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Engineering Strategies for Immunotherapy in Cancer Treatment

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ABSTRACT

Cancer immunotherapy represents a transformative approach to cancer treatment, leveraging the body's immune system to combat malignancies. Despite significant advancements, challenges such as tumor immune evasion, immunosuppressive tumor microenvironments, and delivery inefficiencies persist. Engineering strategies have emerged as critical tools to address these challenges, enhancing the efficacy and specificity of immunotherapies. This paper reviews various engineering approaches, including the development of biomaterials for drug delivery, nanotechnology for targeted immunotherapy, and genetic engineering for optimizing immune cell functionality. Biomaterials facilitate the precise delivery of therapeutics, overcoming biological barriers while minimizing off-target effects. Nanotechnology offers innovative solutions for enhancing drug bioavailability and reducing adverse effects through nanoparticle-based delivery systems. Genetic engineering, exemplified by chimeric antigen receptor (CAR) T-cell therapies, has enabled personalized and highly targeted cancer treatments. However, limitations such as antigen loss, high costs, and regulatory hurdles must be addressed to realize the full potential of these technologies. Future directions emphasize the integration of multi-omic approaches, predictive algorithms, and advanced imaging techniques to refine immunotherapy and bridge the gap between personalized and universal treatment paradigms.

Keywords: Cancer immunotherapy, engineering strategies, biomaterials, nanotechnology, CAR T-cells, genetic engineering.

INTRODUCTION

Cancer Immunotherapy: An Introduction Historically, cancer has been treated with surgery, chemotherapy, and radiotherapy. Targeted agents, mostly tyrosine kinase inhibitors, have recently become a common treatment for many cancers. However, cancer still accounts for 10 million deaths annually. Cancer immunotherapy, drugs or biological agents that enhance the immune response against cancer, is a relatively recent advance that seeks to harness the immune system to treat cancer. Multiple branches of the immune system take part in the elimination, equilibrium, or escape of cancer while minimizing possible autoimmune or allergic reactions. Stimulating an immune response results in the body's "forbidden fruit" becoming targeted by T lymphocytes and natural killer (NK) cells, which usually circulate in the body. After the cytolytic release of perforin and granzyme, the cancer cell becomes targeted, while the tumor microenvironment in which cancer cells navigate through natural killer killing or perforin would similarly be a target. There have been many different strategies for boosting this innate immune system response. Cancer immunotherapy remains an essential modality in the management of cancer, and it is constantly evolving in terms of application, including vaccines, adaptive T-cells, immune checkpoint inhibitors, antibodies, small chemicals, cytokines such as interferon and IL-2 administration, oncolytic viruses, and targeted agents, and combinations of these to best suit the patient. However, it

requires a comprehensive understanding of the biological and engineering aspects that the immune system is comprised of, including memory, specificity, affinity, and the suppressive phenotypes that have evolved to allow the immune system to coexist with us. The concept of testing a patient's immune cells to tailor a patient-specific immune therapy is extremely promising [1, 2].

Overview of the Immune System in Cancer Defense

The immune system encompasses a complex array of biological processes that function, in part, to recognize and eliminate transformed cells that can develop into malignant tumors. The immune defense comprises several kinds of white blood cells, including lymphocytes and macrophages. Tumors consist of clusters of genetically varied cells, some of which can be readily recognized by the immune system. Broadly, immune cells can recognize several peptides called neoantigens that can be derived from tumor neoepitopes. These neoantigens serve as signals for the immune system to eliminate tumor cells. When the immune system is functioning correctly, activated T cells attach to tumor cells and release toxic proteins that kill the tumor cell. Similarly, B cells release chemicals attacking the surface of the tumor cell, and the NK cells can also destroy the tumor cell [3, 4]. Unfortunately, tumors are highly skilled in evading the immune response, and they progress to full-blown cancer. Within the tumor microenvironment, there can be several cells that protect the tumor; for example, M2 macrophages prevent the attack by the immune system. A second group of cells uses immune checkpoints to avoid attack. The most commonly known are PD-1 and CTLA-4, both expressed by T cells. While CTLA-4 and PD-1 can be produced in the receptor-bearing CD8+ and CD4+ T cells, their ligands can be highly expressed by tumor cells, preventing communication and hence attack by T cells. This results in the long-term survival of malignant cells within the tumor. The role of the immune microenvironment is currently under the spotlight for understanding events in cancer. Thus, immunology is becoming a central platform for developing therapies to defeat cancer [5, 6].

Engineering Approaches in Cancer Immunotherapy

Cancer immunotherapy is a burgeoning field of study that attempts to improve the current therapies by employing the body's immune system. The efforts in employing engineering approaches in cancer therapy have applications in both bioengineering and cancer immunology. There has been extensive development in engineering methods used to enhance cancer immunotherapy, typically aimed at improving the tumor microenvironment, the delivery of cells, and the direct engineering of immune cell function. Bioengineers are experts at designing systems to increase the expression of target genes, often in a cell-specific manner. A variety of lentiviral vectors have been designed and created in recent years. A variety of methods might be employed to enhance transduction, such as the usage of galectin-9 and BacMam technology. In the design and delivery of immunotherapeutics, engineering principles may be leveraged to compensate for some of the limitations. The currently available medications are constrained in their effectiveness at treating all types of tumors [7, 8]. The idea of using personalized medicine for cancer patients is becoming increasingly popular among clinicians and patients. It is advantageous to investigate which immune cells are involved in each patient's disease in each individual's therapy. It is important to verify whether patient cells will be effective in a clinical setting and to ensure that they will not cause any unforeseen reactions. Those who have mastered the sciences of genomics and its applications may develop strategies for these patients. Engineers may collaborate with biologists to address these obstacles. The design of immunotherapeutic agents is a long-term goal. There are several technical and biological barriers to using the engineering principles. Chemokines and chemokine receptors will be targeted to recruit immune cells to the site of disease. There are only a few chemokine receptors that would permit the exclusive targeting of specific immune cells in the body [9, 10].

Biomaterials For Drug Delivery in Immunotherapy

Biomaterials for Drug Delivery in Immunotherapy Immunotherapies have demonstrated unprecedented efficacy in patients with various cancer types, leading to the successful approval of several therapies for the treatment of cancer. However, several factors must be overcome to extend the use of immunotherapies to a wider variety of cancer types. In this regard, several engineering strategies seek to improve the effectiveness of conventional immunotherapeutics and enable them to overcome the immunosuppressive tumor microenvironment. Among the engineering strategies that can be employed to improve drug delivery and targeting in immunotherapeutics are biomaterials, which can envelop or concentrate immunotherapeutics of interest to favor drug bioavailability, limit off-target effects, preferentially load or bind specific types of immune cells, and activate drug release at the tumor site. In this way, biomaterials can translate the rapid advancements in cell therapy, which involve genetically engineered immune cells, into cell-free immunotherapy modalities that are easy to manufacture. An ideal material for this purpose should be either foreign or harmless to the immune system, able to favor the

movement of immune cells across barriers (e.g., to tumors and lymph nodes), loaded or efficiently deliver drugs to cells, and avoid clearance by mononuclear phagocytes. Biomaterials are commonly subdivided into two categories: natural and synthetic. Natural biomaterials include polymers, proteins, lipids, and cells produced by living organisms. While natural biomaterials have been used for millennia, the use of natural biomaterials for modern immunotherapy applications has increased due to their generally superior biocompatibility compared to synthetic materials, resulting in rapid translation into patients. In comparison to natural biomaterials, the use of synthetic biomaterials has increased more recently due to improvements in polymer chemistry and materials science that allow for better control over the design of synthetic biomaterial chemical and physical properties. Most importantly, innovative engineering strategies for new materials have led to the development of smart materials for improved control of therapeutic timing and dosage. Unfortunately, limitations in terms of compatibility, stability, and long-term biological effects have been associated with both natural and synthetic biomaterials [11, 12].

Nanotechnology in Enhancing Immunotherapy

Immunotherapy is a modern, promising therapeutic modality for cancer treatment due to its long-term remission and minimal side effects compared to traditional methods. However, due to the complexity of the tumor microenvironment and the differences between individual tumor patients, it has limitations, and some of them are accompanied by immune-related adverse events. Nanotechnology is one of the revolutionary methods to positively influence the therapeutic efficacy of immunotherapy by designing drug delivery systems for the safe targeting of different parts of the tumor, showing great potential in combination or alone as cancer therapeutics. Nanoparticles are a new class of nanomaterials with sizes ranging from 1 to 1000 nm. The unique physical and chemical properties of nanoparticles, in turn, can incorporate various forms of immunotherapy such as adjuvants, antigens, drugs, and gene silencers, representing them as promising candidates for cancer therapeutics. Nanoparticles are used for payloads with different sizes, shapes, surface modifications, and compositions to improve pharmacokinetics, cellular differentiation, and drug efficacy as an alternative for more excellent therapeutic effects. In general, nanoparticles have the potential to administer additional doses of cancer drugs directly. Furthermore, nanoparticles can not only increase the concentration of the therapeutic molecule in the tumor but also avoid direct action in normal tissue, which in turn can overcome the problem of side effects as well as improve efficacy [13, 14].

Nanoparticle-Based Drug Delivery Systems

This paper provides an in-depth review of the strategies employed in the nanoparticle-based drug delivery of immunotherapeutic agents. Nanoparticles are suitable carriers for immunotherapeutic agents due to their features that can encapsulate various antigens, adjuvants, cytokines, and drugs for controlled and sustained release within the body. Natural liposomes and dendrimers are some examples of nanoparticles that have been used to deliver drugs to humans for years. Depending on the material employed for nanoparticle formulation and its surface properties, it is possible to functionalize the nanoparticle surface to make it specific for the target tissue or cells. This targeting ability helps the nanoparticles accumulate within the target tissue and ensures they do not affect non-target cells. In addition to selecting the right type of nanoparticle to use for drug delivery, it is important to optimize its surface properties to improve cell uptake and penetration of the targeted tissue or cells [15, 16]. Various nanoparticle-based drug delivery systems serve the purpose of cancer immunotherapy. Liposomes are spherical vesicular systems with both inner aqueous solutions and outer lipid bilayer structures that can be loaded with drugs of choice. Liposomes have received considerable attention as nanoparticle drug delivery vehicles in medical research. The liposome has a structure similar to the cell membrane and thus can encapsulate a drug in the lipid layer or inside the liposome compartments. This feature makes liposomes one of the most preferred drug delivery systems due to their ability to encapsulate both hydrophilic and hydrophobic agents. Additionally, liposome surfaces can be engineered for the surface expression of ligands that preferentially affect certain cell surface receptors for targeted delivery. Liposomes are usually removed right after they are administered from the circulation by phagocytes in the liver and the spleen. This removal mechanism becomes an advantage in drug delivery as this event can also help in terms of cancer immunotherapy. For example, loading liposomal encapsulated drugs with antigens that target the phagocytic cells will provide an enhanced probability of tumor antigen presentation to T cells. Some studies have looked at using cationic liposomes for improved antigen delivery to antigen-presenting cells. While enhancing lymphocyte response, liposomes loaded with vaccine antigens and natural killer cell stimulatory substances may be a better fit in cancer immunotherapy as they provide enhanced anti-tumor immunity [17, 18].

Genetic Engineering in Immunotherapy

Immunotherapy is among the most promising innovative strategies in cancer treatment. The advent of genetic engineering has allowed significant advances in this field, accelerating the development of new therapies based on the human immune system. Several genetic modification techniques have been developed to enhance immune cell functions to increase their effectiveness in attacking tumors. Engineered immune cells, such as CAR T-cells, have revolutionized the way we treat cancer and have provided accessible and targeted, personalized therapies for patients who previously had no options. Additionally, the possibility of genetically modifying immune cells to provide them with the functional characteristics of long-lived central memory T-cells is expected to result in a more sustained effect against tumors and lower rates of recurrence, providing important potential for further improvements aimed at strengthening, modulating, or reshaping the genetic programs to obtain immune responses of prolonged duration or enhanced effectiveness. The approaches described in this paper face various limitations and open questions, mainly related to safety issues, regulatory perspectives, and clinical practicalities. Possible risks related to genetic modifications, including off-target genotoxicity, the immune response against therapeutic cells, and issues related to the contained use of genetically modified organisms, should be minimized and made tolerable by incorporating sophisticated safety measures. Research within the area of immunotherapy has evolved rapidly in a few decades, driven by innovative technologies such as the breakthrough that came with genetic engineering. In this way, these cutting-edge tools have revolutionized immunotherapy by being able to generate new relevant generations of adoptive immunotherapies. Future developments are expected to further improve genetic modification technologies, making them more flexible speeding up the manufacturing process according to changing therapeutic needs, and guiding the treatment toward a new horizon of fully personalized medicine [19, 20].

Chimeric Antigen Receptor (Car) T-Cell Therapy

In accordance with research and clinical understanding, this paper presents the specified information. All data is already publicly available. Data is in accordance with the high standard of research and reporting principles. T-cells are engineered to express an artificial receptor intended for tumor-associated antigens. Since then, CD19-CAR T-cells have been commercialized and have been administered to 9,000 patients worldwide [21, 22]. CARs are fusion molecules with a scFv region for tumor targeting, spacers, and a transmembrane domain that react to signaling in T-cells. Once the scFv region binds to the antigens expressed, the activation of the signal domain of CAR initiates the command and updates the inhibitory T-cells. There are three different generations of CAR based on the progress of the intracytoplasmic domain. Despite the stringent target validation, side effects can occur. The activation of the T-cells due to the specific binding of scFv toward a target antigen is the first dose of cytokines following the cytokine release syndrome response. The major limitation is tumor-immune evasion via antigen loss. The solid tumor microenvironment can induce antigen loss and reduce antigen expression via the mechanisms of antigen shedding and antigen mutation. The high-cost drugs, production costs, and regulatory challenges can also hinder wide patient accessibility. The affinity of scFv-mediated CAR activation is also due to on-target off-tumor effects and severe side effects. The potential combination of CD19-CAR or tumor antigen CAR with the death ligands of the TNF superfamily molecules increases specificity toward solid tumor antigens. There are ongoing trials with such targeting CARs. The potential combination of the tumor-associated antigen with the tumor suppressor will initiate the target survivin therapy signaling CAR. The potential preclinical study and combination therapy feasibility is being explored. The improvement and reduction of off-target effects of the scFv with unnatural amino acids on the antigen-binding site and the development of specialized scFv structures aim to enhance on-target effects. Preclinical results of wild cysteine and human antibodies improved collagen ten CAR with chain-engineered reductions in off-target effects have been reported. This course will decrease the off-target effects. This result has significant potential in preclinical studies to show activity. Controlling the intensity of the CAR signaling is a way to provoke their proliferation and enhance their activities, and the manipulation of the CAR co-stimulatory domain can optimize and tailor such signals. Engineering CARs with regulatory cassettes, which contain suicide genes and extrinsic apoptosis signaling pathways, has been investigated to delete the administered cells, especially when adverse events occur. Therefore, relatively potent T-cells may be used for optimizing CAR-T and decreasing the number of T-cells administered; a combination with lymphodepletion normally improves in vivo results of the administration and re-infusion. Ongoing preclinical research shows that the killing action of CAR T-cells, which combine with adoptive and/or administration, has potential in the treatment of major cancers. There are several attributes to be addressed in these clinical trials; studies remain to be done to

demonstrate the efficiency of several subjects regarding the clinical usage of various CAR constructs [23, 24].

Future Directions and Challenges in Engineering Immunotherapy

To advance the field of engineering for cancer immunotherapy, future research should emphasize improving the efficacy of the presented strategies with special attention to their safety. Technological advancements in microfluidics, gene editing, and combinational gene transfer have the potential to enable the creation of more translatable off-the-shelf CAR T cell platforms. Additionally, the cross-sectional implementation of multiple strategies combined with immune checkpoint antibody therapy can boost response rates. Multi-omic single-cell analyses, predictive algorithm development, and innovative imaging techniques also promise to personalize immunotherapy interventions further [25, 26]. Translational research is majorly called for in the field of cancer immunotherapy to transfer gene-engineered cell systems from the laboratory into certified commercial production, and from proof-of-concept studies into the clinic. Developing a platform that is individualized according to a network model of the patient profile or an off-the-shelf stem-cell-based platform demands the research community to develop radical new algorithms to describe a borderline between safety and efficacy for producing off-the-shelf universal cell products. In this way, we can improve the medical application for more cancers and bridge the gap between the personalized and universal management of cancer. Indeed, PhDs from all disciplines involved are required to contribute novel ideas and be part of the global scientific strategy for more sophisticated future patient management using CAR T cells or alternative cell-based immune response mediators [27, 28].

CONCLUSION

Engineering strategies in immunotherapy have revolutionized cancer treatment by addressing key limitations of traditional approaches. Biomaterials and nanotechnology have enabled the development of innovative drug delivery systems, improving therapeutic specificity and minimizing side effects. Genetic engineering has transformed the landscape of immunotherapy, providing tools for personalized and highly effective treatments like CAR T-cell therapies. Despite these advancements, challenges such as immune evasion, high costs, and complex regulatory landscapes remain. Addressing these challenges requires interdisciplinary collaboration, translational research, and the integration of cutting-edge technologies. The future of cancer immunotherapy lies in harmonizing engineering innovations with biological insights to create accessible, effective, and patient-specific treatments, offering hope for more comprehensive cancer management.

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