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IMMUNE FUNCTION OF NK CELLS IN CANCER AND THEIR EXPLOITATION IN IMMUNOTHERAPEUTIC

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Abstract
Natural Killer (NK) cells are a type of immune cell that plays a crucial role in defending against tumors and viruses. As part of the innate immune system, NK cells recognize and destroy abnormal cells, preventing tumor development. They are activated upon recognizing abnormal cells and work to eliminate them.Recent research has highlighted the complexity of NK cell responses, including the existence of memory and memory-like NK cell subsets with distinct characteristics and functions. These subsets have been shown to play a key role in immunosurveillance, recognizing and eliminating abnormal cells.NK cells are cytotoxic innate lymphoid cells that produce inflammatory cytokines and chemokines. They are capable of recognizing and destroying transformed or infected cells, making them a key component of the immune response.The role of NK cells in immunity to tumors and viruses has been extensively studied. Research has shown that NK cells are able to recognize and eliminate cancer cells, and that they play a key role in preventing tumor development.

Keywords: Natural Killer Cell,Innate Immunity,Cancer Immunotherapy ,Tumor Progression

Introduction

Natural Killer (NK) cells are a type of immune cell that plays a crucial role in defending against infectious diseases, cancer, autoimmune disorders, and metabolic diseases. They were first discovered in mice in the 1970s [1, 2] by Rolf Kiessling, Eva Klein, and Hans Wigzell, and since then, they have been extensively studied and recognized as a vital part of the innate lymphoid cell (ILC) family [3,4].NK cells are first-line defenders of the immune response, and they work by recognizing and destroying abnormal cells, such as cancer cells or infected cells. They are able to do this through a variety of mechanisms, including the release of cytotoxic granules and the production of cytokines and chemokines [5, 6].Cancer is a significant threat to human health, and traditional treatments such as surgery, chemotherapy, and radiotherapy have limitations [7,8]. The development of resistance to chemotherapy and radiotherapy can response[9,10].lead to cancer recurrence, and these treatments can also have negative side effects, such as reducing physical strength and impairing immune Immunotherapy has emerged as a promising approach to cancer treatment, and NK cells are being explored as a potential tool in this field [11,12]. Immunotherapy works by harnessing the power of the immune system to fight cancer, and NK cells are a key part of this process [13,14].The immune system consists of innate and adaptive immunity, which work together to prevent cancer development through immunosurveillance. Innate immune cells, including NK cells, dendritic cells, monocytes, and macrophages, play a crucial role in this process. NK cells are of particular interest due to their ability to recognize and destroy cancer cells [15,16].

Cytokines play a crucial role in the immune response against cancer. They drive several processes, including

Direct lysis of cancer cells: Cytokines can directly kill cancer cells or facilitate the capture of dead cancer cells.

Antigen processing: Cytokines help process and present antigens from cancer cells to the immune system.

Activation of T cells: cytokines activates, which then mediate an adaptive anti- tumor immune response.

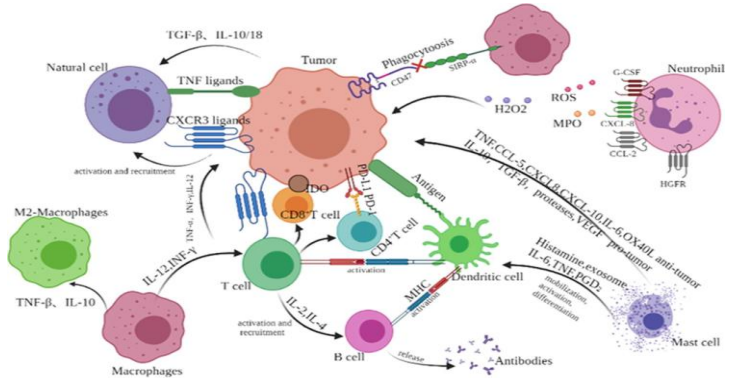

Figure: 1. schematic diagram of tumuor infiiltrating immune cells interactions among each other & with cancer cells

Natural Killer (NK) cells are a type of immune cell that plays a crucial role in defending against viral infections and cancer [17, 18]. They contain granules that release perforin and granzymes, which directly kill cancer cells. NK cells also produce pro-inflammatory cytokines, such as Interferon-gamma (IFN-γ) and Tumor Necrosis Factor (TNF), and chemokines, such as CCL3-5 [19]. These molecules stimulate macrophages to engulf and destroy foreign particles, increase the expression of Major Histocompatibility Complex (MHC) class I on antigen-presenting cells, recruit additional immune cells, and promote cell

Killing [20].

Development, Classification, and Distribution of Nk cells

Natural Killer (NK) cells are a distinct type of lymphocyte characterized by their large size and unique cytoplasmic granules. Discovered in 1975, NK cells are identified by their CD122 expression and the loss of CD34 and CD127 markers. The transcription factors T-bet and Eomes are essential for the differentiation of functional NK cells [21,22]

Key Characteristics:

Large size and unique granules: NK cells are larger than T and B lymphocytes and contain distinct cytoplasmic granules.

CD122 expression: NK cells are associated with CD122 expression [23].

Loss of CD34 and CD127: NK cells lose CD34 and CD127 markers during development.

Distribution and Function

Widespread distribution: NK cells are found in various lymphoid and non-lymphoid tissues, including the bone marrow, liver, lungs, lymph nodes, spleen, and peripheral blood.

Unlicensed NK cells: Unlicensed NK cells play important roles in eliminating viral infections, such as murine cytomegalovirus, and MHC-I+ cells[24].

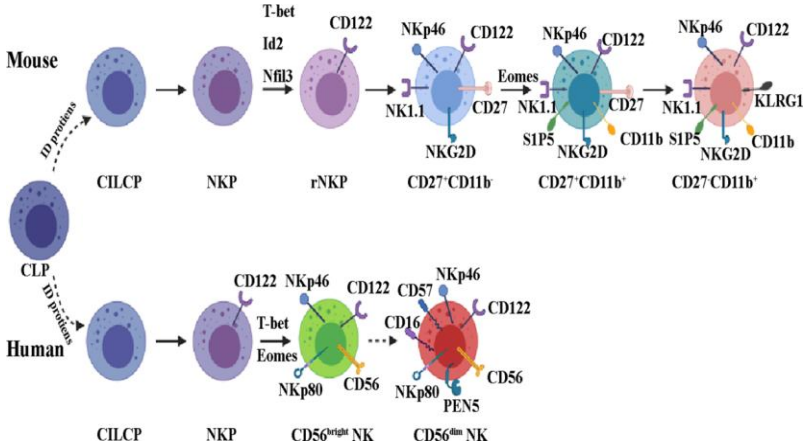

Figure: 2 NK cells development. In mice

Identification and molecular features of Nk cells:

Surface Molecules of Nk cells

Identifying Natural Killer (NK) cells can be challenging due to the variable expression of surface markers. Traditional methods, such as immunohistochemistry, are not always effective in accurately identifying NK cells and their functional status [25].

Challenges

Variable surface marker expression: NK cells express a range of surface markers, making it difficult to identify

them using a single marker.

Limitations of traditional methods: Immunohistochemistry and other traditional methods may not accurately identify NK cells or their functional status.

Proposed Solution

Inclusion of natural cytotoxicity receptor (NKp46): Recent studies suggest adding NKp46, a natural cytotoxicity receptor, to the panel of markers used to identify NK cells.

Focus on functional proteins: The proposal emphasizes the importance of including functional proteins, rather than just surface molecules, in the classification system of NK cells.

Activating and inhibitory signals in Nk cells

Natural Killer (NK) cells receive activating and inhibitory signals that determine their activation and functional status.

Key Player

Natural Cytotoxicity Receptors (NCRs): NCRs are a group of receptors that play a crucial role in NK cell activation.

NCR molecules: Three key molecules, NKp30, NKp44, and NKp46, belong to the NCR group.

NKp30 and its role:

Recognition of B7-H6: NKp30 recognizes B7-H6, a molecule expressed on tumor cells.

Potential treatment option: The interaction between NKp30 and B7-H6 may be used as a novel treatment option in the future.

Subpopulations according to site of maturation

Natural Killer (NK) cells can be divided into subpopulations based on their site of maturation.

Conventional NK (cNK) cells

Location: cNK cells are primarily found in peripheral blood.

Migration: They migrate to specific locations to exert their effects.

Maturation markers

TIM-3, CX3CR1, and ZEB2: High expression of these markers indicates a more mature status of cNK cells.

Nk cell subpopulations according to functional molecules

According to surface CD56 expression, NK cells can be divided into CD56bright and CD56dim. CD56dim NK cells are mainly found in peripheral blood, and are always also CD16-positive, expressing high levels of KIR and LFA-1 and showing cell killing ability.

Adaptive features of nk cells

Although NK cells are considered part of the innate immune system, some NK cell responses exhibit features traditionally ascribed to adaptive immunity, specifically a degree of clonal specificity and memory.

Clonal specificity

Natural Killer (NK) cells exhibit diverse receptor expression patterns, with each receptor present on a random subset of cells.

Key Findings

Variegated receptor expression: NK cells display a unique pattern of receptor expression.

Clonal diversity: Mass cytometry analysis has revealed significant clonal diversity among NK cells.

Unique receptor combinations: Up to 30,000 unique receptor combinations have been identified.

Education

Research on Natural Killer (NK) cells has revealed complex functional changes that occur when they interact with self-MHC molecules.

Key Findings:

Non-binary response: NK cell responses cannot be simply categorized as responsive or non-responsive.

Desensitization mechanism: The functional changes may be better described as a manifestation of cellular desensitization.

Poorly understood mechanisms: The underlying mechanisms driving these processes are not yet fully understood.

Nk cell- medicated anti-tumor mechanisms:

Direct cancer killing

Natural Killer (NK) cells have developed various ways to distinguish between healthy cells and tumor cells.

Tumor Cell Recognition

Loss of MHC-I expression: Tumors that no longer express MHC-I molecules can be recognized by NK cells.
Altered-self proteins: Tumors with stress-inducible proteins can also be identified by NK cells.
Unregulated ligand expression: Cancer cells can express ligands that stimulate NK cell receptors, triggering an immune response.

Indirect cancer killing

Natural Killer (NK) cells play a role in immunomodulatory, influencing the functions of various immune cells.

Immunomodulatory Effects:

Influence on immune cells: NK cells affect the functions of dendritic cells (DCs), macrophages, T cells, and B cells.
Promotion of CTL responses: DCs can cross-present cancer-specific antigens, potentially promoting the production of antigen-specific cytotoxic T lymphocyte (CTL) response.

Nk cell based therapeutic strategies

Various clinical approaches are being explored to harness the power of Natural Killer (NK) cells to kill cancer cells.

NK Cell-Based Therapies:

Cytokine therapy: Using cytokines to stimulate NK cells.
Autologous and allogeneic NK cell therapy: Using a patient's own NK cells or donor-derived NK cells.
CAR-NK cell immunotherapy: Gene-editing NK cells to express chimeric antigen receptors (CARs) for targeted cancer treatment.

Cytokines
Allogenic and autologous nk cells treatment
Antitumour nk cells therapies
Mobilization of endogenous nk cells nk cytokines and superkines

Future perspectives

The future of Natural Killer (NK) cell-based therapies holds promise for innovative cancer treatments.

Emerging Trends:

Optimized cytokine therapy: Refining cytokine combinations to enhance NK cell activity while minimizing side effects.
Gene-edited NK cells: Improving CAR-NK cell therapies for targeted cancer treatment.
Combination therapies: Exploring synergies between NK cell therapies and conventional treatments, such as chemotherapy and checkpoint inhibitors.

Potential Breakthroughs

Advances in NK cell biology and immunotherapy may lead to improved patient outcomes and expanded treatment options.

Conclusion

NK Cells in Cancer Biology

Natural Killer (NK) cells have emerged as key players in cancer biology, exhibiting complex roles in anti-tumor immunity.

Key Findings

Innate memory and memory-like responses: NK cells demonstrate the ability to recall prior activation events, responding to various stimuli, including hapten exposure and virus infection.
Cytokine-induced activation: Combined IL-12, IL-15, and IL-18 activation enhances NK cell responses against cancer.
Interplay with cancer microenvironment: NK cells interact with cancer cells, stromal cells, and extracellular matrix, influencing anti-tumor immunity through metabolite exchange.

Author Contributions

All authors are contributed equally

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Declaration of Competing Interest
The Authors have no Conflicts of Interest to Declare.

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