Potential of NK Cell-Based Immunotherapies against Multiple Myeloma

Subjects: Immunology

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Natural killer (NK) cell-based therapies have emerged as promising anticancer treatments due to their potency as cytolytic effectors and synergy with concurrent treatments. Multiple myeloma (MM) is an aggressive B-cell malignancy that, despite development of novel therapeutic agents, remains incurable with a high rate of relapse. In MM, the inhospitable tumor microenvironment prevents host NK cells from exerting their cytolytic function. The development of NK cell immunotherapy works to overcome this altered immune landscape and can be classified in two major groups based on the origin of the cell: autologous or allogeneic.

NK cells multiple myeloma daratumumab autologous allogeneic

1. Introduction

Natural Killer (NK) cells is powerful members of the innate lymphoid cell family [1] that possess features of “adaptive” or rather, trained immunity [2]. They respond rapidly, without antigen specificity, during cellular transformation or viral infection. As innate lymphoid cells, NK cells target tumor cells through direct target killing and by the release of inflammatory cytokines.

1.1. NK Cell Function

NK cells were thought to be specialized cells geared towards eliminating cancer cells. Specifically, they were described as small granular lymphoid cells that exerted a cytotoxic function against leukemia cells [3][4]. Once it was identified that NK cells were not of the monocyte or T cell lineage, their function and biology became easier to clarify [5]. As opposed to other cells also originating from the common lymphoid progenitor, NK cells do not require prior sensitization to attain cytolytic activity. While they develop in non-nodal sites, such as the bone marrow and liver, they comprise 10–15% of total lymphocytes found in peripheral blood. NK cells constitute an ideal adoptive transfer treatment because of their multifaceted cytolytic biology and diverse mechanisms for activation. Their main function is antiviral, especially against viruses that induce loss of MHC-I expression, such as the herpes virus family. Accordingly, patients with impaired NK cell function are prone to viral infection [6]. Their role in immune surveillance against tumors is also well established [1][7][8].

1.2. Major Subsets of NK Cells

As NK cells express the NCAM-1 molecule, which clusters as CD56, they are identified as $CD56^{+}CD3^{-}$ lymphocytes. The difference in CD56 expression intensity divides NK cells into two major subsets: $CD56^{bright}$ and $CD56^{dim}$ cells, both types with unique functions and capabilities [9]. $CD56^{bright}$ cells produce pro-inflammatory cytokines, have a low expression of killer immunoglobulin-like receptors (KIR) and show a low level of cytotoxic activity. $CD56^{dim}$ NK cells constitute the majority of NK cells in peripheral blood and express greater amounts of CD16 on their cell surface than their bright counterpart.

1.3. NK Cell Activation

In order to carry out any cytotoxic effect, NK cells must first discriminate between target and healthy cells. NK cells have transmembrane receptors known as KIRs that recognize HLA-I haplotypes [10], and that are able to inhibit or activate NK cell function. The KIRs containing immunoreceptor tyrosine-based inhibitory motifs (ITIMs) recruit tyrosine phosphatases and inhibit cell function. KIR haplotypes are classified into groups A and B. Haplotypes in Group A encode only inhibitory receptors with a fixed number of genes, KIR2DS4 being the only exception. Haplotypes in Group B have variable types of KIR, also including genes encoding for activating receptors [11][12].

2. Killing of Tumor Cells by NK Cells

Once a target cell has been identified and the correct NK cell activating receptors have been engaged, granule exocytosis is activated inside the NK cell. Granules containing perforin and granzymes are released with perforin creating a pore in the membrane of the target cell [13]. Both perforin [14] and at least granzyme A and B [15] are needed for tumor cell killing by NK cells. Granzymes enter the cytosol of the tumor target cell through the perforin pore and are able to induce several types of cell death, including apoptosis, necroptosis or pyroptosis, depending on the tumor target [16]. The presence of Fas ligand (FasL) and TNF-related apoptosis inducing ligand (TRAIL) on the surface of NK cells also provide secondary pathways through which to exercise their lytic actions [13]. NK cells have been shown to exert cytotoxicity through FasL expression [17], but it seems that TRAIL is more relevant for NK cell cytotoxicity [18]. NK cells also carry out anti-tumor activities through the production of IFN-gamma. This pleiotropic cytokine is able to induce apoptosis in some circumstances, but also to inhibit angiogenesis and contribute to the activation of both innate and adaptive immune anti-tumor responses [19].

Frequently, tumor cells, and especially metastatic tumor cells, reduce their MHC-I expression, allowing them to escape from recognition by cytotoxic T cells (CTL) and from immune surveillance [20]. In fact, mutations in β2-microglobulin that result in the impairment of MHC-I expression, are associated with resistance to anti-tumor CTL and the generation of evading lesions [21] and also with resistance to immune checkpoint inhibitor immunotherapy [22].

3. NK Cells in Multiple Myeloma

3.1. Current Therapies for Multiple Myeloma

Multiple myeloma (MM) is the second most common hematological malignancy, characterized by the clonal expansion of plasma cells in the bone marrow [23][24]. Once a disorder without effective treatment, over the past two decades, new treatments such as autologous stem cell transplant (ASCT), immunomodulatory drugs (IMiDs), proteasome inhibitors and monoclonal antibodies have improved the survival rates of myeloma patients [25]. Current median survival is 6 years, and relapse, even after complete remission, is very common [25][26][27]. Regarding IMiDs, preclinical data showed that lenalidomide enhances anti-myeloma cellular immunity mediated by $CD8^+$ T cells and by NK cells [28]. Later on, it was described that lenalidomide was able to reduce the expression of PD-1 in $CD8^+$ T lymphocytes and in NK cells, and of PD-L1 in MM cells and bone marrow accessory cells [29]. The combination of expanded NK cells with proteasome inhibitors has also been demonstrated to increase their cytotoxic potential [30].

3.2. Antibody-Based Therapy of Multiple Myeloma

Antibody-based therapies rely on unique or over-expressed proteins on the surface of aberrant cells. In MM, the cell surface single-chain transmembrane glycoprotein CD38 is highly expressed and used as part of the definitive phenotype for MM cells. As MM cells have a high surface density of CD38, it has become the target for antibody therapy [31]. Daratumumab, a fully humanized IgG1 κ mAb, was the first to target CD38 and gain approval for MM treatment. Daratumumab has been approved as both monotherapy and in combination with several regimens of proteasome inhibitors and chemotherapeutic agents [32][33]. It causes the death of myeloma cells primarily through antibody-dependent cellular cytotoxicity (ADCC). This process occurs through the crosslinking of CD38-bound antibody on MM cells by the CD16 receptors on NK cells. Other pathways of action include antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC, [34]).

3.3. MM Microenvironment. NK Cell Dysfunction

Alterations within the bone marrow microenvironment (BMM) guide the progress and ongoing persistence of MM. MM patients show variable infiltration of immune cells, even in the early disease stage [35]. Remarkable changes in immune cell populations begin during precursor stages of MM, particularly MGUS [25]. The BMM contains NK cells, T and B-lymphocytes, a balance of osteoclasts and osteoblasts, fibroblasts, bone marrow stromal cells, endothelial cells, the extracellular matrix and blood vessels. Important growth factors, chemokines and cytokines are secreted by the stroma. Progressive immune deregulation impairs T, B, APCs and NK cell function in the MM niche [36]. Deficits in the humoral immune response are common in MM due to a reduction of bone marrow B-cell progenitors [37].

4. NK Cell-Based Treatment for MM

In order to overcome the above-described NK-cell dysregulation, several clinical studies have and are being carried out with NK cells as adoptive cell transfer therapies in MM patients (see also the recent review by Liu et al. [38]). In order to reach their full potential, NK cells should be activated and expanded ex vivo or supported through the addition of cytokines alongside NK cell infusions. A variety of “feeder” cells engineered to express ligands that

activate the NK cells are used along with cytokines such as IL-2 and IL-15 for the maintenance and expansion of healthy, cytotoxic NK cells. The utilization of NK cells in adoptive cell transfer therapy was first trialed in 1985 on patients with metastatic cancers. The results showed no long-term clinical benefit, but NK cells were detected in the patients' fluids weeks after the infusions [39]. More recent NK cell-based trials have tried to capitalize on NK cell persistence while improving clinical results.

4.1. Autologous NK Cells

Autologous SCT after induction therapy for MM remains the standard of care for patients who are transplant eligible. While effective in temporarily holding the disease at bay, it is not curative. The addition of autologous cell transfer therapies can help prolong the effect of ASCT [40].

4.2. Allogeneic NK Cells

Allogeneic NK cells are a convenient option that does not rely on the viability of patient NK cells. As each patient presents with a different treatment history and unique set of markers, expansion of autologous cells can be difficult and may fail. Induction of remission in patients with advanced acute leukemia was shown in pioneer clinical trials using allogeneic NK cells [41].

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