**Therapeutic approaches to enhance natural killer cell cytotoxicity: the force awakens**

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Scientific insights into the human immune system have led to unprecedented breakthroughs in immunotherapy, and drugs and cell-based therapies that have been developed to bolster humoral and T cell immune responses represent an extended arm and a palpable source of therapeutic power. Although NK cells have long been known to have advantages over T cells in terms of their capacity to induce antigen-independent immune responses against cancer cells, their therapeutic potential in the clinic has been largely unexplored.

Here, we present different pharmacological and genetic strategies to bolster NK cell antitumour immunity. These approaches, as well as advances in our ability to expand NK cells ex vivo and manipulate their capacity to home to sites of tumours, have now armed investigators with a variety of new strategies to harness the full potential of NK cell-based cancer immunotherapy in the clinic.

**NK cell tumour killing**

NK cells can mediate cytotoxicity through several distinct mechanisms. Degranulation is the most straightforward pathway, in which NK cells release cytotoxic granules upon interaction with target cells. This is controlled by NK cells expressing the activating receptor NKG2D and, to a lesser extent, by NKG2A, which is also expressed on T cells. NKG2D and NKG2A can also be engaged by ligands on cancer cells, such as MAGE-A and NY-ESO-1. However, the expression of NKG2A on NK cells is not always balanced by sufficient ligands on cancer cells. Activating receptors include those that can be bound by agonist mAbs, including CD16, NKG2D, and NKG2A.

Genetic manipulation of NK cells before adoptive transfer may allow for the optimization of this pathway, turning tumour and tumour cytotoxicity. NK cells engineered to express an anti-CD16 CAR can mediate tumour cytotoxicity, whereas CAR-engineered NK cells using CARs that express an Fc domain to the CD16 receptor can mediate tumour killing. However, the degree to which these mAbs mediate tumour killing in humans remains to be evaluated.

There are also several investigational strategies to manipulate NK cells to optimize tumour killing. NK cells with small molecule inhibitors of histone deacetylase 9 (HDAC9) can be used to induce NK cell cytotoxicity. Another strategy is to express NK cells with CARs that target tumour antigens, which may improve tumour killing. However, the clinical utility of these approaches remains to be determined.

**Drugs to augment NK cell cytotoxicity and tumour targeting**

Immunomodulatory drugs. The FDA-approved brentuximab vedotin and pembrolizumab can decrease the threshold for NK cell activation. Brentuximab vedotin is a standard therapy for patients with refractory Hodgkin lymphoma. It is also approved for patients with relapsed or treatment-refractory ALK-positive ALK-positive anaplastic large cell lymphoma, and it is currently under development for other indications.

Pembrolizumab is a humanized monoclonal antibody that targets PD-1, a negative regulator of immune responses. It is approved for the treatment of recurrent or metastatic melanoma, as well as several other cancers, and it is currently under development for other indications.

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