory KIR sends a signal to the NK cell that dominates over any activating signal and prevents the NK cell from killing the MHC class I–expressing cell (Fig 1). The ligands for many, but not all, of these IRs are MHC class I molecules, which are expressed on almost all nucleated cells and are often downregulated on viral infection and in cancer cells.^{35,36}

Although NK cells were originally defined by their capacity to lyse target cells, they also produce *IFN-γ* and other cytokines, and in resting conditions the amounts of cytokines remain at low levels. The release of *IFN-γ* by NK cells can in turn further

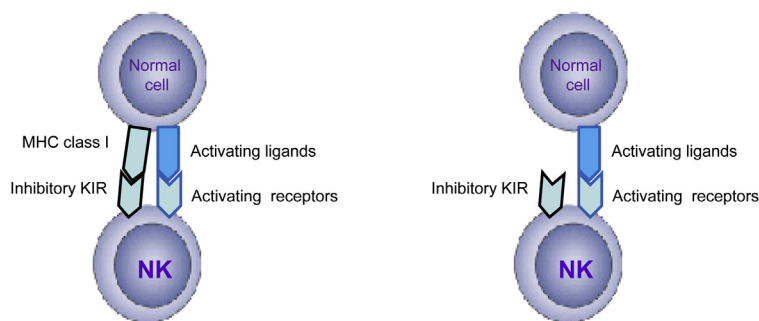


FIG 1. The balance between inhibitory and activating signals that govern NK cell function. The inhibitory killer immunoglobulin receptors (*KIR*) recognize HLA class I molecules on cells and trigger signals that stop the cytotoxicity of NK cells. The ARs recognize determinants associated with infections and tumors and trigger activating signals for NK cells to kill.

activate antigen-presenting cells to upregulate MHC class I and increase their cytokine secretion. At the same time, these antigen-presenting cells also release IL-10 and TGF- β , which can temper or even diminish the IFN- γ secretion by NK cells.³⁷ Together with IFN- γ , NK cells are capable of producing many other important cytokines and chemokines, including myeloid differentiation and activation factors, such as IL-3, GM-CSF, TNF- α , IL-5, IL-13, and IL-10, and chemokines, including CCL2 (monocyte chemoattractant protein 1), CCL3 (macrophage inflammatory protein 1 α), CCL4 (macrophage inflammatory protein 1 β), CCL5 (RANTES), XCL1 (lymphotactin), and CXCL8 (IL-8).^{38,39} In addition, at early stages of differentiation, NK cells produce CXCL8 and express the CD161 molecule, which functions as an AR.⁴⁰

Whereas the biological function of the growth factors secreted by NK cells remains to be clarified, their secreted chemokines are key to their colocalization with other hematopoietic cells, such as DCs, in areas of inflammation. The reciprocal interaction between NK cells and DCs results in a potent and activating cross-talk, which can potentially influence the maturation of both cell types. The cross-talk between NK cells and DCs might take place at different stages of the innate and adaptive immune responses, which indicates that the interaction of these cells plays a role in controlling of the links between innate and adaptive immunity.^{28,41,42} NK cells also influence B-cell differentiation, specifically by producing IFN- γ , which affects immunoglobulin *isotype switching*.^{43,44}

The third function of NK cells is contact-dependent costimulation. NK cells express several costimulatory ligands, including **CD40 ligand** and OX40 ligand, allowing them to provide direct costimulation to T and B cells.⁴⁵ On activation, NK cells express MHC class II molecules and some of the ligands for T-cell costimulatory receptors (CD80, CD86, CD70, and OX40 ligand), and in these conditions NK cells are able to stimulate the proliferation of antigen-specific T cells (Fig 2).⁴⁶ It was also shown that freshly isolated resting and activated NK cells release **exosomes** that express functional proteins of NK cells, including CD56⁺ and perforin, and show cytotoxic activity. These findings suggest another important role of NK cell-derived exosomes in immune surveillance and homeostasis.⁴⁷

NK CELL SUBSETS

NK cells can be divided into 4 different subsets according to their cytokine secretion profiles (Fig 3).

NK1 and NK2 cells

NK cells are an important source of IFN- γ , but they can also produce type 2 cytokines. It has been shown that human NK cells are able to polarize *in vitro* into 2 functionally different subsets, NK1 and NK2, which are analogous to the T-cell subsets T_H1 and T_H2.^{8,48,49} IL-12 drives T cells toward a type 1 phenotype, and IL-4 drives cells toward a type 2 phenotype. In the presence of IL-12 or IL-4, human NK cells could differentiate into NK cell subsets secreting distinct cytokine patterns similar to T cells. NK cells grown in the presence of IL-12 (NK1) produce predominantly IFN- γ , whereas NK cells grown in the presence of IL-4 (NK2) produce IL-5 and IL-13.^{50,51} The cytotoxic capacity of both the NK1 and NK2 subsets did not show any difference; however, CD95 expression was found to be higher in NK1 cells compared with NK2 cells and is more sensitive to antibody or chemically induced apoptosis.⁵¹ T-box transcription factor (T-bet, which is encoded by the *TBX21* gene) is responsible for direct transactivation of the IFN- γ gene and is also expressed in NK cells. In addition, monocytes control NK cell differentiation to effector phenotypes in a *Tbx21*- and *IL-15* receptor (IL-15R) α -dependent manner. This was demonstrated by using *Tbx21*-deficient mice, which lack T-bet. In these mice NK cell differentiation is arrested specifically at the CD11b^{hi}CD27^{hi} stage, resulting in the complete absence of terminally differentiated CD11b^{hi}CD27^{low} NK cells. *In vivo* depletion of myeloid cells and *in vitro* coculture experiments demonstrate that spleen monocytes mediate the terminal differentiation of peripheral NK cells in a *Tbx21*- and IL-15R α -dependent manner.⁵²

In contrast to the diminished levels of IFN- γ ⁺CD56⁺ NK1 cells, high levels of IL-4⁺CD56⁺ NK2 cells in PBMCs of asthmatic patients were shown. Similar to T_H2 response, NK2-type cytokines are dominant in asthmatic patients, and the tumor microenvironment supports their role in the pathogenesis of asthma and cancer.^{48,49} Potent antigen-presenting DCs (IFN-DCs) generated *in vitro* from monocytes express CD56 on their surface together with cytotoxic activity and also show partial phenotypic and functional characteristics of NK cells.⁵³

NK regulatory cells

IL-10- and TGF- β -secreting NK regulatory cells play major roles in immune regulation in the context of viral infection and promote transplant and pregnancy tolerance.⁵⁴⁻⁵⁶ IL-10 has been

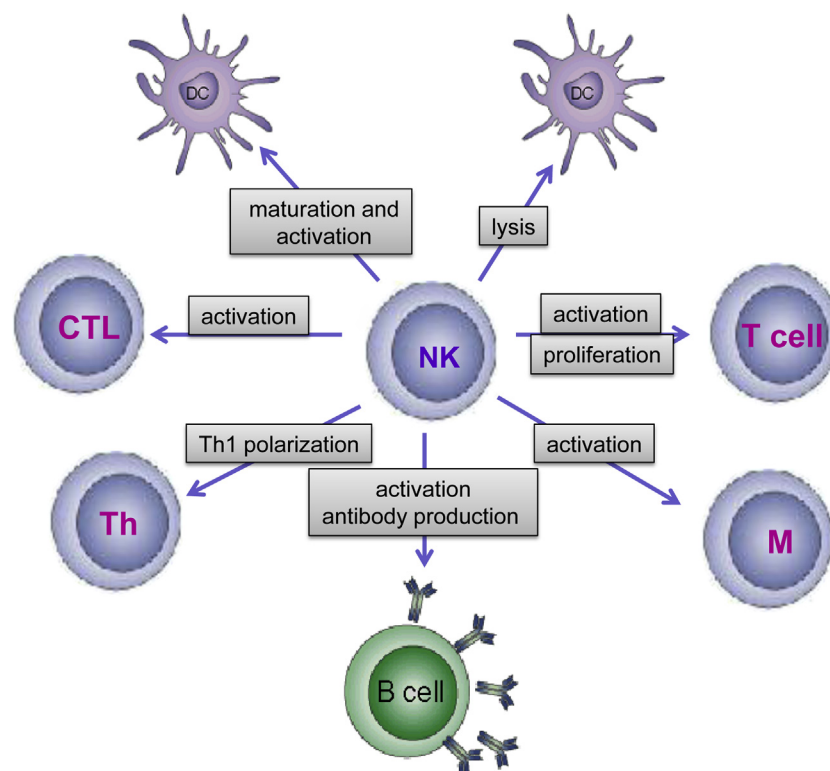


FIG 2. Functions of NK cells. NK cells play an important role in innate and adaptive immunity. They stimulate maturation of DCs and eliminate immature DCs. They are involved in activation of monocytes (*M*) and cytotoxic T cells (*CTL*) and regulate T-cell activation and proliferation through direct cellular contacts. NK cells produce cytokines that influence T_H cell polarization, and activated human NK cells stimulate B cells to secrete immunoglobulins.

shown to suppress both cytokine production and antigen-specific proliferation of T_H1 and T_H2 cells. Similarly, our results showed that IL-10-secreting cells suppress both allergen-stimulated T cells and purified protein derivative-stimulated T-cell proliferation, whereas IFN- γ -secreting NK cells did not show any suppression.⁵⁷ Human IL-10-secreting and nonsecreting NK cell subsets enabled us to demonstrate the *in vivo* existence of a regulatory NK cell subset, which indeed might play an immunoregulatory and suppressor role.

NK17 cells

The IL-17 family comprises 6 different cytokines: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. IL-17A is expressed by activated $CD4^+$ T cells,⁵⁸ more recently characterized as ***T_H17 cells***,⁵⁹ but also cells of the innate response, such as $\gamma\delta$ T cells and NK cells.^{60,61} A novel subset of human NK cells was phenotypically characterized as $CD56^+CCR4^+ROR\gamma^+Tbet^+IL-23R^-$, expressing mature NK cell markers and the ligand for CCR4 and producing IL-17 and IFN- γ . In a mouse arthritis model increased IL-17 production was associated with disease exacerbation along with reduced NK cell frequencies. Conversely, increased NK cell activation shows the inhibition of T_H17 cell function through NK cell-derived IFN- γ .⁶² These findings suggest that NK cells might be protective in patients with T_H17 -mediated arthritis. An NK17 cell subset, characterized by the expression of CD56 and CCR4 and production of IL-17 and IFN- γ , was identified from IL-2-activated normal human

peripheral blood. Decreased NK cell frequency or function has been shown in response to IL-17 *in vitro*, but other cytokines or cell types might indirectly mediate NK cell inhibition *in vivo* in patients with T_H17 -mediated disease.⁶³ Hence enhanced NK cell function would be advantageous in this autoimmune disease model, as well as in tumor or infection models, although in an IL-17-independent manner.

NK22 cells

In the gut expression of the transcription factor ROR γ t, which is involved in the development of lymphoid tissue inducer cells, defined a previously unknown subset of $NKp46^+CD3^-$ lymphocytes. Unlike ROR γ t⁻ lamina propria and dermal NK cells, gut ROR γ t⁺ $NKp46^+$ cells produce IL-22 and are called NK22 cells.^{58,59} Increased IL-22 mRNA and protein levels were detected in inflamed ileal mucosa of patients with ankylosing spondylitis. This coincided with an increased frequency of IL-22-producing $NKp44^+$ NK cells in lamina propria mononuclear cells of these patients. These findings indicate a tissue-protective role for NK22 cells.⁶⁴ In contrast to this study, NK22 cell counts increased and showed correlation with disease activity in patients with rheumatoid arthritis. Therefore NK22 cells might play a role in the pathogenesis of rheumatoid arthritis with the secretion of IL-22 and TNF- α .⁶⁵

NK22 cell-secreted cytokines stimulate epithelial cells to secrete IL-10, proliferate, and express a variety of mitogenic and antiapoptotic molecules, suggesting that NK22 cells provide an innate source of IL-22 that might help constrain inflammation

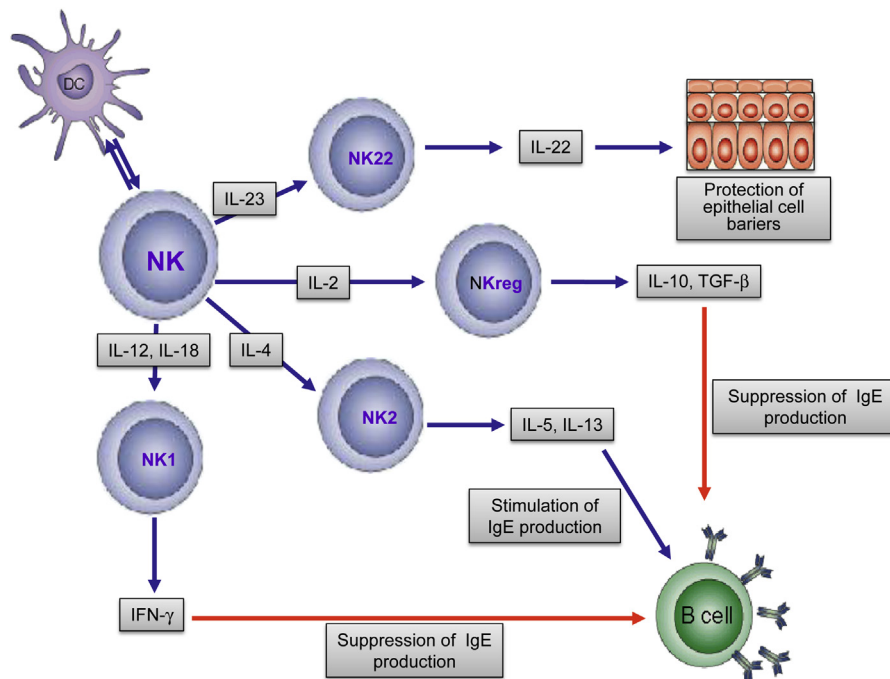


FIG 3. NK cells are divided into 4 different subsets according to their cytokine secretion. NK cells have been detected in close contact to DCs. NK cells grown in IL-12 and IL-18 (NK1) produce IFN- γ and inhibit IgE production, whereas NK cells grown in IL-4 (NK2) produce IL-5 and IL-13 and stimulate IgE production. NK regulatory cells produce IL-10 and TGF- β and suppress IgE production. The IL-22-secreting NK22 subset might have a role in the protection of epithelial cell barriers.

and protect mucosal sites.⁶⁶ NK22 cells released the B-cell survival factor *B cell-activating factor of the TNF family (BAFF)*, suggesting a potential role of NK22 cells in promoting B cell-mediated mucosal immunity.⁶⁷ IL-22 plays an important role in pathogen defense, wound healing, and tissue reorganization, which can have both proinflammatory and anti-inflammatory capacities. This cytokine is also secreted by T_H17 cells, T_H22, natural killer T cells, $\gamma\delta$ T cells, and also ILCs.^{68,69}

NK CELLS AND MEMORY

NK cells have memory similar to that seen in adaptive T cells, indicating that various subsets or lineages of these cells can be recalled in response to various pathogens or cytokines. It has been shown that mice deficient in T and B cells acquire antigen-specific immunologic memory to hapten-based contact sensitizers that is mediated by a subset of primed hepatic NK cells.^{70,71} Subsequent work has demonstrated that NK cells also acquire long-lived memory for diverse viral antigens.⁷² Among NK cells, only a small fraction are specific for any given antigen, and there are no markers at present that can be used to identify a memory NK cell subset. Memory NK cells seem to be extremely rare in peripheral blood and were unexpectedly found to reside only in the liver and not in the spleen.⁷³

In a recent study it was demonstrated in mice that NK cell-mediated contact sensitivity develops rapidly and depends on IL-12, IFN- γ , and IFN- α receptor.⁷⁴ In another study it was shown that NK cell memory of haptens and viruses depended on CXCR6, a chemokine receptor on hepatic NK cells that was required for the persistence of memory NK cells but not for antigen recognition. Thus hepatic NK cells can develop features

of adaptive immunity to structurally diverse antigens, an activity that requires NK cell-expressed CXCR6.⁷¹

NK CELLS AND CELL SUBSETS IN ALLERGIC RESPONSES

Allergic diseases are caused by inappropriate immunologic responses to harmless antigens driven by the T_H2-mediated immune response and have been increasing in prevalence in the developed world over the past few decades. Atopic diseases, including atopic dermatitis (AD), food allergy, allergic rhinitis, asthma, and anaphylaxis, have significant associated morbidity along with large health care expenditures. It is now well established that the imbalance of T_H1/T_H2 T-cell polarization and the bias toward T_H2 cytokine production plays a pivotal role in both the initiation and maintenance of these events.⁷⁵⁻⁷⁷ Numerous studies have demonstrated increased frequency of allergen-specific T_H2 cells producing increased IL-4, IL-5, and IL-13 levels in the peripheral blood of patients with AD.^{78,79} Although the role of NK cells in patients with allergic diseases is poorly described, recent studies suggest a role for NK cells in allergy.^{80,81}

The expression of NK cell costimulatory, inhibitory, and apoptotic receptors in polyallergic atopic patients shows heterogeneity in immune regulation. Findings of reduced frequencies of CD16⁺CD56⁺ NK cells in polyallergic patients⁸² initiates questions for further characterization of NK cell subsets. Except for CD40, there was no clear difference for the expression of costimulatory molecules between the polyallergic patients and healthy subjects. Although the *in vivo* relevance of low CD40 expression of NK1 and NK2 cell subsets in

polyallergic patients is not clear, it might be related to immunoglobulin regulation.⁸³

NK cells involve skin immune responses to haptens by secreting type 1 cytokines and inducing keratinocyte apoptosis. Most of the NK cells isolated from the skin of patients with allergic contact dermatitis showed a CD3⁺CD16⁺CD56^{high} phenotype. This NK cell population also expressed NKG2A, intermediate to high levels of perforin, and the ARs NKG2D, p44, and NKp46 but lacked NKp30 and killer immunoglobulin-related receptors. The CXCR3⁺CCR6⁺CCR5⁺ chemokine receptor is an asset for homing into inflamed skin present in skin NK cells; however, they do not express CD62 ligand and CCR7 for lymph node homing. These findings indicate that both innate and adaptive immune mechanisms are important in skin allergic responses to haptens and full expression of allergic contact dermatitis.⁸⁴

DCs, long recognized as key initiators of adaptive immunity, are now also seen as crucial regulators of innate immunity, particularly NK cell function. *In vitro* studies support a role for both cytokines and cell-cell contact in the enhancement of NK cell function and proliferation. Similar to the role of DCs in the polarization of T_H1 and T_H2 subsets, it has been shown that NK cells support DCs to the induction of appropriate T_H responses.⁸⁵⁻⁸⁸ The lymph nodes are another important site at which NK cells and DCs might come in contact. CD56⁺CD16⁺ NK cells help with DC maturation, production of IL-12, and killing of those DCs that did not undergo maturation; however, CD56⁺⁺CD16^{+/-} NK cells respond to maturing DCs by producing IFN- γ and cooperate with DCs in inducing an efficient T_H1 response in lymph nodes.⁸⁹⁻⁹¹ In peripheral blood NK cells CD56⁺⁺CD16^{+/-} cells are able to respond to DCs by proliferating and producing IFN- γ , and this NK cell subpopulation was found to be significantly reduced in patients with allergic rhinitis and intermittent asthma. This was reflected by reduced NK cell-mediated IFN- γ production on DC encounter. The capability of promoting DC maturation, killing immature DCs, or both was also reduced in most patients. This finding indicates the role of NK1 cells in the control of T_H2-driven inflammation.⁸⁵

Compared with nonatopic subjects, increased NK cell expression, mean percentage of IL-4⁺ NK cells, and IL-13 secretion in patients with allergic rhinitis have been shown. The cytotoxic capacity of NK cells in patients with allergic rhinitis was also higher compared with that seen in healthy subjects. The importance of NK cells in innate immunity, their role in the immune responses, and their different cytokine patterns might be important in changing the cytokine milieu and the induction of T-cell deviation.⁹² NK cells express CMKLR1, a receptor for the proresolving mediator resolvin E1. Resolvin E1 is an endogenous proresolving mediator for allergic airway responses. Decreased resolvin E1-mediated resolution of allergic inflammation was seen when NK cells were depleted. These findings indicate that NK cells might play a role in resolvin E1-mediated resolution of allergic airway inflammation.⁹³

Isolation of IFN- γ -secreting and IFN- γ -nonsecreting NK cells from peripheral blood enabled us to demonstrate the *in vivo* existence of human NK cell subsets similar to T_H1 and T_H2 cells. The IFN- γ -secreting NK cell subset was composed of primarily IFN- γ -secreting cells but contained almost no IL-4, IL-5 and IL-13-secreting cells. In contrast, the IFN- γ -nonsecreting NK

subset was composed of IL-4-, IL-5-, and IL-13-producing NK cells. Similar to freshly purified IFN- γ -secreting or IFN- γ -nonsecreting NK cell subsets, *in vitro* differentiation of NK cells led to distinct patterns of cytokine production. The IFN- γ secretion was significantly increased by IL-12 and decreased by IL-4 stimulation. IL-4 and IL-13 secretion by NK cells was oppositely regulated by IL-4 and IL-12. IL-4 significantly increased and IL-12 suppressed the IL-13 secretion of NK cells. Freshly purified IFN- γ ⁺ and IFN- γ ⁻ or *in vitro* differentiated NK1 and NK2 subsets showed similar cytotoxicity to the NK-sensitive erythromyeloid cell line K562. These findings support that circulating NK cells retain effector subsets in human subjects with distinct cytokine profiles and might display different inflammatory properties.⁸³

AD is a relapsing inflammatory disease of the skin characterized by frequently eosinophilic inflammation. Adaptive antigen-dependent immunity is critical for AD pathogenesis; however, AD can involve both adaptive and innate, T cell-independent immune responses.^{94,95} The functional immunoglobulin isotype regulatory capacity of NK cells was investigated by coculturing *in vitro*-differentiated NK cell subsets with PBMCs or B cells. In both PBMCs and B-cell cultures, NK1 cells showed a significant anti-IgE effect, whereas NK2 cells did not influence IL-4 production and sCD40L induced IgE production. The anti-IgE effect of NK1 cells was inhibited by blocking IFN- γ , demonstrating the important role of IFN- γ on inhibition of IgE synthesis.^{79,83}

CONCLUSION

Although remarkable progress has been shown in understanding NK cells and NK cell subsets, their role in patients with allergic diseases is an enigma. It is well known that NK cells appear to play important roles in viral infection, cancer immunity, transplantation, pregnancy, and autoimmunity, and there is good evidence that NK cells also take part in allergic diseases through their contribution to allergen-specific immune suppression and IgE production. Recent developments support that NK cells actively participate in a number of allergic diseases.

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