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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.)

Key words: *Natural killer cells, allergic inflammation, NK1, NK2, NK22*

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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

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 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 (FcRγIII) 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 (FcγRIII) 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 differential 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.

γδ T CELLS: A subpopulation of T cells located at epithelial barriers and sites of inflammation. γδ 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.

ISOTYPE 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.

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