Insights in Stem Cells

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# Stem Cell Research 2017-Natural Killer Cells: From Defence to Immunotherapy in Cancer- Darji A-Cadila Pharmaceuticals Ltd

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**Abstract:**

Natural killer (NK) cells are central components of the innate immunity. The numerous mechanisms used by NK cells to regulate and control cancer metastasis' include interactions with tumor cells via specific receptors and ligands as well as exerting direct cytotoxicity and cytokine-induced effector mechanisms. NK cells are also clinically important and represent a good target for anticancer immune therapy in which the host immune system is harnessed for anticancer activities. They also display impaired functionality and capability to infiltrate tumors in cancer patients. In this review, we provide an overview of our current knowledge on NK cell in oncology and immunotherapy. Although NK cells might appear to be redundant in several conditions of immune challenge in humans, their manipulation seems to hold promise in efforts to promote antitumor immunotherapy. Therefore, efforts to enhance the therapeutic benefits of NK cell-based immunotherapy by developing strategies are the subject of intense research.

**Background:**

Efficient immune responses to pathogen invasion in body are counteracted by coordinated interplay between both adaptive and immune effector systems. Natural killer (NK) cells are effector cells of the innate immune system that exert direct cytotoxic functions. These are determined by a finely tuned balance of signals delivered by inhibitory and activating receptors. There are two types of adaptive immune responses: humoral immunity, mediated by antibodies produced by B lymphocytes, and cell-mediated immunity, mediated by T lymphocytes. The innate immune system includes: Natural killer cells, mast cells, eosinophils, basophils, and the phagocytic cells which include macrophages, neutrophils, and dendritic cells, and function within the immune system by identifying and eliminating pathogens that might cause infection. NK cells are unique, however, as they have the ability to recognize stressed cells in the absence of antibodies and major histocompatibility complex (MHC), allowing a much faster immune reaction. The discovery that a unique type of lymphocyte was responsible for natural or spontaneous cytotoxicity was made in the early 1970s by Rolf Kiessling and Hugh Pross. NK cells are defined as large granular lymphocytes (LGL) and constitute the third kind of cells differentiated from the common lymphoid progenitor-generating B and T lymphocytes. They are known to differentiate and mature in the bone marrow, lymph nodes, spleen, tonsils, and thymus, where they then enter into the circulation. With all the studies conducted on NK cell biology it helps to understand the regulation of NK cell function and thereby helps to utilize role in immunotherapy for treatment of cancer.

**Biology of Natural Killer Cells:**

Natural killer cells (also known as NK cells, K cells, or killer cells) are the effector lymphocytes of the innate immune system. The primary role of NK cells is to provide frontline defense against tumors and microbial-viral infection. They are known to exert direct cytotoxic effect on the target cells by the release of interferon γ (IFNγ) which further boosts the cell immunogenicity. They also have role in adaptive immune response through interaction with dendritic cells, macrophages, T cells and endothelial cells. They possess a distinct characteristic to differentiate between target cells and other healthy 'self ' cells which in order controls the initiation of the cytolytic activity and avoids the damage of the tissues. Initiation of cytolytic activity involves variety of cell surface activating and inhibitory receptors. NK cell typically expresses three to four inhibitory receptors and several activation receptors. The inhibitory receptors consist of killer immunoglobulin-like receptors (KIR) or Ig like receptors (CD158), the C type lectin receptors (CD94-NKG2A) and leukocyte inhibitory receptors (LIR1, LAIR -1) which recognize self-MHC class I molecule and prevent NK cell activation. The activating receptors are the natural cytotoxicity

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receptors (NKp46, NKp44), C type lectin receptors (NKG2D, CD94-NKG2C) and the Ig-Like receptors (2B4). The activation of NK cells is triggered when they encounter cell which lacks self MHC class I molecules by a phenomena classically known as 'missing self ' hypothesis. When the cells undergo stress the constitutive expression of MHC Class I molecule is lost which allows the selective toxicity towards the stressed cells. The apoptosis of the target cell once recognized by NK cells takes place either through the involvement of perforin or through caspases. One more mechanism of killing of tumor cells by NK cells is antibody dependent cellular cytotoxicity (ADCC) as NK cells express low affinity receptor for IgG FcγRIII (CD16). Human NK cells are classified into two subsets on the basis of immunophenotype and function: CD56dimCD16bright and CD56brightCD16dim. More than 90% of NK cells in the peripheral blood and spleen are CD56dimCD16bright, they express perforin, produce IFNγ on interaction with variety of tumor cells in vitro and have high cytotoxic activity. The remaining 10% of NK cells present in lymph nodes and tonsils are CD56brightCD16dim, they lack perforin and are involved in production of cytokines and exherts low cytotoxicity. The cytokines produced by these cells in turn regulate the downstream adaptive immune responses by T cells. The cytokines which regulate the NK cell functions are IL-2, IL-15, IL-12 and IL-18. IL-15 has the pivotal role in NK cell development and maintenance. The cytokines responsible for inhibition of NK cell activation and function are transforming growth factor-beta (TGF-β) and IL-10. Tumor cells secreting TGF- β lead to down-regulation of activating receptors NKp30 and NKG2D which results into NK dysfunction. IL10 produced by acute myeloid leukemia (AML) blasts, up regulates NKG2A leading to impairment of NK cell function.

**Conclusion:**

Research for all these years have led to significant advances in understanding the molecular mechanism involved in NK cell mediated antitumor activity. Both inhibitory and activating NK cell receptors play important role in molecular recognition of innate immunity. The in vitro studies with human and mouse cells and in vivo human data suggest that NK cell have important role in early control of viral infection, in hematopoitic stem cell transplantation, in tumor immunosurveillance and also several other disease. Although little is known about the fate of NK cells after transfusion, they are the potential tools for cancer therapy both due to cytotoxic ability and the possibility of ex vivo expansion. Progress is required to achieve the maximum therapeutic benefit with minimal associated adverse effects. The major focus now is onto the development of therapeutic regimens for various types of disease.

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