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The role and mechanism of natural killer cells in human and animal immunity

Bilata Tsion[1], Shimelis Ephrem[2]

[1]Associate Researcher of Veterinary Microbiology, Animal Health Institute, Sebeta, Ethiopia,debelatsion224@gmail.com.

[2]AddisAbaba University College of Veterinary Medicine and Agriculture Bishofitu, Ethiopia.

Abstract

Natural killer (NK) cells represent a highly specialized lymphoid population initially identified by a potent cytolysis activity against tumor or virus-infected cells. They serve these roles through multiple mechanisms that collectively exert both direct antiviral and anti-tumorresponses, while also helping to shape the adaptive and innate immune responses. NK cells also secrete several cytokines such as interferon-, tumor necrosis factor- (TNF-), granulocyte-macrophage colony-stimulating factor (GM-CSF), and chemokines (CCL1, CCL2, CCL3, CCL4, CCL5, and CXCL8) that can modulate the function of other innate and adaptive immune cells. In this review, we condense the function and mechanism of NK cell education related to their human and animal, effector functions such as cytokine production, anti-Tumour cytotoxicity, role in the clearance of viral and bacterial infections, and the clinical utilization of donor-derived or genetically modified NK.

Keywords: *Cytotoxicity, Natural killer cell, tumor.*

Abbreviations: -IFN-γ: interferon-γ NKC: Natural killer cellTNF-α: tumor necrosis factor-α GM-CSF: granulocyte-macrophage colony-stimulating factor

1. Introduction

Natural killer (NK) cells are used to distinguish the difference between normally healthy cells and abnormal cells by using a sophisticated repertoire of cell surface receptors that play a key role in the host immune response to certain infections and malignancies by direct cytolysis of infected or transformed cells and by secretion of potent immune mediators [1, 2, 3]. NK cells represent a highly specialized lymphoid population initially identified by a potent cytolysis activity against tumor or virus-infected cells. Different from T or B lymphocytes, they do not express clonally distributed receptors for antigens while their function is finely regulated by a balance of inhibitory and activating receptors [4;2]. NK cells represent 5-20% of circulating lymphocytes in humans [5; 6]. There are numerous studies in mice supporting the notion that NK cells are involved in the elimination of tumor cells through multiple mechanisms that collectively exert both

direct antiviral and anti-tumor responses, while also helping to shape the adaptive and innate immune responses [7; 8]. NK cells, therefore, offer great potential for effective cell therapy as long as high numbers of functional cells can be obtained, which are not overstimulated by cytokines and are able to proliferate *in vivo*[9; 10]. The percentages of NK cells among lymphocytes range between about 2-5% in the spleens and BMs of inbred laboratory mice [11] and about twice that number in wild-caught mice [12; 13].

NK cells secrete several cytokines such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and chemokines (CCL1, CCL2, CCL3, CCL4, CCL5, and CXCL8) that can modulate the function of other innate and adaptive immune cells. NK cells are identified as CD3-NK1.1+ cells in C57BL/6, FVB/N, and NZB strains of mice. BALB/c, CBA/J, AKR, C3H, DBA/1, DBA/2, NOD, SJL, and 129 strains of mice do not express NK1.1 and NK cells in these mice can be identified as CD3-CD49b+ cells [14]. They are distinguished by their unique functions and expression of surface antigens. These cells mediate first-line defence by direct cytotoxicity, without prior immunization, against various types of target cells that lack or down-regulate major histocompatibility complex class-I molecules and thereby escape detection by cytotoxic T-lymphocytes [15; 16]. Different NK cells and adaptive immune lymphocytes have multiple common characteristics, however, the NK cells utilize unique signalling pathways that offer exclusive ways to genetically manipulate to improve their effector functions [17].

NK cell cytotoxicity is regulated through the recognition of target cells by integrating positive and negative signals from activating and inhibitory receptor-ligand interactions [18]. Many inhibitory NK cell receptors are specific for self MHC class I and are important to ensure the self-tolerance of NK cells. Loss of MHC class I upon viral infection or malignant transformation can, therefore, result in the so called “missing-self” reactivity of NK cells. NK cells discriminate between infected and healthy cells using an extensive panel of cell surface receptors, both activating and inhibitory. Among the various receptor families involved in this process, Ly49 receptors have proven themselves to be particularly important for MCMV detection by murine NK cells. These polygenic and polymorphic receptors are clustered at the NK Cell Complex on mouse chromosome 6 [19]. They are stochastically expressed as disulfide-linked homodimers primarily on the surface of NK cells, but also on subsets of monocytes, macrophages, dendritic cells (DCs), and T cells [18]. In terms of ligand specificity, inhibitory Ly49 receptors recognize self-MHC class I molecules (MHCI, also called H-2 in mice), whereas their activating counterparts can bind to various protein determinants of infection [20; 21]. Natural killer (NK) cells can control and prevention of tumors and viral-caused infections disease by producing cytokines and by directly lysing target cells [22]. Cytokine-activated NK cells are used in vaccine and adjuvant development [23]. Natural killer cells are the main agents of innate immunity that are involved in decreasing local tumor growth and the risk of metastasis as a result of their cytotoxic effects and the release of immune-stimulatory cytokines such as IFN-gamma [24]. Currently, NK cells have emerged as the main component of adaptive immunity and a prominent therapeutic target for cancer immunotherapy and infection control. NK cells exhibit a miscellaneous signal of phenotypes and function [25].Therefore, the aim of this review was to condense the function and mechanism of NK cells related to their human and animal, effector functions such as cytokine production and anti-tumor cytotoxicity, role in the clearance of viral and bacterial infections, and the clinical utilization of donor-derived or genetically modified NK cells.

2. Materials and Methods

2.1 NK cell Immune mechanisms

NK cells are innate lymphoid cells that activated fatly when the host animal is infected with pathogen at the first time of infection and also posse’s adaptive characteristics allowing them to

integrate innate and acquired immune responses [23]. Natural killercell can be activated by the incorporation of signals received by cytokine receptors and activation and inhibitory receptors recognizing ligands expressed by cells after virus-infection [22]. The mechanisms of NK cell elimination of MCA-induced sarcomas involve molecules like NKG2D, IFN-γ, and perforin [26; 27]. The intra-tumoral NK cells are also known to have reduced pro-inflammatory cytokines and cytokine receptors expression which might hamper their antitumor response in the tumour microenvironment [28].The perforin-dependent NK cell activity was reported to control B cell lymphomas and mammary carcinoma [29]. At the centre of this balance resides a group of receptors that allow the relay of intracellular signalling via intrinsic or associated cytoplasmic molecular motifs for various kinases or phosphatases [30-33].

Unlike T and B lymphocytes, NK cells will not rearrange their genes encoding for receptor antigen recognition, but they have the ability to recognize target cells directly through inhibitory or activating receptors expressed on the cell surface. Several mechanisms have been proposed to explain NK cell education, one of the models being disarming model.The first checkpoint is the expression of MHC-I molecules [34; 35]. In fact, downregulation of MHC-I is observed during tumour transformationor viral infection and prevents the binding of inhibitory receptors of NK cells to the target cell [36]. NK cells are stimulated at the time of vaccination against pathogenic infections such as influenza, yellow fever, and tuberculosis. Stimulation of antigen-presenting cells by live attenuated or whole inactivated vaccines, or by the use of adjuvants causes to develop and maintain the NK cell activity that playsan important role in T cell enrolment and memory cell formation [23].

2.2 NK Cell Development

NK cells are believed to be relatively short-lived, and at any one time, there are likely more than 2 billion circulating in an adult [37].NK cells are part of our first line of defence against cancer cells and virus-infected cells. The bone marrow is the main site for NK cell development. Any NK cell attaches to a target cell, releases chemicals that breach its cell wall, and causes it to lyse (break up). NK cells are small lymphocytes that originate in the bone marrow and develop without the influence of the thymus. An intact BM microenvironment provides NK cells with both cellular substrates and signals required from several stromal factors to sustain cell proliferation and differentiation [38; 39]. NK cell precursors (NKPs) in the BM are derived from hematopoietic stem cells that give rise to immature NK (iNK) cells and mature NK (mNK) cells [40]. mNK cells egress from the BM and represent the main NK cell population in the peripheral lymphoid organs, such as the spleen. The NK cell maturation process in the BM has been well characterized based on the differential acquisition of NK cell receptors and the achievement of their full effector's functions.

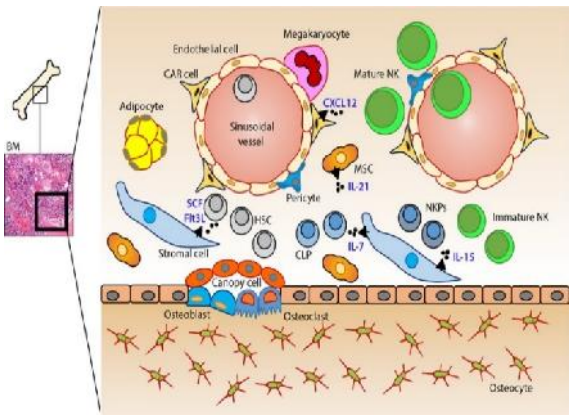

Figure 1: Murine bone marrow niche where natural killer (NK) cells develop

Among the many cell types of the immune system, NK cells are one of the earliest cell types to arrive at target organs of inflammation [41]. Bone marrow-derived NK cell precursors undergo a maturation process that leads to the acquisition of their effector functions, changes in the expression of chemotactic receptors and adhesion molecules, and their migration from the bone marrow through the blood to the spleen, liver, lung and many other organs. The distribution of NK cells is not static because these cells can recirculate between organs [42].

2.3 Function of NK cell

The functional outcome of NK cells is determined by integrating both activating and inhibitory signals resulting in a highly controlled responsewhich mediates cytotoxicity against transformed cells and, in addition, the release of cytokines critical to the immune response. The importance of NK cell-mediated immune-surveillance in the control of tumour growth has been evaluated in NK cell-deficient mouse models with limited information in humans. Humans with NK cell deficiencies are plagued with persistent acute viral infections, especially herpes simplex virus [43]. NK cells were subsequently shown to play an important role in host defence both against tumour cells and against cells infected with some, though not all viruses. These cells, which constitute 5%-10% of lymphocytes in human peripheral blood, do not express the membrane molecules and receptors that distinguish T- and B-cell lineages [10]. During inflammation NK cells are rapidly recruited from the blood into injured tissues where they interact with other cell types of the innate immune system. NK contact with cytokines like interleukin (IL)-12 and IL-15, produced by dendritic cells (DCs) undergoing maturation, is crucial for enhancing NK-cell cytotoxicity and for inducing NK cells to release IFN-ɣ and tumour necrosis factor (TNF), thus enabling them to affect neighbouring cells [44-46].

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2.4 Molecular mechanisms

NK cells are lymphocytes that are classically referred to as part of innate immunity. NK cells were first described for their ability to kill leukemic cells without prior specific sensitization [47]. They represent a small proportion (4-15%) of blood lymphocytes and do not express a specific receptor for antigens dependent upon RAG-mediated rearrangements [**Error! Reference source not found.**]. NK cell function is regulated by a multiplicity of activating and inhibitory receptors. Their natural cytotoxicity is largely under the control of natural cytotoxicity receptors, and their antibody-dependent cytotoxicity is linked to the engagement of CD16/FC*γ* RIIIa (Goodier, Nielsen). Human NK cells are characterized as CD3- NKp46+CD56+ cells [14]. In humans, blood NK cells can be divided into two major subtypes: CD56bright and CD56dim, corresponding to sequential steps of differentiation [15]. The former subtype represents about 10% of circulating NK cells. In recent evidence has given a direct role of NK cells to the cytolysis of activated T cells. Interestingly, apoptotic cells can up-regulate NKp46 expression by NK cells, leading to increased natural cytotoxicity toward vimentin $^{+}$CD4 T cells, which could be interesting due to the high numbers of apoptotic T cells found in the liver [49]. On the other hand, IL-10 is able to block vimentin secretion by macrophages[50].

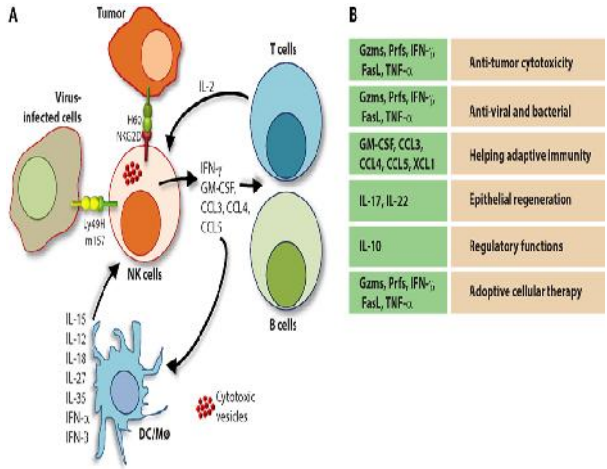

Figure 2: Role of a "third signal" in natural killer (NK) cell activation

NK1 cells produce IFN-γ but almost no IL-4, IL-10, or IL-13. NK2 cells do not secrete IFN-γ but produce IL-13. Another subset of NK cells has a regulatory function, secretes IL-10, and dampens immune responses. It has been suggested that NK cells exposed to moderate levels of IL-12 secrete IFN-γ, but if exposed to very high levels of IL-12, they produce IL-10. These regulatory NK cells may reduce the severity of virus induced immune pathology [17].Activating stimuli may be delivered to NK cells through triggering via Toll-like receptors (TLRs) including TLR2, TLR3, TLR7/8, TLR9, interleukin receptors (IL-2, IL-12, IL-15, IL-18), and combinations thereof (e.g., IL-2 + IL-15, IL-2 + IL12, IL-12 + IL-18), or activators receptors representing an array of different molecules expressed on their surface including natural cytotoxicity receptors (NCRs), NKG2D, NKG2C (a lectin-type triggering receptor which dimerizes with CD94), 2B4 (CD244), NKp80, DNAM- 1, NTB-A, and the receptor for IgFc (CD16) [51;52]. In addition, IL-4 can also inhibit Ly49 receptor expression [53;54], suggesting a functional role in the innate immunity response. Finally, human NK cells cultured for the short term with IL-4 did not release interferon (IFN)-*γ* and showed no cytolyses activity in response to stimulation through the NKp46-activating receptor.

3. Conclusion and Recommendation

In this review, we condense the function and mechanism of NK cell education related to their human and animal, effector functions such as cytokine production, anti-Tumour cytotoxicity, role in the clearance of viral and bacterial infections, and the clinical utilization of donor-derived or genetically modified NK. Introduction Natural killer (NK) cells distinguish between normal healthy cells and abnormal cells by using a sophisticated repertoire of cell surface receptors [1; 2], playing a key role in the immune response to certain infections and malignancies by direct cytolysis of infected or transformed cells and by secretion of potent immune mediators [3]. NK cell precursors (NKPs) in the BM are derived from hematopoietic stem cells that give rise to immature NK (iNK) cells and mature NK (mNK) cells [27]. NK cell Molecular Mechanisms Activating stimuli may be delivered to NK cells through triggering via Toll-like receptors (TLRs) including TLR2, TLR3, TLR78, TLR9, interleukin receptors (IL-2, IL-12, IL-15, IL-18), and combinations thereof (e.g., IL-2 + IL-15, IL-2 + IL12, IL-12 + IL-18), or activator receptors representing an array of different molecules expressed on their surface including natural cytotoxicity receptors (NCRs), NKG2D, NKG2C (a lectin-type triggering receptor which dimerizes with CD94), 2B4 (CD244), NKp80, DNAM- 1, NTB-A, and the receptor for IgFc (CD16)

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