Natural Killer Cells in Adoptive Cell Immunotherapy for Cancer

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Abstract

Natural Killer (NK) cells are a distinct subpopulation of innate lymphoid cells with the innate capacity to recognise and destroy cancerous and virally-infected cells. NK cells play a crucial role in anticancer immunity due to their various cytotoxicity mechanisms and capacity to modify the immune response through cytokine production. When NK cells were utilised as immunotherapeutic agents and demonstrated safety and efficacy in the treatment of patients with advanced-stage leukaemia, this role was made clear almost two decades ago. Following the groundbreaking achievements of CAR-engineered adoptive T cell treatment and the development of technologies that can transform cells into potent antitumor weapons, interest in NK cells as a potential immunotherapy option has surged tremendously in recent years. Strategies for the development of NK cell-based therapies emphasise co-stimulatory signalling, checkpoint inhibition, and cytokine armouring to increase NK cell potency and persistence. They also aim to reroute NK cell specificity to the tumour through the expression of CAR or the use of engager molecules. The first generation of NK cell treatments have shown excellent efficacy and amazing safety in the clinic, yielding promising outcomes and igniting strong interest in further research. In this Review, we discuss numerous strategies to increase NK cell cytotoxicity and longevity, assess prospects and obstacles, and consider how the design of future NK cell products will be influenced by the lessons learnt from the clinic and the particular intricacies of each malignancy.

Keywords: Long-lived plasma cells • IgA • T cell •

Antibody

Introduction

Using modified immune effectors in adoptive cell therapy, a promising new treatment option for solid and haematological cancers with few other choices is being explored. Autologous Chimeric Antigen Receptor (CAR) T cell treatment, the first to approach clinical translation and commercialization, has produced long-term sustained remissions in many cases for patients with aggressive B cell malignancies. Nevertheless, difficulties persist despite these gains. The lengthy vein-to-vein time and higher expenses associated with CAR T cell therapy's sophisticated manufacturing process create a challenge for patients who, because of their quickly advancing illness, are in dire need of treatment [1]. Additionally, the need for the patient's own cells as the source material limits eligibility because many patients are frequently extensively pretreated and lymphopenic and might not have enough cells to produce a viable product.

In the clinic, neurotoxicities and CAR T cell-related Cytokine-Release Syndrome (CRS) are additional concerns that necessitate inpatient monitoring. Utilizing CAR T cells in an allogeneic situation necessitates extra genetic editing methods to eliminate the TCR because T cells recognise and mediate a response against non-self via the T cell Receptor (TCR). This reduces the danger of Graft-versus-Host Disease (GvHD) [2]. Natural Killer (NK) cells, on the other hand, are desirable candidates for universal cellular immunotherapy because they are able to recognise their targets without regard to the presence of the Human Leukocyte Antigen (HLA).

An intricate network of activating and inhibiting receptors that can distinguish between healthy and "stressed" cells regulates the action of NK cells' effectors. Whether or not NK cells send out a "kill" or "not kill" signal is determined by the accumulated cues brought on by receptor-ligand interactions. By recognising inhibitory Killer Cell Immunoglobulin-like Receptors (KIRs), which bind self-MHC class I molecules and signal to cease NK cell action, healthy cells are protected. As opposed to this, NK cells attack abnormal self-cells like tumour cells through the mechanism of missing-self recognition [3]. Tumor cells downregulate MHC class I molecule expression in an effort to evade T cell responses and upregulate activating ligands that are induced by stress, such as DNA damage or malignant transformation. These different characteristics give NK cells special advantages for allogeneic medicinal uses. Different NK cell products can be created for cancer treatment thanks to the quick development of novel approaches and the appearance of next-generation technology that enable deeper biological investigations [3]. With the help of next-generation CAR molecules, engineered TCRs, and pre-complexing with cell engagers, we are able to direct NK cells' specificity toward tumours. In this Review, we describe how these special qualities of NK cells are used for adoptive NK cell immunotherapy and give an overview of the evolving engineering strategies to increase NK cell potency and persistence. Finally, we offer a viewpoint on the potential and difficulties that lie ahead as we work to combat solid tumours, protect immune effector cells from the suppressive pressures present in the tumour microenvironment, and develop tools to monitor and address unintended safety concerns.

Biological properties of NK cells

It seems sense to use innate immunity to increase the range of antitumor responses. A role in tumour immunosurveillance is suspected for NK cells, which are specialised immune effector cells within the innate immune system. This hypothesis is supported by preclinical and clinical studies that show a correlation between low NK cell activity and increased cancer susceptibility and higher risk of metastasis. Although it is yet unknown whether NK cells emerge from a distinct set of precursor cells or from multipotent progenitors that also give rise to T lymphocytes, B lymphocytes, and myeloid cells, NK cells are thought to grow from CD34+ progenitor cells in the bone marrow. NK cells lack the expression of the clonotypic TCR and the accompanying CD3 complex, which are necessary for signal transduction, in contrast to T cells and NKT cells. Based on the relative expression of the surface proteins CD56 and CD16, NK cells are often divided into two groups: CD56 bright CD16 low/- (immunomodulatory, cytokine-producing) and CD56 dimCD16+ (cytotoxic) [4].

Strongly cytotoxic, NK cells trigger a powerful immune response by creating immunological synapses with their targets and releasing cytolytic granules and cytotoxic cytokines. Additionally, they can identify antibody-coated cells via their FcRIIIA (CD16) receptor, leading to the generation of cytokines and Antibody-Dependent Cellular Cytotoxicity (ADCC). Due to their capacity to produce a variety of cytokines and chemokines, which influence the activity of dendritic cells, macrophages, and neutrophils, as well as B cell and T cell responses, NK cells have also been referred to as "immune-regulatory" cells.

Memory-like function in NK cells

These cells were interestingly able to reawaken after a dormant period upon cytokine stimulation or activation of activating receptors and displayed an increased IFN response mimicking the memory-like characteristics of adaptive immune cells. Later, Todd Fehniger's team proposed that human NK cells should also possess memory-like characteristics. Their research supported this theory by showing that human NK cells preactivated with IL-12, IL-15, and IL-18 and then rested for 1 weeks-3 weeks were able to produce an increased IFN response in response to cytokines or K562 leukaemia cells [5].

NK cell source and donor selection The viability of autologous NK cell treatment applications is limited because cancer patients' NK cells frequently have a defective phenotype indicated by altered gene expression profiles and reduced cytotoxic capability. Additionally, autologous manufacturing platforms are laborious and may restrict accessibility if patients are unable to contribute enough cells for engineering and downstream processing. Current NK cell therapy programmes heavily rely on allogeneic sources to avoid the drawbacks of autologous methods because allogeneic NK cells do not result in GvHD. Peripheral blood mononuclear cells, cord blood, immortalised cell lines, Haematopoietic Stem and Progenitor Cells (HSPCs), and induced pluripotent stem cells are some of the sources from which NK cells can be obtained (iPSCs) [6]. All sources have moved into in-human investigations, are capable of producing clinically useful cell dosages, and are amenable to CAR receptor engineering. Despite this, they have special advantages and difficulties, and they could have various underlying transcriptional, phenotypic, and functional characteristics.

Ensuring genomic fidelity in NK cell therapies

Therefore, it is crucial to develop platforms for product screening and characterization in order to spot undesired genomic changes brought on by off-target nuclease activity. As the science develops, worries that some genetic modifications can unintentionally result in malignant mutations continue to echo in the background [7,8]. The US National Institutes of Health (NIH) created the Somatic Cell Genome Engineering (SCGE) programme to address this need. It has two main goals: first, to give researchers financial support to enable the translation of genome editing technologies into the clinic; and second, to encourage the creation of more thorough assays to examine any potential adverse biological effects that may arise from the use of these tools. Additionally, a number of platforms have been created to examine the fidelity of genome editing, including GUIDE-Seq, CIRCLE-Seq, and rhampSeq, which depend on sequencing technologies to objectively detect potential double-stranded break sites in the genome. Furthermore, tests like high-throughput genome-wide translocation sequencing using linear amplification may be used to reveal unexpected genomic rearrangements [9, 10]. Implementing such assays in the development of cell treatments will be crucial as these technologies develop and change, allowing for a better understanding of the efficacy and safety of cellular products such modified NK cell therapies.

Conclusion

Engineered cellular immunotherapies continue to expand dramatically, with a variety of techniques swiftly moving from preclinical research into clinical trials. The most recent development in the field of cell and gene therapy is best exemplified by a recent publication on *the in vivo* editing of hepatocytes in patients with transthyretin amyloidosis. In a related endeavour, a method for enabling T cell-targeted *in vivo* CAR transfection utilising lipid nanoparticles has been devised to target cardiac remodelling in the context of myocardial damage by Fibroblast Activating Protein (FAP)-redirected CAR T cells. Furthermore, recent research has shown that therapeutic genes (such CAR and TCR) can be delivered to T cell populations *in vivo* using Nipah lentivirus vectors that are directed to CD3, CD8, and CD4. By avoiding the need for significant ex vivo manufacture, cutting costs, and speeding up therapy delivery, these technological advancements offer a fresh perspective on off-the-shelf tailored therapeutics. Targeted viral vectors are easily available to be supplied to patients as needed.

Targeted in vivo editing may be used to modify tumour cells in a way that makes them more susceptible to anti-cancer drugs or gets rid of their resistance mechanisms. Although most recent efforts have been on CAR T cell treatment, *in vivo* engineering may also be useful for NK cell-based therapies, such as to increase tumour sensitivity to NK cell-mediated cytotoxicity or to enhance endogenous NK cell function and persistence. As the industry continues to advance quickly, it is crucial to be informed about any potential safety hazards connected to these different gene editing techniques because worries about potential off-target effects are quite pertinent. These worries are justified, and the recent suspension of numerous ongoing cell therapy trials due to chromosomal abnormalities, treatment-associated AML/Myelodysplastic Syndrome (MDS), or malignant transformation of the infused CAR T cell product serve as reminders of the significance of carefully examining the safety of engineered products. Additionally, it is crucial that cell therapy programmes put in place pipelines for comprehensive product screening to evaluate any undesired genetic alterations that can have negative impacts. The initial support required to start these efforts may be provided by utilising resources like the NIH's SCGE programme. Although NK cell-based immunotherapy is positioned as a secure over-the-counter antitumor treatment, significant problems still need to be answered. As the profession develops strategies to deal with issues unique to each disease indication, it will be crucial to clarify the critical factors that govern NK cell potency and persistence.

Finally, in order to maintain excellent product quality, it will be crucial to develop and put into practise the best techniques for NK cell multiplication and cryopreservation. Logistically, it will be crucial to create interdisciplinary team structures including researchers, physicians, and regulatory authorities in order to collectively map out a comprehensive route to clinical translation for developing NK cell treatment programmes.

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