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Emerging Strategies and Rules for T-Cell Receptor Derived Therapy (A Review)

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Abstract

TCR-based therapies represent a groundbreaking step forward in cancer immunotherapy, leveraging the immune system's ability to identify and kill cancer cells. This review explores the latest strategies and regulation updates influencing TCR-targeted therapies, presenting an integrated picture of their scientific rationale, recent developments, and prospective future directions. The review first describes the fundamental mechanisms of TCR-derived therapy, highlighting how TCRs recognize intracellular tumor-associated antigens presented by major histocompatibility complex (MHC) molecules. The review then discusses some of the main challenges of the field, including antigen specificity, TCR affinity, off-target toxicity, and tumor heterogeneity, which hinder the discovery of safe and effective therapies. New technologies like gene editing, synthetic biology, and high-throughput screening are revolutionizing TCR design and delivery to target more precisely and with improved safety profiles. At the same time, regulatory mechanisms are being reformatted to address the challenges of engineered T-cell therapies through revised guidelines and oversight. Clinical trials have also produced promising outcomes, especially in hematologic malignancies and a few solid tumors, demonstrating the therapeutic potential of TCR-based therapies. Results from case studies identify successes and limitations, giving useful insights to maximize treatment effectiveness. In the future, the review underlines the need to create predictive models, investigate combination treatments, and provide more widespread access to personalized immunotherapies. With ongoing advances in research and development, TCR-derived therapy has the potential to become the cornerstone of future cancer treatment—subject to scientific, clinical, and regulatory matters being resolved in harmony.

Introduction

The rapid advancement of T cell receptor (TCR)-derived therapies has opened new avenues for targeted cancer treatment, emphasizing the importance of understanding emerging strategies and regulatory frameworks. These innovative therapies harness the specificity of TCRs to recognize and target cancer-specific antigens, potentially offering more precise and effective treatments compared to traditional approaches. As research progresses, scientists are exploring various strategies to enhance TCR-derived therapies, including the development of engineered TCRs with improved affinity and specificity, as well as the incorporation of safety mechanisms to mitigate potential off-target effects (1). These innovative therapies harness the exquisite specificity of T cell receptors (TCRs) to recognize and target tumor-associated antigens, offering potential advantages over conventional cancer treatments. By leveraging the natural ability of TCRs to detect subtle differences between healthy and cancerous cells, these approaches aim to enhance

the precision and efficacy of cancer immunotherapy. Recent developments in TCR-based therapies have led to the emergence of several promising modalities. Engineered TCR-T cells involve genetically modifying a patient's T cells to express TCRs specific for tumor antigens, enabling them to recognize and eliminate cancer cells more effectively. This approach combines the power of adoptive cell therapy with the specificity of TCR-mediated recognition. Soluble TCR bispecific molecules represent another innovative strategy (2). These engineered proteins typically consist of a tumor-specific TCR fused to an anti-CD3 antibody fragment. By simultaneously binding to tumor antigens and T cells, these molecules can redirect and activate T cells against cancer cells, potentially overcoming some limitations of traditional bispecific antibodies. TCR-mimic antibodies offer yet another unique mechanism of action. These antibodies are designed to mimic the binding properties of TCRs, recognizing peptide-MHC complexes on the surface of cancer cells (3). This approach aims to combine the specificity of TCRs with the favorable pharmacokinetic properties and manufacturing advantages of antibodies. As the field of TCR-derived therapies continues to evolve rapidly, regulatory bodies worldwide are working diligently to establish comprehensive guidelines. These efforts focus on several critical areas to ensure the responsible development and implementation of these novel treatments: 1. Safety assessment protocols are being developed to evaluate potential off-target effects, cytokine release syndrome, and other adverse events associated with TCR-based therapies. 2. Manufacturing standards are being established to ensure the consistent production of high-quality, safe, and effective TCR-derived products across different facilities and batches. 3. Clinical trial design guidelines are being formulated to address the unique challenges posed by these therapies, including patient selection criteria, dosing strategies, and appropriate endpoints for efficacy assessment. By addressing these regulatory aspects, the field aims to accelerate the translation of promising TCR-derived therapies from the laboratory to the clinic while maintaining the highest standards of patient safety and treatment efficacy (4).

The Basic of TCR-Derived Therapy

The details concerning the improvement and application of TCR-derived therapy in clinical practice were not given in recent reviews, although detailed history was shown. From a technical point of view, therapy targeting minor histocompatibility antigens, tumor antigens, and some virus antigens can be thought to be possible. Tumor-antigen-derived therapy has been clinically examined until now. The outcome of this trial revealed both the success and several potential troubles that may prevent its clinical use. In this review, we will first describe the basics and history of TCR-derived therapy, then focus on the future issues of TCR-derived therapy (5). First, the TCR has hypervariable structures that complement the CD8 TCR, which has been in the mainstream of analysis. To maintain such exceedingly large hypervariability, the CD8 counterpart in the TCR contacts not the conserved region but just a site close to conserved residues after the peptide, which is presented by MHC class I. By analyzing the reported crystallography of the TCR-peptide-MHC complex, all contacts are concentrated in approximately a 10 Å contact area (6). With this protein-protein contact behavior, TCR can sufficiently recognize not all, but a variety of peptide structures presented by MHC. Of course, from the physiological point of view, we recognize an incredible necessity of co-recognition by costimulatory molecules. On the other hand, it seems that CD8 and TCR have adopted unique and clever means to recognize the antigen by using the same molecular shape. Therefore, the TCR can be said to be an excellent tool for counteracting selected peptide-MHC complexes with soluble TCR protein and TCR-gene-modified antigen-specific T-cell induction (7).

Definition and Mechanisms

As cancer and some infectious diseases are still not fully treated today, the maintenance of the immune T cell system is a necessity now. The immune system is supposed to be a comprehensive balance to distinguish nuisances or microbial antigens that are collected from the body. How does a T cell recognize the microbe protein, such as a virus, in the cell, so that all infected cells are destroyed? How do foreign tissues, for example, nucleated cells, differentiate from self in terms of immune exclusion and then release protection against outside organisms? The T-cell receptor, a major histocompatibility complex peptide complex, is an important area; the carbohydrate complex is the second area. These two complex areas are supposed to provide the answer (8). The five rules are that MHC > TCR > MHC binds 12 amino acids as a precedent, but regarding the TCR of the MHC peptide bond to imitate the association; a two-cation interaction of the TCR groove coexists with the pocket of the MHC; an accessible T-cell receptor is approximately anchored on the main rigid axis to an MHC peptide; there is a joining peptide of the TCR; the TCR is suitable from the middle under the butyl belt; the TCR interacts with stress, specificity, and selectivity, although this TCR domain is combined with MHC peptides. These two areas contain the five items and grow several different standards (9).

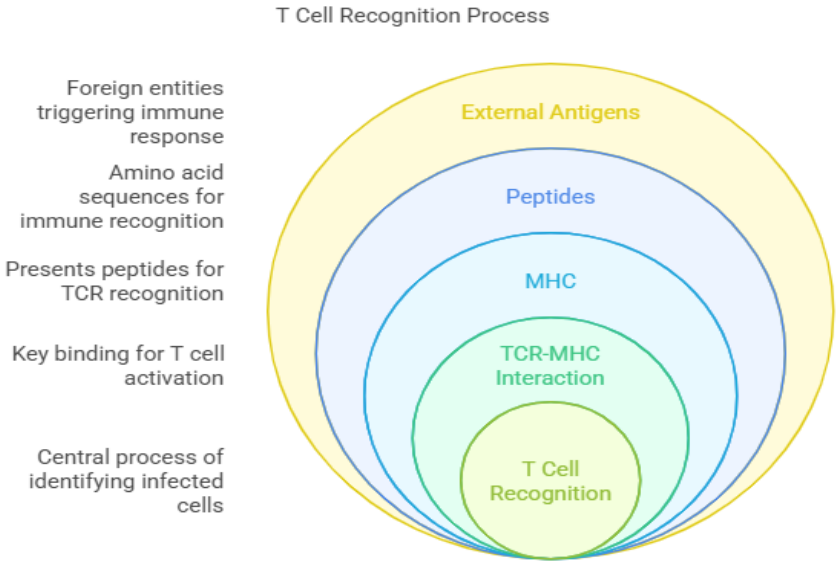

Figure 1: T-Cell recognition process

Current Challenges in TCR-Derived Therapy

Although TCR-derived therapies have gained considerable attention and progress in preclinical and clinical studies, bringing them into clinical therapy presents challenges due to data gaps and translational problems. Firstly, TCR engineering for personalized therapy and other innovative strategies raises safety concerns that limit the translation of TCR therapy. The development of recombinant TCRs offers an attractive strategy to identify TCRs of therapeutic relevance. However, due to MHC restriction and the need for thorough analysis of the safety of cross-reactivity, it is necessary to select TCRs specifically targeting shared antigens from mutations or cross-enhancement. Secondly, recognized ideal quality TILs with definitive anti-tumor activity in vitro pose serious obstacles. High-quality TILs must be composed of cancer-specific T cells or tumor-specific TCRs (10). Additionally, the tumor microenvironment can limit the efficacy of T cells. Furthermore, manipulation using TALENs/CRISPR has been employed to construct allogeneic tumor-reactive TCR transgenic human T cells, which have shown success in murine

models. However, allogeneic tumor-reactive TCR-T cell therapy in humans may trigger serious side effects, especially severe and lethal GVHD. The expression features of certain genes involved in TCR-T function were altered in these cells, and the important feature of the uniform differentiation state of the clone was lost (11).

Autoimmune Reactions

At first, the autoimmune reactions seemed unlikely since clones of regulatory T cells have been shown to recognize antigens with a low affinity. Therefore, differentiation of the immune system between self and non-self was supposed to be ensured dominantly by T-cell selection mechanisms in the thymus and negatively via clonal deletion, i.e., via elimination of negative selection of T cells after T-cell receptor tolerization. The first signal supporting this idea was brought by quite a rare autoimmune polyendocrinopathy with immune deficiency, where mutations were found in the gene encoding the regulatory transcription factor FOXP3. This is one of the main factors allowing T regulatory cell development and, when it goes wrong, autoimmune symptoms develop. Later, various other regulatory T-cell mutations were linked with severe autoimmune symptoms, confirming the general model of differentiating between self- and non-self-reactivity post-thymically and on a per cell basis (12). Moreover, the appearance of Treg cells can be forced by manipulating their TCR specificity with the tumor antigen, i.e., by transducing reactive T cells after growth inhibition into T cells recognizing the antigen (13). This has been known before, but now it has been shown that T cell clones starting from naive precursors with divergent TCR sequences can be used instead of precursor identical reactive T cell clones. As an upshot, adoptive therapeutic anti-tumor immunity can be exploited to favor autoimmune immune suppressor interference in the recipient tumor microenvironment, without causing additional damage to healthy tissues unless autoantigen reactions in the microenvironment can favor competition with tumor antigen reactive immune cells and thereby contribute to immunotherapeutic efficacy (14).

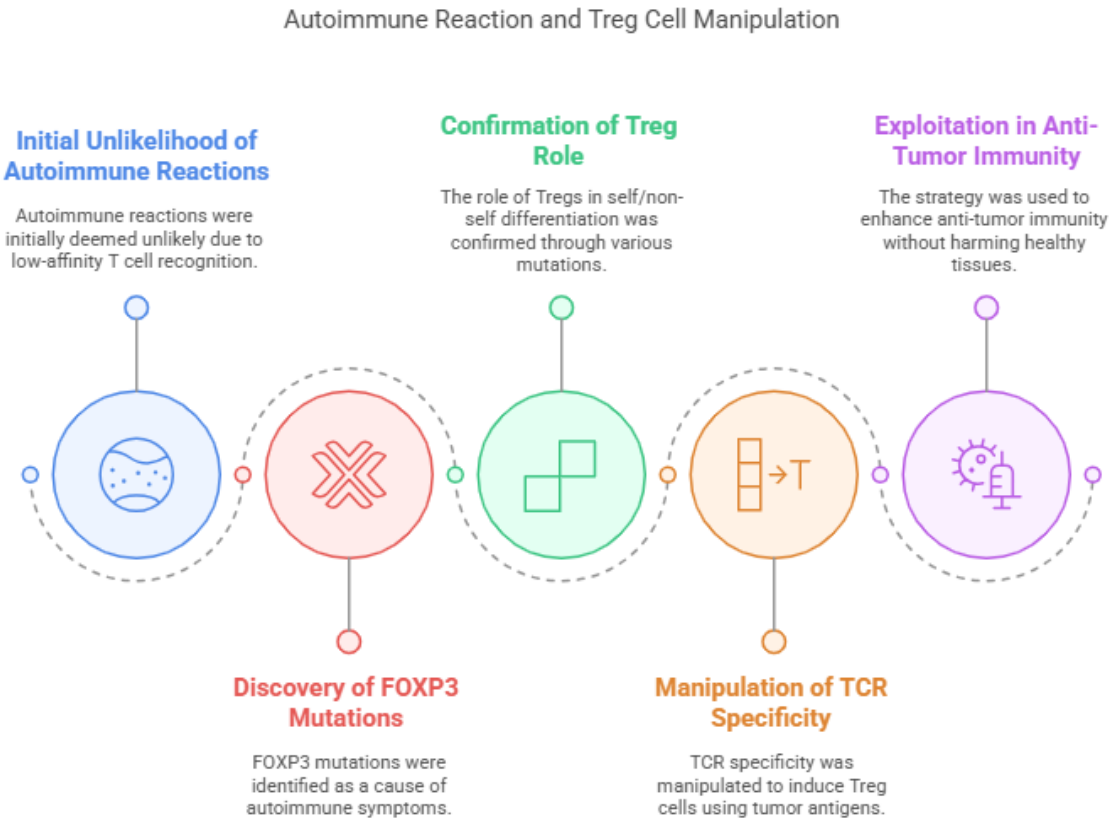

Figure 2: Autoimmune reaction and Treg cell manipulation

Emerging Technologies in TCR-Derived Therapy

TCR therapeutics, PD-1 inhibitors, and tumor neoantigens demonstrate that the core principles of T cell immunity are applicable to new immunotherapeutic strategies to enforce targeting patient-specific MHC-peptide complexes presented on autologous malignant cells. In addition to the long-established restriction of tumor rejection associated antigens for recognition by patient autologous T cells, these CD8 TCR therapeutics have established active TCR mispairing as an uncrossable barrier to the conventional in vivo administration of redirected TCRs as soluble molecules. In this context, strategies to redirect the specificity of αβ T cells with recombinant TCR chains, or even to generate high affinity TCR mimicking soluble polypeptides, were further complicated by an apparent hierarchy in functional avidity of CD8 TCR/peptide-MHC complexes. Fortunately, recent progress in understanding the TCR/pMHC interaction, coupled with new methods to manipulate TCR and pMHC expression in patient-derived αβ T and TCR expression systems, has identified many new solutions to this problem. These TCR-binding platforms are of great value in analyzing T cell-pMHC interactions and have inspired several clinically relevant immunotherapeutic strategies yet to be tested (15).

CRISPR/Cas9 Editing

CRISPR/Cas9 technology has made great progress in editing a specific target. Indeed, with a deeper understanding of this system, it is possible to use programmable nucleases to modify the TCR genes in order to make the recognition of cancer antigens more efficient in solid tumors. The

major disadvantage of these modified allogeneic effectors is the possibility of enhanced immune rejection. According to different strategies to edit TCR genes of immune cells, two of the most used are multiplex single-guide RNA based and pairs of nickases approach. TCR γδ iNKT cells are already modified and utilized for infusion in more than 50 cancer patients, thanks to CRISPR/Cas9. The possibility to edit alloreactive TCR in vitro using CRISPR/Cas9 recruitment strategies to prevent clinical events due to GVHD is a new hope developed for allo-HSCT recipients (16). In fact, when the editing of TCR and additional editing of the HLA class I and II alleles on T cells is associated, such as the deletion of both TCR and HLA can be achieved simultaneously in T lymphocytes. This edited T cell requires the presence of selected HLA of an alternative TCR to be eliminated from healthy hematopoietic cells. Simultaneously, the expression of a second pathological antigen can be activated more selectively and may reduce selective pressure. Finally, there is a low risk of possible primary tumors that may require HLA loss. Hyperediting via the base editor technique could provide lasting HLA absence. TCR αβ + GuideRNA/Cas9 and CD3fl/fl + GuideRNA/Cas9 methods can obtain tumors with increased lipid repair rates in the tumor milieu, promote the effects of CAR T cell therapy, and produce subtype-specific changes in lymphocyte activity and transcriptome without signs of immune destruction (17).

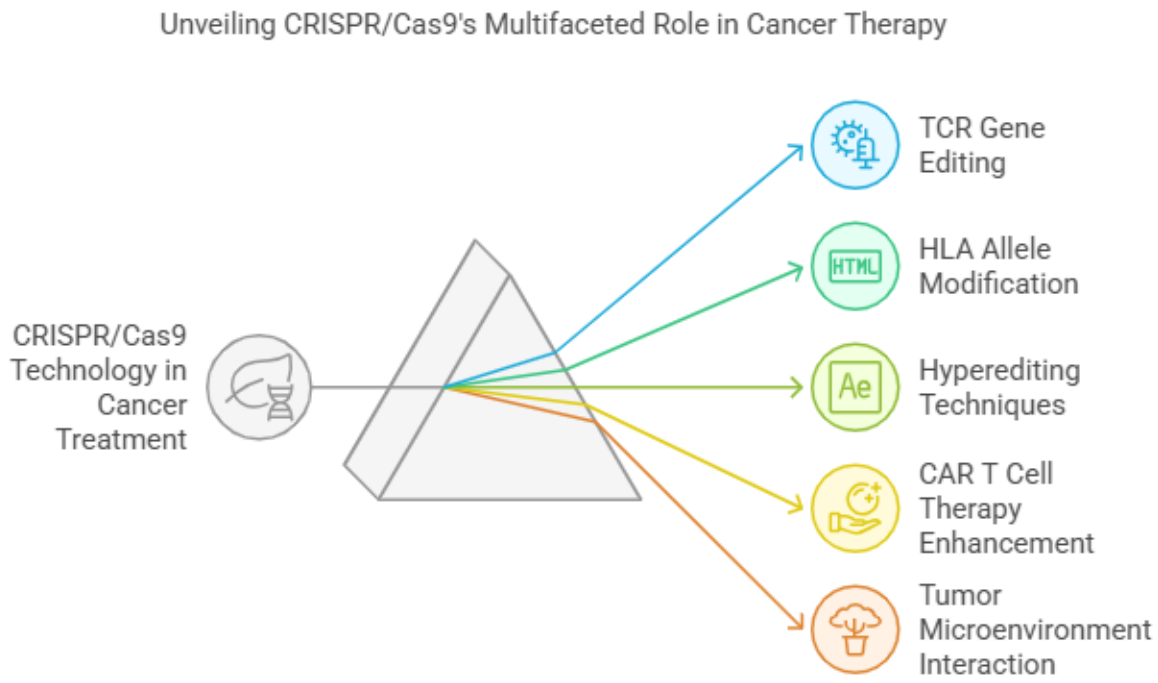

Figure 3: Unveiling CRISPR/Cas9's Multifaceted role in cancer therapy

Regulatory Considerations for TCR-Derived Therapy

T cells have the highest cytolytic ability but have limited cell proliferation. T cells suffer a limited lifespan and play a strong immune role for a short time. Our T cell receptor-derived therapy allows large quantities of high-affinity TCRs to be expressed by APCs to prime T cells so that effector T cells can home to a specific lesion site, proliferate, and verify specificity and activity. It induces stronger anti-tumor responses. It takes advantage of the ability of T cells, allows T cells to recognize a broader range of target antigens, controls T cells in the lesion to secrete more cytokines,

and can reach other long-acting effects to improve the efficacy of our tumor (18). Our new research provides the rules and strategies for TCR-derived therapy. Optimal therapeutic responses require both targeted in vivo T cell priming and efficient effector T cell trafficking to the site of action. Currently utilized TCRs can weakly mobilize CD8+ T cell effector function and must be further engineered to match the activity of directly transduced CD8+ T cells. Each engineered MAPC was capable of eliciting secondary T cell activation with a different unexpected peptide. The catalytically impaired D227A Mapk13 mutant was selected to modulate TCR affinity due to its efficient bypass of negative selection in the thymus (19).

FDA Guidelines

In the USA, new cellular therapies that focus on modifying a patient's own immune cells have already been practiced. The development and dissemination of new cellular therapies are made following the guidelines issued by the relevant regulatory authorities. Some of these therapies have been approved as rapidly as they have shown evidence of suitable safety and efficacy in controlled clinical trials (20). According to requirements, therapeutic clinical trials should be designed to demonstrate the effectiveness of the new therapeutic agent via reliable, substantial, and marked improvements in objective parameters such as extension of survival or demonstration of improvement in laboratory biomarkers to predict the clinical benefit (21). The development and dissemination of TCR-based antitumor T cell therapies are in their infancy in comparison with CAR T-cell therapies, and additional data that show effectiveness and increased safety and that enroll more subjects are needed. Special care should be given to avoid off-target responses. Moreover, a reliable strategy should be developed to control the potential toxicities and to establish safety during the initial stages of clinical development, with finite duration and degree to prevent severe, long-term, and unpredictable toxic responses (22).

Clinical Trials and Case Studies

Our case studies provide proof-of-principle evidence of CR-patient host interactions and may impact future strategy and rules for TCR-based therapy. First, submit all proposed CR mouse and human TCR sequences to bioinformatic analysis to anticipate off-target potential both in clinical and commercial applications, ensuring minimally off-target, safe, and feasible drug production (23). Bioinformatic methods have been developed that can be used to reveal and confirm the possibility for TCRs to target TAs in all individuals in advance. Exome sequencing can be used to accurately identify the predicted high-affinity target of the TRBC1 and TRBC2 gene-TAs and to present these defined antigens with defined antigen presentation capacities. Then, TCR modification to the normal human T cells for testing is feasible based on patient-specific TCR antigen biometric analysis, allowing for the exploration of the expansion and modification of normal human T cells (24). In clinical trials, three key factors are: the first factor is the level of expression of the soluble tumor-associated gene cassette, which represents the cancer type; the second factor is that the differentiated normal host tissue does not co-express a similar level of adjacent protein. If a similar gene expression is observed, the tissue may be a target for TCR-related toxicity and a no-go option (25). Third, the pre-therapy TCR-TA epitope should be in the extracellular compartment before binding to the TCR-TA extracellular domain. This approach can reduce the release of multiple antigenic TAs and the potential for neutrophil-independent toxicity. Finally, we would suggest an alternate protocol when developing the therapeutic TCR-TA using an endo-shuffling method to package for rapid therapy. Implement ex-vivo gene therapy, and before depleting TCR-αβ in patients, intrapatient production of off-the-shelf axi-cel arrived. The TCR-γδ weaponry uses chemically programmed RMA clones or integrates into the host T cell

niche using a CAR-based strategy and the designed large-scale drug prodigious TCR-niche. What, indeed, is the safety to set? How can we overcome the toxicity on model 2 (26).

Success Stories

Human blood contains T lymphocytes expressing a diverse number of T cell receptor clonotypes exhibiting a broad range of affinities, capable of recognizing peptides associated with self or non-self major histocompatibility complex molecules. When the immune system mounts a physiological response toward malignant, infected, and transplanted cells, TCRs with the highest affinity and antipathogen/vaccine frequency expansion are detected, sometimes comprising almost 50% of the CD8+ T cell compartment. These T cells constitutively express higher levels of molecules associated with effector function, including cytolysis and cytokine production, and have been maintained by homeostatic control in the memory pool. These T cells are often detected within the tumor-infiltrating lymphocyte population. The association between TCR, T cell/HLA, and antigen has allowed the identification of the antigens recognized by TIL or other T lymphocytes infiltrating normal and neoplastic tissue (27). The first successes of TCR-derived therapy to treat viral infections and cancer were achieved with TIL. Tens of patients have experienced either dramatic clinical responses or transient decreases in disease burden after being treated with autologous TIL that were previously expanded in vitro and then infused, with minimal conditioning. Tumor regressions, and sometimes even the eradication of disseminated cancer, have been described after the transfer of TIL reactive towards various antigens inside HLA-A2 or other HLA molecules, downstream of progressive cancer metastases (28). The eradication of melanoma cell populations undergoing regression in situ was demonstrated after treatment. Multiple forms of progressive neoplastic disease responded to TIL, irrespective of human leukocyte antigen haplotype and mutational burden. The general rules indicate that TIL can cure patients affected by those types of cancer recognized by T cells before treatment. TIL derive from the invasive front of the tumor itself, are partially exhausted, and are still highly sensitive to MHC/TCR signaling. Tumor regression occurred mostly in patients who experienced prolonged in vivo persistence of the transferred TIL. In only a subgroup of cases, the clinical responses were mediated by TCR-engineered autologous T lymphocytes persisting and functionally active for extended periods of time after adoptive transfer (29). By definition, T-cell receptor-engineered T cells are defined as genetically modified TIL or peripheral blood-derived polyclonal or oligoclonal ex vivo expanded T cells. The TCR they express could be selected within high or low frequencies from a natural or phage display library or still engineered. The identification and validation of potent transgenic TCR products is rapidly evolving. A strategy to genetically modify T lymphocytes aimed at expressing high-affinity TCR T cells capable of recognizing peptides associated with non-self MHC proteins, in HLA-A or HLA-B-restricted and non-MHC-restricted fashion, has been developed. TCR-derived T cells have been tested in the human host in the setting of latent and persistent viral infections, cancer, autoimmune, and inherited disease. The in vivo persistence of TCR T cells has been demonstrated after adoptive transfer, in disseminated cancer and during hematopoietic engraftment. Data from ongoing randomized multicentric phase III trials testing leukemia and blood-related disorders addressed with TCR-derived T cell infusions will become available soon. Key technical developments addressed by TCR clinical translation were the lack of homogeneous and equally potent TCR technologies associated with broad antigen recognition and/or increasing clinical safety. Fundamental insights concerned the number of required transgenic T cells, their persistence, the recruitment of the autologous immune system, and immune memory. Whether TCRs could also help hematopoietic/allogeneic stem cell transplantation will be addressed (30).

Table 1: Emerging Strategies and Safety Considerations in T-Cell Receptor (TCR)-Derived Therapy for Cancer Treatment

Category	Description	Emerging Strategies	Safety Considerations	Clinical Implications
Combination Therapies	Enhance T cell efficacy	Neoantigen vaccines + checkpoint blockade, radiation/chemotherapy priming	Monitor for increased toxicity	Improved tumor targeting and immune response
Engineering Innovations	Improve T cell function	Chemokine receptor modification, chimeric switch receptors (CSR), cytokine support	Assess for off-target effects	Enhanced T cell persistence and tumor infiltration
TCR Libraries	Expand TCR availability	Healthy donor TCR libraries, scalable production	Validate specificity and cross-reactivity	Enables off-the-shelf therapies for diverse patients
Specificity Validation	Ensure TCR specificity	TCR fingerprinting, bioinformatic peptide prediction	Exclude patients with unintended HLA matches	Reduces risk of adverse reactions
Safety Pipeline	Standardize safety protocols	TCR fingerprinting, peptide validation, endogenous presentation testing	Implement rigorous screening processes	Protects against unforeseen toxicities
Clinical Guidelines	Optimize therapeutic outcomes	MHC restriction, tumor antigen selection	Tailor therapies to individual patient profiles	Maximizes efficacy while minimizing risks

Future Directions and Opportunities

After more than two decades of development, TCR-based strategies became varied and purposeful while uncovering new issues and problems. To exert influence over engineering T cells in cancer immunotherapeutic clinical practice, rather than blindly moving forward, it bears a greater responsibility to take potential risks into consideration by looking back at the past and facing the future. Chimeric antigen receptor gene-modified T cell therapy has attracted much attention and is changing the world of oncology, but TCR-derived techniques are also worth exploring in the field of cell engineering and therapeutic applications, especially with the understanding of how to achieve a better and safer way. It's crucial to address the practical problem of improving the cost-effectiveness and persistence of modified T cells, for example, by incorporating costimulatory molecules, modifying the TCR itself, or delivering sufficient lymphodepletion (31).

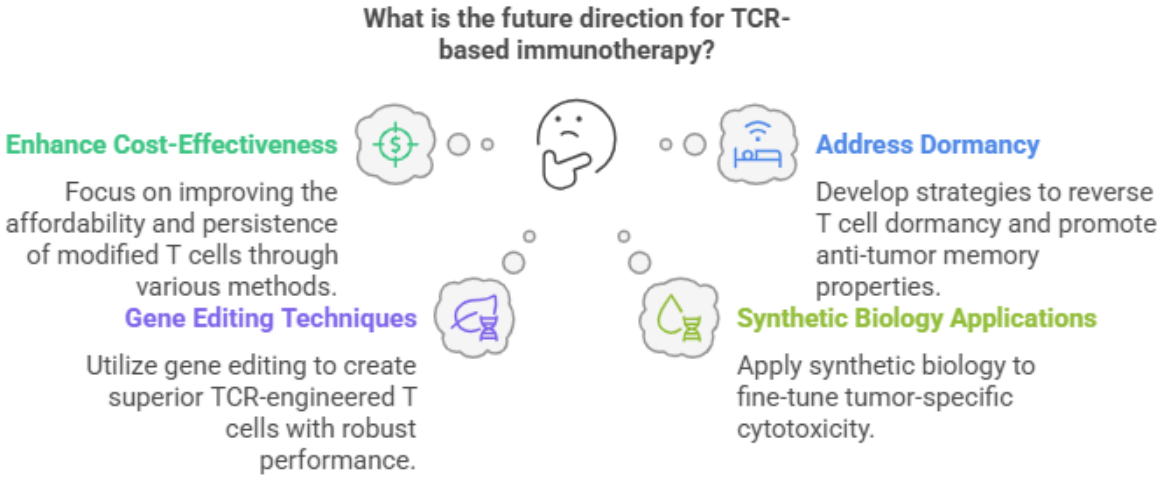

Figure 4: Future direction of TCR- based immunotherapy

These could be well understood and solved in future development. However, specific T cells entering into a dormant phase are always seen as obstacles that require dormancy-reversing interventions. Considering the potential long-term neurological toxic effects, what are feasible mechanisms or strategies for promoting the generation and expansion of TCM cells or generating other phenotypes with anti-tumor memory properties in adoptive T cell transfer? Should they be incorporated into the future direction of preclinical or clinical practices, together with designing safeguards? Gene editing techniques, including genome, epigenome, and chromatin reconfiguration, could ultimately answer the above questions and architect superior TCR-engineered T cells with robust performance and conforming safety. For riboregulation with enhanced safety and programmable gene expression, synthetic biology, which is an interdisciplinary field in which the principles of engineering are applied to biological systems, should return the supple and fine-tuning control over tumor-specific cytotoxicity, ultimately optimizing the therapeutic strategies. As a result, the limits of oncology in immunotherapies are gradually being overcome with the alacrity in development pace (32).

Conclusion

In short, T-cell receptor-based therapies are a potentially revolutionary technology in the field of cancer immunotherapy, particularly for use in solid tumors. By taking advantage of progress in antigen targeting, TCR engineering, and synergistic therapeutic strategies, these methods aim to bypass traditional hurdles like tumor heterogeneity and immunosuppressive microenvironments. Even with the existence of persisting challenges, ongoing progress in the optimization of TCR affinity, resistance mechanisms to tumor microenvironments, and safety considerations is making TCR-T therapies ready for clinical relevance. As the studies continue to enhance these methods, TCR-T therapies have the potential to provide durable responses and improved outcomes for patients with otherwise refractory cancers.

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