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Commentary

Clinical Applications and Mechanisms of Natural Killer Cells: A Commentary

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DESCRIPTION

Development and differentiation of NK cells

NK cells originate from Hematopoietic Stem Cells (HSCs) in the bone marrow and undergo a series of developmental stages characterized by distinct surface marker expression and functional maturation:

Early development: NK cell progenitors emerge from HSCs in the bone marrow and migrate to secondary lymphoid tissues, such as the spleen and lymph nodes, where they undergo further differentiation.

Maturation and activation: NK cells acquire surface receptors and cytotoxic effector molecules during maturation, which are crucial for their effector functions. Important receptors include activating receptors (e.g., NKp46, NKp30, NKG2D) that recognize stress-induced ligands on target cells and inhibitory receptors (e.g., killer cell immunoglobulin-like receptors, KIRs) that recognize self-Major Histocompatibility Complex (MHC) class I molecules.

Peripheral regulation: NK cells complete their maturation in peripheral tissues, where they encounter and respond to environmental stimuli, such as cytokines (e.g., interleukin-15, IL-15) and interactions with other immune cells.

Mechanisms of NK cell function

NK cells employ multiple mechanisms to eliminate target cells and modulate immune responses:

Cytotoxicity: NK cells induce apoptosis in target cells through the release of cytotoxic granules containing perforin and granzymes. Perforin creates pores in the target cell membrane, allowing granzymes to enter and initiate apoptosis.

Antibody-Dependent Cellular Cytotoxicity (ADCC): NK cells express Fragment crystallizable (Fc) receptors (CD16) that bind to the Fc portion of antibodies bound to target cells. This interaction activates NK cell activation and enhances target cell lysis.

Cytokine production: NK cells secrete cytokines (e.g., interferon-gamma, IFN-γ, tumor necrosis factor-alpha, TNF-α) and chemokines (e.g., CCL3, CCL4) that regulate inflammation, recruit other immune cells and modulate adaptive immune responses.

Regulation of immune responses: NK cells interact with dendritic cells, macrophages and T cells through direct cell-to-cell contact and cytokine signaling, influencing the activation, differentiation and function of these immune cells.

Regulation of NK cell activation

NK cell activity is tightly regulated by a balance between activating and inhibitory signals from surface receptors:

Activating receptors: Recognize stress-induced ligands (e.g., MICA/B, ULBP1-6) on target cells and trigger NK cell activation and cytotoxicity. These receptors play a crucial role in tumor surveillance and response to viral infections.

Inhibitory receptors: Interact with self-MHC class I molecules on healthy cells, providing an inhibitory signal that prevents NK cell activation and protects healthy tissues from NK cell-mediated attack.

Licensing and education: NK cells undergo a process known as "licensing" or "education," where they acquire functional competence through interactions with self-MHC class I molecules during development. Licensed NK cells exhibit enhanced responsiveness to activating stimuli and are more effective in target cell lysis.

Role of NK cells in disease and clinical applications

NK cells plays a significant role in immune surveillance against infections and malignancies and their dysregulation is implicated in various diseases:

Viral infections: NK cells contribute to early defense against viral infections, including herpesviruses, influenza and hepatitis viruses. They recognize infected cells and limit viral replication through cytotoxicity and cytokine production.

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Cancer immunotherapy: NK cells are being increasingly explored for their potential in cancer immunotherapy. Strategies include adoptive NK cell transfer, cytokine stimulation (e.g., IL-2, IL-15), and monoclonal antibody therapies (e.g., anti-CD20, anti-CD19) that engage NK cells in ADCC against tumor cells.

Autoimmune diseases: Aberrant NK cell activation and cytokine production have been implicated in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus. Understanding NK cell dysregulation may offer insights into disease pathogenesis and therapeutic strategies.

Transplantation: NK cells play a dual role in transplantation as mediators of graft rejection (particularly in haploidentical stem cell transplantation) and regulators of Graft-*Versus*-Leukemia (GVL) effects in allogeneic hematopoietic stem cell transplantation.