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NK cell subsets in autoimmune diseases

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ABSTRACT

Natural killer (NK) cells are lymphocytes of the innate immune system. They not only exert cell-mediated cytotoxicity against tumor cells or infected cells, but also play regulatory role through promoting or suppressing functions of other immune cells by secretion of cytokines and chemokines. However, overactivation or dysfunction of NK cells may be associated with pathogenesis of some diseases. NK cells are found to act as a two edged weapon and play opposite roles with both regulatory and inducer activity in autoimmune diseases. Though the precise mechanisms for the opposite effects of NK cells has not been fully elucidated, the importance of NK cells in autoimmune diseases might be associated with different NK cell subsets, different tissue microenvironment and different stages of corresponding diseases. The local tissue microenvironment, unique cellular interactions and different stages of corresponding diseases shape the properties and function of NK cells. In this review, we focus on recent research on the features and function of different NK cell subsets, particularly tissue-resident NK cells in different tissues, and their potential role in autoimmune diseases.

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1. Introduction

Natural killer (NK) cells are lymphocytes of the innate immune system. They act as innate sentinels through recognition and killing infected, transformed or autoreactive cells utilizing a mechanism of directed exocytosis of specialized cytotoxic granules, which contain perforin, granzymes, and Fas ligand [1–3]. A balance between negative and positive signals transmitted via germ line-encoded inhibitory and activating receptors controls the function of NK cells [1–4]. Besides target cell killing, NK cells are a major source of cytokines and chemokines. After interaction with susceptible target cells or upon activation by cytokines (such as IL-15, IL-12, and IL-18), NK cells produce IFN-γ and TNF-α or other cytokines. Thus, NK cells also play regulatory role by promoting or suppressing functions of other immune cells through secretion of cytokines and chemokines [1–3]. NK cells can shape the adaptive immune response by cross-talk with other immune cells such as T cells, B cells and dendritic cells and by producing cytokine or chemokines. They can regulate the immune response by killing antigen-presenting cells (APCs) or overactivated T cells or by producing antiinflammatory cytokines (such as IL-10) to prevent too strong inflammatory response [1–3]. However, the role of NK cells is not helpful in all situations. Overactivation or dysfunction of NK cells may be associated with pathogenesis of some diseases. For example, NK cells are found to act as a two edged weapon and play opposite roles with both regulatory and inducer activity in autoimmune diseases [5,6]. Although the precise mechanism for the opposite effects of NK cells was not fully elucidated, the importance of NK cells in autoimmunity might be associated with different NK cell subsets, different tissue microenvironment and different stages of corresponding diseases. In this review, we focus on the features and function of different NK cell subsets, particularly tissue-resident NK cells in different tissues, and their potential role in autoimmune diseases.

2. Phenotypic and functional characteristics of different NK cell subsets

NK cells are a heterogeneous cell population and divided into different subsets based on their surface phenotype or cytokine secretion pattern. Until now, various murine and human NK subsets with distinct phenotypic and functional properties have been identified (Tables 1 and 2) and they usually represent distinct stages of a linear development process. Moreover, different NK cells are found to locate in different immune organs and anatomy sites, demonstrating that the microenvironment influences the differentiation and function of NK subsets.

2.1. $CD56^{dim}$ and $CD56^{bright}$ NK cell subsets

It is widely accepted that human NK cells can be divided into two subsets based on their cell-surface density of CD56: $CD56^{dim}$ NK and $CD56^{bright}$ NK cells [7,8]. In human peripheral blood lymphocyte population, approximately 10% of NK cells express high levels of CD56 ($CD56^{bright}CD16^{negative/dim}$), while the more abundant NK cell subset expresses CD56 at low density ($CD56^{dim}CD16^{bright}$). $CD56^{dim}CD16^{+}$ NK cells exert higher natural cytotoxicity and express higher levels of Ig-like NK receptors than $CD56^{bright}$ NK cell subset, yet $CD56^{bright}$ NK cells exert relatively lower cytotoxic capacity but can produce abundant amounts of cytokines such as IFN-γ, TNF-α, IL-10, IL-13, and GM-CSF. The $CD56^{dim}CD16^{+}$ NK population is predominant in peripheral blood, whereas $CD56^{bright}$ NK cells are more abundant in secondary lymphoid tissues (such as lymph nodes and tonsils), particularly rich in immune tolerance organs, such as the human liver and uterus [7,8]. The distribution of NK cell subpopulations in the various tissues is determined by chemokine receptors on NK cells and chemokines secreted in sites of tissues. $CD56^{bright}$ NK cells express CCR7, which promotes entry into secondary lymphoid organs, but do not express CXCR1, CXCR2, and CX3CR1, which contribute to migration toward sites of infection or inflammation. $CD56^{bright}$ NK cells also express high levels of CD62L, a receptor required for lymphocyte homing to secondary lymphoid organs [9]. Both $CD56^{bright}$ and $CD56^{dim}$ NK cells express high levels of transcription factors Eomes and T-bet, which are capable for the expression of cytotoxic granule constituents [10].

It is accepted that $CD56^{bright}$ NK subset is a regulatory NK cell population and play major roles in maintaining immune homeostasis in both physiological and pathological conditions by secreting immuno-regulatory cytokines. However, they can also become cytotoxic upon appropriate activation through inflammatory cytokines or triggering of co-activating receptors, thus can mediate killing of target immune cells such as autologous activated T cells or immature DCs for regulation of immune response. $CD56^{dim}$ NK cells are natural cellular cytotoxic killer cells and exert major early immunosurveillance against infected or malignant cells. They are also potent producers of cytokines (such as IFN-γ and TNF-α) upon recognition of susceptible target cells. The inflammatory microenvironment and the cross-talk with other cells at the inflammatory sites may shape the phenotypic, homing and functional properties of NK subsets. Although mainly in peripheral blood, inflammatory microenvironment (such as IL-18) may promote CCR7 reexpression on $CD56^{dim}$ NK cells, thus making $CD56^{dim}$ NK cells obtain the potential to migrate to lymph nodes where they can cross-talk with DCs and T cells and further influence the shaping, polarization and function of adaptive T cell responses [11].

Table 1
The phenotypic and functional characteristics of human NK subsets.

NK subset	Phenotype	Transcriptional Factor	Effector molecule	Function
Circulating $CD56^{bright}$ NK	$CD49a^{-}CD103^{-}CD62L^{+}$ $CCR7+$ $NKG2A^{+}NKG2C^{+}KIR^{-}CD16^{low/-}$	$Eomes^{high}T\text{-}bet^{+}PLZF^{low}$	Cytokine secretion $Granzyme^{low}$	Immunoregulation Low cytotoxicity
Canonical $CD56^{dim}$ NK	$CD49a^{-}CD103^{-}$ $CD62L^{\pm}$ $CXCR1^{+}CXCR2^{+}CXCR3^{+}$ $NKG2A^{+}NKG2C^{\pm}KIR^{+}CD16^{high}$	$Eomes^{high}T\text{-}bet^{+}PLZF^{low}$	$Granzyme^{high}$	Immunoregulation Cytotoxicity Immunosurveillance
Adaptive $CD56^{dim}$ NK	$CD49a^{-}CD103^{-}$ $CD62L^{-}$ $CCR5^{high}$ $CXCR1^{+}CXCR2^{+}CXCR3^{+}$ $NKG2A^{+}NKG2C^{high}KIR^{high}CD16^{high}$	$Eomes^{high}T\text{-}bet^{high}PLZF^{-}$	$Granzyme^{high}$	Memory Adaptive activity Immunosurveillance
Tissue-resident NK	$CD56^{bright}CD49a^{+}CD103^{+}CD62L^{-}$ $NKG2A^{+}NKG2C^{high}KIR^{high}CD16^{-}$	$Eomes^{low}T\text{-}bet^{low}PLZF^{?}$	$Granzyme^{low}$ Cytokine secretion	Limited immunoregulation Moderate immunosurveillance Maintaining homeostasis