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Natural Killer Cells: Development, Maturation and Increasing Clinical Application

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Abstract:

Natural Killer cells were originally described as large granular lymphocytes with natural cytotoxicity against tumor cells. They were also named as "Natural Killers" or "K cells" because of their ability to recognize and kill stressed cells in the absence of antibodies. Natural killer cells are effectors lymphocytes of the innate immune system that control several types of tumors and microbial infections by limiting their spread and subsequent tissue damage. They constitute a minor subset of normal lymphocytes that initiate innate immune responses toward tumor and virus-infected cells. They can mediate spontaneous cytotoxicity toward these abnormal cells and rapidly secrete numerous cytokines and chemokines to promote subsequent adaptive immune responses. They do not require activation to kill cells that are missing self markers of Major Histocompatibility Complex Class1. Natural Killer cells express several activating and inhibitory receptors that recognize the altered expression of proteins on target cells and control the cytolytic function. These cells utilize unique signaling pathways that offer exclusive ways to genetically manipulate to improve their effectors functions. Natural Killer cells have great therapeutic potential to treat cancer and enhance the benefits of hematopoietic cell transplantation. Promising data suggest that NK cells are effective at preventing relapse or treating acute myeloid leukemia. Here, we summarize the recent advances made in the understanding of how NK cells develop, mature, and their potential translational use in the clinical science.

Keywords: Natural Killer Cells, Chimeric Antigen Receptor, Asthma, Cancer Immunotherapy.

Abbreviations:

NK: Natural Killer

HSC: Haematopoietic Stem Cell

BM: Bone Marrow

PB: Peripheral Blood

ILCs: Innate lymphoid cells

IFN: Interferon

PRRS: Pattern Recognition Receptors

TNF: Tumor Necrosis Factor

GM-CSF: Granulocyte Macrophage Colony Stimulating Factor

VEGF: Vascular Endothelial Growth Factor

DCs: Dendritic Cells

CLP: Clonogenic Lymphoid Progenitor

CAR: Chimeric Antigen Receptor

MHC: Major Histocompatibility Complex

LGL: Large Granular Lymphocytes

Introduction:

The innate immune system is the first line of defence against infections. It is non-specific and less effective than the acquired immune system. This immune system involves the physical barriers of the skin and other epithelial surfaces, mucus layers containing inflammation, defensins, and various cells, including phagocytes, dendritic cells, mast cells and natural killer cells. Natural killer cells (NK), also known as large granular lymphocytes (LGL), are initially developed within the primary lymphoid tissue of the bone marrow where they undergo positive and negative selection to remove self-targeting cells. NK cells are cytotoxic; small granules in their cytoplasm contain special proteins such as perforin and proteases known as granzymes. Once they have matured, they move to secondary lymphoid tissues to undergo terminal maturation and act as a prominent member of immune system [20]. NK cells consist of 10%-15% of peripheral blood mononuclear cells. NK cells have morphology of large, granular lymphocytes with the central role of killing the virus-infected and malignantly transformed cells. They play an important role in reproduction processes, hematopoietic regulation, as well as in several *in vivo* immune system reactions [23].

Natural killer cells are divided based on their distinct function such as NKtolerant ($CD56^{bright}$ NK cells or $CD27^{-}$ $CD11b^{-}$), NKcytotoxic ($CD56^{dim}$ NK cells or $CD11b^{+}$ $CD27^{-}$ NK cells), and NKregulatory cells ($CD56^{bright}$ NK cells or $CD27^{+}$ NK cells). NK cells are mainly composed of $CD56^{bright,}$ found in secondary lymphoid tissues, liver, skin, and bone marrow. $CD56^{dim}$ NK cells are mostly found in the peripheral blood and are characterized by their killing activities [52]. They are always CD16 positive. CD16 is key

mediator of antibody dependent cellular cytotoxicity (ADCC). $CD56^{bright}$ can change into $CD56^{dim}$ NK cells by acquiring CD16 [37]. NK cells can be identified by the presence of CD56 and the absence of CD3 ($CD56^{+}$, $CD3^{-}$). NK cells (belonging to the group of innate lymphoid cells) are one of the three kinds of cells differentiated from the common lymphoid progenitor, and the other two being B and T lymphocytes [37].

Natural killer cells are known as a separate lymphocyte lineage, having both cytotoxicity and cytokine-producing effectors functions [49]. NK cells contain about 20–30% of total hepatic lymphocytes in healthy human liver and 10% of lymphocytes in lungs. They are large, granular, bone marrow-derived lymphocytes and they are characterized as CD56 positive and CD3 negative [10]. They are localized in the spleen, lymph nodes, bone marrow, and peripheral blood to carry out immune surveillance. They are also found in mucosal tissues such as lungs, colon, small and large intestines [19]. Based on cytokine secretion profiles, NK cells can be classified as NK1, NK2, or NK22 [47].

NK cells identify stress cells as a result of malignancy or infection and rapidly respond by secreting various cytotoxic granules or death receptor ligands. NK cells also exert cytotoxicity, immune-regulatory functions in by releasing various chemokines and cytokines such as tumor necrosis factor (TNF) - α, interferon (IFN)-γ, chemokine (C-C motif) and granulocyte-macrophage colony-stimulating factor (GMCSF). NK cell acts as non-MHC-restricted cytotoxic cells towards transformed or virally infected target cells. It was first detected in blood [18]. NK cells (innate immune cells) have spontaneous cytolysic activity against virus-infected cells and tumor cells. NK cells upon activation secrete several chemokines (CCL1, CCL2, CCL3, CCL4, CCL5, and CXCL8) and cytokines such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), granulocyte macrophage colony-stimulating factor (GM-CSF), that can modify the function of innate and adaptive immune cells [36].

NK Cells involved in tissue building, remodeling, and angiogenesis by secreting various vascular endothelial growth factor (VEGF), stromal cell-derived factor-1, IL-8 and interferon gamma-inducible protein-10 (IP-10) [50]. The quality and intensity of NK cell cytotoxicity and cytokine responses depends on interactions with T cells, dendritic cells (DCs) and macrophages as well as cytokine microenvironment [32]. The NK cells development involves various stages such as maturation, expansion, and acquisition of specific receptors. NK cell receptors are independent of RAG-mediated recombination and germ-line encoded. The development of NK cells depends on various factors such as cell-intrinsic signals (transcription factors) and external signals (cytokines and growth factors). NK cells play a major role in the host-rejection of both tumors and virally infected cells [26].

Natural Killer Cells Development

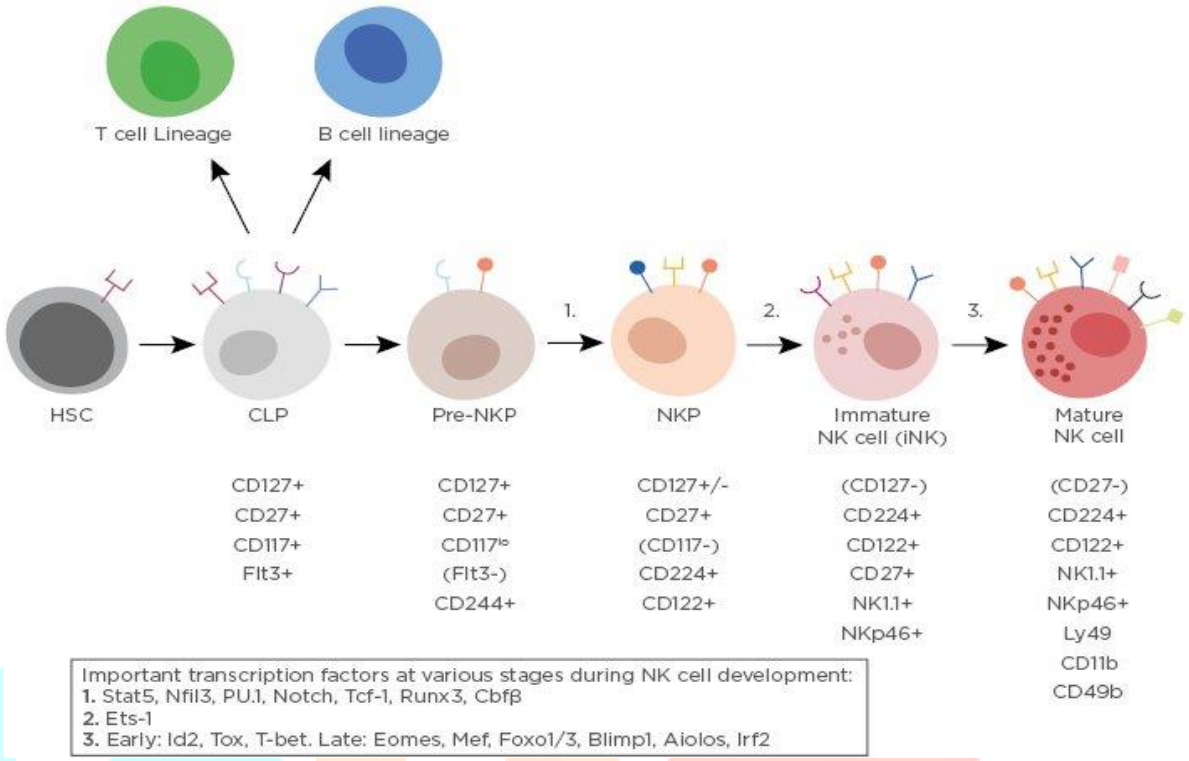

Fig.1. An overview of natural killer cell development

Natural Killer cells derived from the Clonogenic Lymphoid Progenitor (CLP) differentiate into a pre-NKP population, identified by its expression of CD117 and lack of CD122 expression. After becoming an NK cell precursor (NKP), the cells start expressing NK cell markers (NK1.1 and NKp46) and are considered to be immature NK cells at this stage. As they mature further, they acquire CD49b and CD11b expression and lose the expression of CD27. Fully mature NK cells are able to express cytolytic molecules and cytokines (including IFN-γ). Transcription factors also play important roles in governing lymphocyte fate from the CLP. A simplified list of transcription factors driving the NK cell lineage is shown in the box and the numbers on the diagram indicate where they have been identified at the different stages during development. 'Early' and 'Late' indicates when they are thought to be important during the maturation process [21].

It was initially thought that Natural killer cells were exclusively developed in the bone marrow. However, recent studies in humans and mice suggest that they can also develop and mature in secondary lymphoid tissues (SLTs) including tonsils, spleen, and LNs [40]. About 2–5% of NK cells are found in the spleens and BMs of inbred laboratory mice. NK cells are most similar to a group of lymphocytes known as innate lymphoid cells (ILCs). ILCs are further categorized into three distinct groups and are present in both humans and mice. NK cells are related to group 1 ILCs as both produce interferon-gamma (IFN-γ) and tumor necrosis factor (TNF)-α upon stimulation. They have cytolytic functions that resemble those of CD8+ cytotoxic T lymphocytes [1]. They are distinguished by their unique functions and expression of surface antigens. NK cells lack the clonotypic T cell receptor (TCR) of T and NKT cells and its associated signal-transducing adaptor [27].

Applications of Natural Killer Cells

Fig.2. Natural Killer Cell in Various Treatments

1) Bacterial and viral infections

Natural killer cells are essential components of innate immune system and act against variety of pathogens by Pattern recognition receptors (PRRs) which recognize pathogen-associated molecular patterns (PAMP) [44]. Activated NK cells contribute to antibacterial activity through PRRs by eliciting the production of TNF and IFN-γ [15]. NK cells directly contribute to antifungal activity through releasing cytotoxic granules containing perforin (membrane disrupting protein) by damaging fungal membranes, direct phagocytosis and the production of inflammatory mediators [33]. Human natural killer cells act as phagocytes against *Candida albicans* and mounting an inflammatory response that modulates neutrophils antifungal activity [15].

NK Cells promoting fungicidal activity of neutrophils by producing GM-CSF which is critical for controlling *C. albicans* infection. They also contribute to antimicrobial activity against intracellular pathogens [6]. NK cells lyse infected cells and release intracellular pathogens including bacteria and viruses. Thus, expose them to adaptive cell-mediated immunity [42]. They also produce inflammatory cytokines, such as IFN-γ and have ability to detect infected cells without direct involvement of MHC-I complex. Therefore, intracellular pathogens that evade CD8+ T cell response remain vulnerable to NK

cells [22]. Various studies suggested that NK cells play an important role in various viruses such as HIV, Herpes virus, Ebola virus and Cytomegalovirus (CMV) [31]. Infection of cytomegalovirus is characterized by the significant down-regulation of MHC class I on the membranes of infected cells, which helps CMV to evade detection and cytolysis by the killer T cells. Thus, NK cells play a major role in controlling CMV infection [12].

2) Cancer Immunotherapy

Natural killer cells play an essential role in cancer immune surveillance by eliminating tumor cells. They also conjoin with adoptive immune system for antitumor immunity [43]. Sullivan et al. showed increased incidence of MCA-induced sarcoma in RAG2−/−γc−/− mice lacking both adaptive and NK cells immunity as compared to RAG2−/− mice lacking only adaptive immunity. NK cells have application in cancer treatment and showed benefits in hematopoietic cell transplantation. A study by Sullivan et al. provided further evidence for the role of NK cell in immunosurveillance where the incidence of MCA-induced sarcoma was greater in RAG2−/−γc−/− mice (lacking both adaptive immunity and NK cells) when compared with RAG2−/− mice (lacking only adaptive immunity) [46].

3) NK Cells as Regulatory Cells

NK cells played a role as regulatory cells which affect various cell types, such as T cells, B cells, DCs and endothelial cells. NK cells have potential to kill immature DC in humans as well as in mice, thereby influencing DC homeostasis. NK cell–mediated cytotoxicity of target cells leads to the cross-presentation of antigens by subsets of DCs that induces robust antigen-specific adaptive immune responses includingCD4+ T cells, CD8+ T cells, and immunoglobulin G. Thus, NK cells provide a new and powerful approach for vaccine development [17].
NK cell play a vital role in vasculopathy, organ dysfunction, xenograft, allograft and immunologic attack in various pathological circumstances by providing adherence to endothelial cells such as CD62L (L-selectin) through its binding to addressins, CX3CR1 through its binding to membrane-bound CX3CL1 (fractalkine) and $\alpha_4\beta_1$ integrin (VLA-4) through its binding to VCAM-1 [53]. NK cells activated through CX3CL1, which leads to the killing of endothelial cells. Bolovan et al., reported that NK cell involved in the pathogenesis of vascular injury, such as the endothelial damage induced through human cytomegalovirus (CMV) infection [8].

4) Tumor Therapy

The potential role of NK cells in tumor immune surveillance was evidenced after their initial characterization. NK cells can detect and lyse tumor cells by undergoing malignant transformation by detecting changes in surface expression of self-MHC-I molecules on autologous cells [41]. NK deficient mice showed *in vivo* impairment of tumor cells rejection and suppression of tumor metastasis and outgrowth [25]. NK cells mediate ADCC by recognizing antibody-coated targets through allelic polymorphisms within CD16 [51].
Cartron et al., showed the therapeutic response of NK cells in patients with follicular non-Hodgkin lymphoma by demonstrating association of 158V polymorphism with higher responses to rituximab therapy. Other monoclonal antibodies such as alemtuzumab (CD52 on CLL), cetuximab (EGFR on colorectal cancer) and trastuzumab (Her2 on breast cancer), also showed NK cell mediated ADCC [11]. Various studies showed promising approach of NK cells in anti-tumor activity for the treatment of hematological malignancies including acute lymphoblastic leukemia and acute myeloid leukemia [48].Transfusion of NK cell have a relatively low risk of graft versus-host disease (GvHD) [28].

5) Cytokine Therapy

NK cell function can be activated and increased by several cytokines such as IL-2, IL-12, IL-15, IL-18, and IL-21. IL-15 found to be the most promising cytokine for activation of NK cells. In a phase I clinical trial, infusion of IL-15 showed safe tolerance, proliferation and expansion of NK cell together with other antitumor immune cells such as CD8+ T cells and γδ T cells and reduction of lung lesions into the metastatic malignant patients [13]. In preclinical studies, IL-15-1L-15Rα-Sushi-Fc (super agonist) promoted NK cell mediated antitumor activity against lung, breast and colon carcinomas. Thus, holds a promising approach in the clinical trials [24].

6) Bone Marrow Transplantation

NK cells found to be first lymphocytes to repopulate in peripheral blood after Allogeneic or Autologous bone-marrow transplant. Incompletely MHC matched NK cells identified by immunophenotyping have future role in rejecting residual leukemia in allogenic bone marrow transplant. *In vitro* donor NK cells were able to lyse recipient leukemic blast targets [39]. NK cells play a role in bone marrow cell allograft rejection in irradiated mice since from early 1970s [14]. Bone marrow transplantation is currently used in the treatment of a variety of disease such as neoplastic and non neoplastic diseases. NK cells are able of mediating resistance to both allogenic and autologous bone marrow cell grafts. It therefore may be advantageous to deplete such cells in bone marrow transplant recipients before hematopoietic stem cell transfer. One of the studies of bone marrow transplantation involves the occurrence of graft-versus-host disease, which results when alloreactive immune competent T cells are present in the marrow graft [35]. Mouse and human lymphokine-activated killer cells which comprise activated NK cells and T cells, have been shown to suppress alloreactivity; this result suggests that these cells can suppress the generation of graft-versus host disease in vivo by acting as veto cells [5].

7) Chimeric Antigen Receptor (CAR) Therapy

In preclinical models, CAR-transduced NK cells (ganglioside GD2, 2B4 (CD244) receptor, CD138, and CS1) effectively killed tumor cells *in vivo* and *in vitro* [3]. NK cells expressing NKG2D-DAP10-CD3ζ showed enhanced cytotoxic, antitumor activity and cytokine secretion against osteosarcoma. Large-scale production of CAR NK cells hindered due to difficulties in the transfection of PB NK cells. Therefore, human NK92 cell line (activated NK cells) designed and used for NK cell immunotherapy because of their relative ease in transfection [36].

8) Lung Treatment

The lungs, a special site that is frequently challenged by tumors, pathogens and other environmental insults, are populated by large numbers of innate immune cells. Lung cancer are of two types, non-small-cell lung cancer (NSCLC; ~80%) and small-cell lung cancer (SCLC; ~20%) is the leading cause of death related to cancer worldwide [9]. NK cells are cytotoxic lymphocytes that were originally defined based on their antitumor effects and ability to kill various cancer cells including lung cancer by responding rapidly to invading pathogens and killed them efficiently [34]. The most direct evidence of an anti-lung cancer role for NK cells comes from *Kras*-driven spontaneous lung cancer and cancer cell-injection experiments in mice, in which mice lacking NK cells were generated by *Nfil3* knockout or administration of antibodies against NK1.1 or asialo-GM1. NK cells are mostly present in the invasive margin surrounding the tumor lesions [38].

9) Asthma

Asthma is a chronic airway inflammatory disease. The majority of cases are of allergic asthma which is typically characterized by type2 immune responses. Asthma can be caused and exacerbated by various factors, such as environmental pollutants, allergens, obesity and viral infections [7]. Peripheral blood NK cells percentage increased in acute asthmatic children relative to children who are in a stable state after prednisolone therapy [29]. Barning et al. (7) and Duvall et al. (16) showed that severe asthmatic patients have fewer NK cells or loss of NK cells in both the peripheral blood and BALF than healthy individuals. In healthy individuals and patients with mild asthma, NK cells in the peripheral blood can induce the apoptosis of eosinophils efficiently. In contrast, despite displaying a more activated phenotype, the cytotoxicity of peripheral blood NK cells from patients with severe asthma is impaired, and the decreased cytotoxicity can be exacerbated by corticosteroids [16].

10) Autoimmune Disease

Autoimmune disease caused by the failure of the immune system to distinguish self from non-self (loss of self tolerance) and are classified as systemic or organ specific. They are characterized by the autoantibody production and hyper activation of T cells which can caused damaged to several multiple organ or tissue. Recent studies suggested that natural killer cells found important components of innate immune system. They have been used in treatment of various autoimmune diseases such as Systemic Lupus Erythematosus (SLE), autoimmune liver disease and type I diabetes mellitus. Depending on cell subset, disease stage or type and microenvironment, NK cell play pathogenic or protective role in autoimmune disease [30]. SLE is a progressive autoimmune disease with various clinical manifestations which affects several organs including nervous system, heart, lungs, blood, and skin [2]. They are characterized by the presence of hyperactive B cells and activated T cells, which form immune complex that leads to inflammation. Recent study has examined the cytokine profiles and direct cytotoxic action of natural killer cells in the pathogenesis of SLE. Suarez et al., reported that caspase 3 activity was higher in NK cells from patient with SLE than those from healthy donor [45].

11) NK cells as Aging

Aging is associated with changes in the immune system. Both (innate and adaptive) arms of the immune system are involved. Natural killer cells are part of the innate immune system. They participate in host defense by eliminating cells that are virally infected, transformed, or senescent. They are also able to modulate the adaptive part of the immune system. The overall percentage of NK cells among peripheral blood lymphocytes is increased in healthy aging but there is a decrease in the CD56brightCD16− NK cell subset and an expansion of CD56dimCD16+ NK cells. NK cells are powerful protectors from virus-infected, tumor, and senescent cells [52].

Conclusion:

Natural killer cells possess promising potentials as a therapeutic tool to treat a number of maladies including malignancies. NK cells are a key component of the immune response and play vital roles in controlling and eliminating both virally-infected and cancer cells. Although our knowledge of basic NK cell biology and innate immunity continues to grow rapidly and many studies have shown that the development and function of NK cells is highly dynamic, there is still much to be investigated. The effectors function of these NK cells must be further studied, with a predominant focus on immunotherapies along with the prevention of infectious diseases and cancer. Increased understanding of

NK cell receptors and functions has already led to the development of novel therapeutic strategies in immunotherapy of malignancy.

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