Biological characteristics of NK cells and their application in cancer treatment

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Abstract. The leading cause of mortality among people is cancer. Traditional medicine, however, has significant dangers and negative effects. Because of its great effectiveness, lack of side effects, and safety, cellular immunotherapy has been utilized extensively in the treatment of malignancies in recent years. While various treatment options have many benefits, they also present unique issues and difficulties. In certain ways, NK cell immunotherapy can make up for these deficiencies. It is not necessary to rely on the patient's distinct immune cells because they may be made from allogeneic cells. Additionally, it can successfully cure the majority of solid tumours, get rid of cancer cells that are resistant to chemotherapy and radiation treatment and metastasis, and enhance the body's immune system, which is the present study's emphasis. As a result, this article begins by introducing the basic traits of NK cells, including traits, uses, activation methods, and how NK cells destroy other cells in an immune response. The use of NK cell therapy in treating different cancers, including hematological malignancies, is then emphasized. Finally, NK cell treatment for cancer development and potential issues are examined. In the future, it will serve as a reference for the treatment of tumours.

Keywords: Cancer, immunotherapy, NK cells.

1. Introduction

Chemotherapy, radiation, and surgery are the standard cancer treatments. All malignancies can be successfully treated surgically, however often only one malignant tumour can be removed at a time. As they travel via the blood arteries and lymphatic system, cancer cells spread to other organs where they might thrive. Radiotherapy is a treatment method that uses radiation to kill cancer cells. Patients with advanced cancer should avoid this. Chemotherapy is a type of medical procedure that coordinates the growth, invasion, and metastasis of cancer cells to destroy them. However, it cannot differentiate between healthy and cancerous cells in the human body, just like radiation therapy. In addition to eliminating cancer cells, they inevitably harm healthy cells in the body, which has detrimental side effects.

Immune cell therapies have effectively changed cancer treatments in recent years. Immune cell therapies are combined with chemotherapies and radiation therapies to cure patients more effectively. As an immunotherapy, natural killer (NK) cell therapy has shown its efficiency when being used to treat cancer. The data supporting the significance of NK cells in cancer immunotherapy is growing, and both pre-clinical and clinical study findings are encouraging [1]. It has demonstrated a wide potential for growth. This overview describes the basic properties of NK cells, how NK cells interact with tumour cells, and how NK cell therapy is used to treat cancer.

2. The biological characteristics of NK cells

When NK cells were first discovered in mice, scientists discovered that big granular lymphocyte subtypes, which are separate from T and B lymphocytes, displayed cytotoxic activity against mouse tumour cell lines. NK cells lack the B and T cell surface antigens CD19/TCR/CD3 phenotypically, although they do express CD16 and CD56. Approximately 90% of NK cells in the peripheral circulation display low levels of CD56 but high levels of CD16 (CD16brightCD56dim), and these cells are regarded as "mature" NK cells with strong cytotoxicity. The remaining 10% of NK cells are categorized as "immature" because they are CD16dimCD56bright. NK cells, which are often present

in lymphoid organs produce a range of cytokines in response to stimulation. An equilibrium between receptor activation and inhibition mediates the activation of NK cells. Granzymes and perforin, among other things, are released into tumour cells by NK cells as a result of their interaction with Fas ligands on NK cells. This leads to a caspase cascade response and ultimately death in tumour cells. NKG2D, NCRs (NKp46, NKp30, and NKp44), and DNAM-1 are examples of activating receptors that are produced by NK cells and coordinate their triggered cytotoxic activity. These receptors have been linked to the activation of a variety of malignancies by NK cells upon engagement with ligands [2].

3. The effect of tumour microenvironment on NK cells

Both immune-suppressive cytokines, which prevent NK cell activation, and interference with NK cells' normal operation can be secreted by tumour cells. Due to the ability of tumour cells to produce inhibitory signals and specifically modify the NK cells' immune phenotype, preventing NK cell infiltration and activation, abnormally functioning immune cells in the tumour microenvironment interfere with NK cell activation and prevent NK cells from performing their killing function. TGF, VEGF, PGE2, and IL-10 are secreted by tumour cells, and they not only prevent T cells from proliferating but also suppress the production of molecules that are similar to MHCI. TGF-β not only prevents human NK cells from producing IFN-γ through the CD16 receptor, but it also has an impact on the granzyme cycle, which prevents NK cells from killing antibody-dependent cells. Myeloid progenitor cells and immature myeloid cells make up the heterogeneous myeloid-derived suppressor cells (MDSCs) [3]. In the tumour microenvironment, hypoxia induces MDSCs to activate arginase and increases the production of inducible nitric oxide synthase, both of which prevent T-cell activation via the NO signaling pathway. Additionally, MDSCs release IL-10, which, via membrane-bound TGF-β, polarizes tumour-associated macrophages in the direction of M2-type anti-inflammatory macrophages. The killing of mice by IL-2-activated NK cells has been reported in the literature to be inhibited by co-culturing NK cells with Gr-1, CDllb, and MDSCs through the membrane-bound TGF-β and STAT5 signalling pathways Leukemia cells NK cell target cells YAC-1 [4]. The tumour microenvironment contains very few CSCs, but those that do have the ability to inhibit the immune system through the actions of STAT3 and NF-kB. The NF-kB pathway may function as an inhibitor of the NK cells' ability to kill by increasing the sensitivity of many cancer cells to NK cell destruction when the activity of the pathway is inhibited. Macrophages are often divided into the M1 and M2 kinds, with the M1 type having anti-inflammatory properties and the M2 type typically being thought of as pro-inflammatory macrophages. By secreting chemokines CXCIB, CCL2, and certain cytokines, tumour cells induce the recruitment of macrophages and inflammatory-suppressive regulatory T cells to the tumour site and have a cell-killing impact. Regulatory T cells primarily affect NK cell activation by secreting TGF-β, which controls NK cell activity. By stifling the creation of the chemokine receptor CCR5, regulatory T cells in the tumour microenvironment impede CCR5-dependent DC recruitment in lymph nodes. Regulatory T cells suppress NK cell activity in gastrointestinal mesenchymal tumours by secreting IL-4 and indoleamine 2,3 dioxygenase in response to IL-2 stimulation [5].

4. Application of NK cell immunotherapy in different cancer treatments

4.1. Hematological malignancy

Patients with advanced hematological malignancies are still being treated with the transplantation of allogeneic bone marrow stem cell. However, significant problems such graft rejection and acute or chronic graft versus host disease (GvHD) might arise due to the divergent leukocyte antigen profiles of the recipient and donor. To decrease the negative effects, new strategies must be created. Since NK cells seldom attack cells carrying HLA class I molecules [6], they may be a better option for transplantation than T cells in lowering the danger of graft against host response. A greater patient

survival rate has also been connected to the idea that unrestrained NK cells can perform their anti-tumor activities more efficiently [7].

The introduction of genetically altered NK cells known as CAR-NK cells, activating NK cells with cytokines, and employing NK cell-directed monoclonal antibodies are some other methods for using NK cells to combat hematological malignancies. However, there are several challenges with the CAR-NK cell approach, including challenges with large-scale proliferation, brief lifetime, and transduction and modification challenges. More promising clinical data are still required to demonstrate the potential of CAR-NK cell treatment [8].

4.1.1 Leukemia

An abnormality in the bone marrow and blood differentiation of hematopoietic stem cells results in leukemia, a malignant tumor. Patients who undergo chemotherapy or radiation treatment for leukemia are often more susceptible to infections, adverse effects, and immune cell inactivation. In their review, Michaela Allison et al. argue that NK cells are essential for the damage of cancer cells. Numerous activating and inhibitory receptors on NK cells control their function by signaling either activation and ensuing cytotoxicity or inhibition and continued surveillance. Increasing the activation of NK cell is the goal of NK cell-mediated immunotherapy. NK cells can reliably determine the severity, impact of therapy, and prognosis of several types of acute leukemia, according to Dong et al. [9].

4.1.2 Lymphoma

The term "lymphoma" describes cancerous lymphatic tumours. A network of capillaries carrying lymph fluid or white blood cells connects the lymph system, a group of nodes or glands spread out across the body and a component of the immune system. Given that it may move throughout the body across the lymphatic system, cancer which impacts this system is regarded as being highly severe. But thanks to recent developments in medicine, this disease is now more curable than ever before, and it has been mostly defeated.

The largely incurable illness known as follicular lymphoma (FL) is characterized by high response rates but frequent relapses. Researchers have demonstrated that dendritic cells produced from monocytes that are loaded with apoptotic lymphoma cells can cause immunological responses against FL cells, skewing the Th1 response. IFN-DC promotes considerable IFN-g production, increased cytotoxicity receptor expression, and efficient NK cell activation. This demonstrates that the addition of autologous FL cells that have undergone apoptosis to IFN-DC can enhance the efficacy of therapeutic cancer vaccines. Examining the expression of CD25 on CD56+ NK cells reveals that IFN-DC stimulation is the primary trigger of NK cell activation.

4.1.3 Myeloma

The patient with Myeloma (MM) will benefit the most from NK cell-based therapy. However, NK cells from the host body are unable to perform their cytolytic role in MM due to the hostile tumour microenvironment. To tackle this altered immunological environment, NK cell immunotherapy has been developed. There are two basic groups of cells based on where they came from: autologous and allogeneic. Natural killer (NK) cells, active group of the congenital lymphoid cell family with the characteristics of having adaptive or trained immunity, react quickly and irrespective of antigen specificity to viral infection or cellular transformation. NK cells are innate lymphoid cells that specifically attack tumor cells on contact and release pro-inflammatory cytokines to do so. According to C. Reina-Ortiz et al., unfavorable microenvironments usually cause patient NK cells to lack robustness for the development of MM [10]. Adoptive therapy with functionally activated NK cells is essential for boosting currently available MM treatments. Trials in the clinic investigate this immunological niche. NK cells should be stimulated and enlarged in vitro or supported with cytokines like IL-2 and IL-15 to reach their full capability. To do this, "feeder" cells are used, which express ligands that stimulate NK cells. According to certain studies, patient NK cell infusions are possible, and autologous NK cells have anti-myeloma efficacy. Clinical studies demonstrate the safety and

dosage restrictions of adaptive cell treatments employing autologous and allogeneic NK cells, with an emphasis on research and development for better long-term therapeutic results. The field of cancer immunotherapy is developing, concentrating on the cytolytic potential of NK cells, overcoming obstacles, and experimenting with various NK cell kinds [11].

4.2. Bladder cancer

The risk of disease recurrence and worsening is high in non-muscle invasive bladder cancer (NMIBC), a diverse condition. One of the largest lymphocyte loads, along with neoantigenic loads and lymphocyte responses, are present within the tumour. Intravesical Mycobacterium bovis BCG, an inactivated form of Mycobacterium tuberculosis and the oldest immunotherapy still in use, is the only first-line treatment for NMIBC. However, a cystectomy is the only cure for illnesses that get worse after receiving BCG treatment. Although immune-centered treatment has a history of being effective, NMIBC relapse prevention and slowing disease progression are often not achieved with current BCG delivery techniques. NK immune cell biotherapy for bladder cancer can immediately activate the body's immune system and cause the body to develop anti-tumour immune responses, therefore halting the spread and recurrence of cancer cells, in addition to precisely eradicating any residual, minute tumour foci. The ectodomain of NKG2D receptor was fused with 4-1BB and cd3z to produce chimeric antigen receptor (car)-NK cells. The results suggest that the use of vehicle NK-based cell therapy as a possible BC treatment strategy may be supported by the use of epigenetic inhibitor drugs [12].

4.3. Colorectal

The problem of a high incidence of colorectal cancer has become more and more prominent as modern living standards have improved, changing people's lifestyles and dietary patterns, particularly the increased consumption of high-calorie, high-fat, and high-protein foods like chicken, duck, fish, and meat. One of the malignancies with the highest incidence rates worldwide is colorectal cancer (CRC).

Umbilical cord blood NK cell therapy is one of the most promising "alternative" therapies for patients with colorectal cancer. eUCB NK cells have strong anti-tumour activity in vitro and in vivo and may be suitable for patients with advanced colorectal cancer. This new attempt seems to rekindle the desire of researchers to explore NK cells. The traditional NK cell expansion technology is to add cytokines such as IL-2 and IL-15 into the NK cell culture system to promote the proliferation of NK cells, but it has not been widely used due to low expansion efficiency and insufficient purity. In addition, researchers found that there were a large number of NK cells in HT29 tumours, but not in LoVo tumours, which may explain the difference in the response of the two to eucb NK cells. That is, if NK cell infiltration is insufficient, it may lead to ineffective NK cell therapy. On the contrary, if combined with bevacizumab, the therapeutic activity of eUCB NK cells can be significantly improved [11].

Whether eUCB-NK cells are applied alone or together with bevacizumab for the treatment of colorectal cancer, they are a good new treatment option. In addition, it has been found that chemotherapy and monoclonal targeted drugs combined with NK cell therapy can improve the anti-tumour killing properties of drugs, improve the basic immune status of colorectal cancer patients, reduce the toxicity and side effects of chemotherapy and targeted drugs, and improve the quality of tumour-bearing survival to a certain extent, and prolong the survival period.

5. Summary

There are several techniques to treat various tumor kinds. The research of NK cell treatment has gained prominence due to the distinct characteristics of NK cells and their crucial role in the elimination of cancer cells. Due to the malfunctioning of NK cells in cancer patients, research mostly focuses on restoring NK cell activity. This may be accomplished in a number of methods, including

by using CAR-NK cells, cytokines, and other chemicals. The bulk of clinical test results that show the efficiency of NK cells come from research for treatments for hematological malignancies, even if more effective and useful methods to use NK cells as "live drugs" for solid tumours have yet to be discovered. More efficient methods to activate and expand NK cells are also needed for the future development of NK cell therapies.

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