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Future Prospects of Natural Killer Cell-Based Targeted Immunotherapy of Cancer

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Natural Killer (NK) cells are a fundamental component of the innate immune system, capable of recognizing and destroying tumor cells as well as cells that have been infected by viruses or bacteria [1]. NK cells play an important role in adaptive immunity by modulating dendritic cell function as well as controlling antigen-specific T cell responses. Recent finding have shown that NK cells have memory, even though they do not rearrange their antigen receptors. The NK cell functions are regulated by a delicate balance of activating and inhibitory signals received through distinct classes of receptors found on their cell surface [2]. The ability of NK cells to kill tumor cells has made NK cells very attractive in immunotherapy. More importantly, unlike conventional therapies, NK cell mediated therapy is more effective against metastasis. In early experiments, NK cells were activated by IL-2 ex vivo and adoptively transferred to the patients (LAK therapy) with advanced metastatic renal cancer and melanoma along with IL-2 infusions [3]. However, the dose of IL-2 was toxic for the patients and therefore, this adoptive transfer of NK cells (LAK therapy) did not produce the expected success. In future, enhancing the NK cell function by tyrosine receptor kinase (ckit) as well as fms-like tyrosine kinase (flt3) along with low doses of IL-2 and IL-15 is expected to produce better outcome for immunotherapy of cancer.

Patients with acute myeloid leukemia (AML) undergoing haploidentical stem cell transplant (SCT) had improved disease-free survival rate and reduced relapse in killer cell Immunoglobulin-like receptor (KIR)-ligand mismatch. This underscores the importance of NK cells in allogenic hematopoietic SCT for hematological malignancies [4]. NK cell alloreactivity resulted in better bone marrow engraftment and reduced the graft-versus-host disease (GVHD). However, the type of NK cell preparation, the KIR phenotype of donor and the subset of NK cell population, the effect of NK–mediated killing of specific tumor, need to be considered for the successful use of NK cells in SCT for leukaemia.

Identification and characterization of NK cell receptors and their ligands over the last two decades have shed light on the molecular mechanisms of NK cell activation by tumor cells. The finding of inhibitory receptors supported the 'Missing self' hypothesis proposed by Karre whose pioneering work showed that NK cells killed tumor cells that lacked major histocompatibility complex (MHC) class-I molecules [5]. The inhibitory receptors recognize MHC class I molecules whereas, the activating receptors recognize a wide variety of ligands. The activating receptors include the natural cytotoxicity receptors NKp30, NKp44 and NKp46, natural killer group [6] 2D (NKG2D), natural killer receptor protein 1 (NKR-P1), lectin-like transcript 1 (LLT1) receptor, and NK-T-B antigen A (NTB-A) [7]. NKG2D receptor is expressed on NK cells and T cells and plays an important role in immune surveillance. Soluble ligands for NKG2D (sMIC) deactivates NK immunity against leukaemia and colon adenocarcinoma. In animal models, tumor cells expressing high levels of NKG2D ligands are efficiently rejected by NK cells. Therefore, increasing NKG2D ligands on tumor cells is a promising strategy to activate antitumor immunity. Tumor cells express ligands for NK cell inhibitory receptor and thus escape NK mediated killing. Glioblastoma express the LLT1 receptor that interacts with the inhibitory receptor NKRP1-A (CD161) for immune evasion. Blocking this inhibitory signal is a promising strategy to eliminate glioblastoma and other tumor cells that express LLT1.

In addition to the activating and inhibitory receptors, NK cells express several members of the signalling lymphocyte activation molecule (SLAM/CD150) that play an important role in the regulation of NK cell function. 2B4 (CD244) and CS1 (CD319, CRACC) are two members of the SLAM family that promises targeting NK mediated cytolytic function against tumor cells [8,9]. Soluble form of the ligand for 2B4, CD48 is elevated in patients with lymphoid leukaemia. 2B4 signalling by recombinant antigen-specific chimeric receptors costimulated NK cell activation to leukaemia and neuroblastoma cells. This indicates that antigen-specific 2B4 expressing NK cells may be useful in adoptive immunotherapy of leukaemia and other cancers. A monoclonal antibody against CS1 receptor (Elotuzumab, Huluc63) has shown promising results against multiple myeloma. Anti-CS1 mab enhances killing of myeloma cells by activating natural cytotoxicity as well as by inducing antibody-dependent cellular cytotoxicity (ADCC). A combinational therapy of anti-CS1 mab and bortezomib has showed better promise in patients with relapsed/refractory multiple myeloma [10].

In conclusion, current insights into the molecular mechanism of NK cell activation have opened the possibility of specific targeting of cancer cells by NK cells. At present, we do not have complete knowledge of the activating ligands and the complex interplay of inhibitory and activating signalling mechanisms involved in NK mediated killing of cancer cells. Future NK based immunotherapy should focus on blocking the inhibitory signals as well as enhancing the activating signals received from cancer cells to achieve better outcome in cancer therapy.

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