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INDUCED PLURIPOTENT STEM CELL DERIVED CHIMERIC ANTIGEN RECEPTOR NATURAL KILLER CELL THERAPY: A POTENTIAL BRANCH OF ACCESSIBLE CANCER IMMUNOTHERAPY

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ABSTRACT

Cancer Immunotherapy is a growing field in methods of cancer treatments, harnessing the body's natural immune system to target specific malignant cells, especially using the natural killer (NK) cells. Providing expansion in the utilization of immunotherapy is the chimeric antigen receptor (CAR)-NK cell therapy, utilizing NK cells' ability to target and kill cells and modifying them to detect the once genetically disguised malignant cells. However, challenges such as scalability and limited sources have hindered CAR-NK therapy's actual implementation. Induced pluripotent stem cells (iPSCs) have provided potential solutions to overcome these challenges, as they are known to be self-renewable, “off the shelf”, and can be derived from any source of somatic cells. IPSCs are laboratory induced stem cells, and can differentiate into various types of cells, including NK cells. By combining both technologies, iPSC derived CAR-NK cell (CAR-iNK) therapies can provide the accessibility and scalability which were previously a concern; they are even able to drastically lower costs for cancer therapy, thereby allowing CAR-iNK therapy to be easily accessible for many. This paper will focus on the utilization and efficacy of CAR-iNK therapies by exploring the generation of iPSCs and expansion of CAR-NK cell therapies, along with evaluating multiple preclinical and clinical trials. Potential advantages and applications of CAR-iNK therapy will further be discussed, as well as prospects of CAR-iNK therapy's widespread implementation.

KEYWORDS: Immunotherapy, Malignant, Natural Killer Cells, Chimeric Antigen Rreceptor, Induced Pluripotent Stem Cells, Somatic Cells.

INTRODUCTION

The neoteric technology of induced pluripotent stem cells (iPSCs) by the Yamanaka Group in 2006 has generated numerous opportunities for the development of allogeneic cancer immunotherapy due to their “unlimited supply”. Relying on transcription factors of OCT 4, KLF 4, SOX 2, and C MYC proteins, mature somatic cells are genetically modified to revert to pluripotent stem cells, then revised to become the desired somatic cell - in this scenario, the immune cell branch of NK cells.[1] Coalesced with the advanced science of CAR-NK Cell therapy to equip the iPSC-NK to identify the previously undetectable cancer cells, the newly modified iPSCs are suitable to treat a great quantity of patients, potentially creating cancer immunotherapy easily accessible for many. Clinical trials are underway, and this concept may soon become a reality.

The Disease

Cancer is a malignant condition noted for its heterogeneity, originating through the incessant unregulated proliferation of genetically mutated somatic cells.[2] Through multiple chromosomal aberrations of deducting or summation of chromosomes causing aneuploidy, the cancerous cells will divide through mitosis incessantly, its nucleus capable of duplicating without processing the ligands of cyclin protein, leading to the production of oncogenes.[3] The referred cells are incapable of doing their said functions and constitute to malignant tumours. Chemical, physical, oncogenic carcinogens are known to have impacts on the development of malignant cells. Cancer cells proliferate through a multistep process named angiogenesis, allowing new blood vessels to sprout from nearby vessels. Integrins, a type of matrix protein, are attached to all cells, including cancer cells, and send chemical signals causing the cancer to metastasise. Malignant cells adapt to evade the anthropoid immune system through many methods.[4] Examples include by reducing NKG2D ligands, altering the expression of HLA class 1 molecules, and displaying false checkpoint inhibitors for NK cells to label said cells as typical somatic cells, thereby preventing NK cells from releasing cytotoxic contents from the lytic synapse to kill the malignant cell.

Immune System

Natural resistance of human anatomy has advanced, developing lymphocytes of the innate immune system to defend against foreign invaders or autologous cells. NK cells develop from hematopoietic unipotent stem cells to lymphoid progenitors from the bone marrow and grow into becoming a type of white blood cell. They circulate via the circulatory system, spleen, bone marrow, and liver, detecting foreign bodies of virus and rogue cells, and have evolved to detect cancerous cells using inhibitory and activating receptors.[5] In the context of malignancies, altered expression patterns of ligands on malignant cells can reduce inhibitory signalling such as Killer Immunoglobulin-like Receptors (KIRs), and

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CD94/NKG2A. A balance between inhibitory and activating receptors will further reach disequilibrium as cancerous cells increase activating signals, making them susceptible to NK cell recognition and cell destruction. Activating ligands include stress-induced proteins (e.g., MICA/MICB), tumour-associated antigens, and other stress-induced ligands. However, as mentioned above, malignant cells will adapt its genetic composition to prevent the recognition of NK cells.[6]

IPSC Derived NK Cells

IPSCs can differentiate into numerous types of cells and can be applied to NK cells. Cell sources are derived from adult somatic cells, extracted from various sources such as skin fibroblasts or blood cells. Through retroviruses or lentiviruses, transcription factors OCT 4, KLF 4, SOX 2, and C MYC are integrated, and are capable of reverting somatic cells into pluripotency. The transcription factors carry reprogramming factors, and through transduction, allow the retrovirus to bind to the cell and deliver their genetic content into the cell's genome. The gene expression of the somatic cell will be changed, and specific genes are activated, reverting the somatic cell into pluripotency. By modulating the environment of the cultured cells and adding cytokines IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 an unlimited expansion amount of iPSCs derived CAR NK cells can therefore be obtained.[7]

Clinical Trials of iPSC derived NK cells

Many iPSC derived NK cell clinical trials have undergone Stage 1. A clinical trial conducted on 12 patients with solid tumours, 6 with non-cutaneous melanoma, 4 with cutaneous melanomas, 1 with non-small cell lung cancer and 1 with triple-negative breast cancer. Of these, 6 have shown improvement and reduced tumour burden as of 16 May 2022.[8]

To further evaluate the efficacy of iPSC derived NK cells, a clinical trial conducted included 11 patients with relapsed/refractory cell lymphoma who were treated with hnCD16-expressing iPSC derived NK cells and anti-CD20 antibody. Of these, 7 patients achieved complete response, including 2 patients who were treated with autologous CD19 CAR-T cell therapy, but to no avail.[9]

CAR-NK Cell Therapy

NK cells naturally have the capability to detect and destroy malignant cells; however, when tumours adapt their genetic combination to evade detection, it allows malignancies to grow without the dangers of NK cells. CARs are recombinant receptors for antigens acting as a guide to allow NK cells to detect malignancies.10 Following a similar route of CAR-T Cell therapy, CAR-NK cell therapy is an emerging potential immunotherapy utilising the cytotoxic capabilities of NK cells, combined with the technology of CAR. Unlike CAR-T cells, which require individualised engineering, NK cells can be derived from various sources, and can be used as an "off-the-shelf" therapy. Incorporating iPSCs derived NK cells further expand on this (as mentioned above) as said cells could self-renew indefinitely in culture, allowing quick and straightforward obtainment for patients. advantageous where a substantial number of NK cells are necessitated. CAR technology relies on combining an extracellular antigen recognition domain, a transmembrane domain, and intracellular signalling domains. An extracellular domain, derived from sources including monoclonal antibodies, is implemented on the surfaces of NK cells to recognize a specific type of malignant-associated antigen, and allows CAR-NK cells to recognize and detect the cancer cells exhibiting the targeted antigen.[11] Common antigens aimed by engineered CAR-NK cells include CD19, CD20, GD2, and CD33, but will vary depending on the type of cancer. The transmembrane domain of CAR allows the receptor to bind to the NK cell membrane, while the intracellular signalling domain is responsible for activating CAR-NK cells when malignant cells are detected. CAR-NK cells are then grown in labs, generating an abundant amount of cancer detecting cells ready to be infused back into the patient. Customization for individual cancers is required to provide the highest quality of CAR-NK cells, allowing the cells to specifically recognize and detect a certain type of malignancy.

Clinical Trials of CAR-NK Cell Therapy

Many CAR-NK therapies are undergoing Phase I and II of clinical trials. A clinical trial administering 11 patients with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia (CLL) concluded that 73% of patients had a response to the CAR-NK therapy, and 7 of the 11 patients had complete remission of cancer. No major toxic effects have taken place, and results were seen within 30 days after infusion of all dose levels as of February 2019.[12]

A Chinese team reached the results; in 10 patients as of 18 July 2022, all patients with grade 3-4 bone marrow suppression have recovered within a month, and 6 patients achieved a complete response in antileukemic efficacy a month after infusion of CAR-NK cells.[13]

Combining Technologies

CAR-iNK therapy has the potential to create a branch of easily accessible cancer immunotherapy for many. Combining the technologies of IPSC and CAR – NK cells will further the betterment of cancer therapy. It provides an “off the shelf” therapy, making it readily available for patients, eliminating a large amount of individualised treatment, simultaneously reducing time and costs, have unlimited supply, is consistent, stable, and safe.[11] CAR-iNK therapy utilises NK cells' unique recognition mechanism and powerful cytotoxic capabilities, meanwhile provides accessible immunotherapy for many. Following the recent successes of immune cell-based therapies, CAR-iNK therapy has the capacity to broaden this field and provide a new branch of cancer immunotherapy. NK cells typically derived from donors have a larger chance of rejection, activating immunogenicity, leading to adverse immune responses due to human leukocyte antigen (HLA). However, by generating iPSCs with HLA-C retaining methods, 12 haplotypes of HLA-C retaining iPSCs can cover 95% of the global population, allowing most people to receive this treatment.[14] Other various genetic modifications are potential routes as well. IPSCs can be generated into NK cells, and after the NK cells undergo the process of CAR, they will be able to detect malignant cells and act as cancer detectors.

Clinical trials of CAR-iNK

Phase one of clinical trials of FT596 is completed. It is a first in class, multi-antigen targeted, off the shelf, iPSC-derived CD19 CAR NK Cell therapy in relapsed/refractory B-cell lymphoma, where 8 of 11 efficacy-evaluable patients achieved an objective response, 7 with complete response at a single dose of >_ 90 million cells. As of June 25, 2021, no graft-versus-host disease (GvHD) or immune effector cell-associated neurotoxicity syndrome (ICANS) were noted. The FDA approved all requests for FT596 treatment, recognizing its importance in cancer immunotherapy.[15]

Cartherics, a company specialised in immunotherapy and partnered with institutions such as Monash University and the Peter MacCallum Centre has successfully manufactured

genetically enhanced CAR-NK cells via iPSCs creating cryopreserved CAR-NK cells which are delivered on demand for patients. Their manufacturing system has yielded ~10^5 Genetically edited iPSC CAR-NK cells with deleted immune suppression genes from a single iPSC in less than 30 days. The manufactured cells display potent, on-target cytotoxic functionality against multiple ovarian cancers, solely killing cancer cells, and are being evaluated by institutions such as the Therapeutic Goods Administration Australia as of May 23, 2020.[16]

CONCLUSION

The field of CAR-iNK therapy is rapidly evolving, and continuous refinement of this technology will allow this therapy to soon become reality. Although there are remaining concerns regarding its efficacy, clinical trials hold promise to this field. Its utilisation as a renewable source of CAR-NK cells make them capable of large-scale manufacturing while maintaining precisely targeted immunotherapy accessible for many.

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