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Application and development of TCR-T in tumor therapy

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Abstract. As cancer has gradually become the world's deadliest long-term disease, the impact on the public health has been devastating. Especially the Melanoma which is a cancer with a very high malignant and a high fatality rate. With the emergence of adoptive cell therapy(ACT) based on T Cell Receptor-Gene Engineered T Cells (TCR-T), good results have been obtained in scientific research and clinical fields for a variety of malignant tumors. As TCR-T continues to enter the clinic, the FDA also has approved the first case of TCR-T in 2022, and more and more basic researches and clinical trial projects based on TCR-T are gradually being carried out. However, TCR-T therapy still has some defects, such as non-tumor tissue damage caused by off-target effect and insufficient affinity with tumor tissue. Therefore, the affinity and anti-tumor effectiveness of TCR-T should be improved in multiple aspects, and multi-field cooperation should be carried out to promote the development of basic research, a number of products should be introduced into the clinic, and the intervention of economic means to improve the accessibility of TCR-T. Not only brings the Gospel of cure to patients in the field of solid tumors, but also produces innovation in the field of non-solid tumors.

Keywords: T cell receptor-gene engineered T cells, adoptive cell therapy, tumor therapy.

1. Introduction

Cancer has gradually become the most lethal long-term disease in the world, especially the Melanoma which is a cancer with a very high malignant and a high fatality rate [1]. Resulting in the deepening of medical understanding of cancer and the limitations of traditional therapies for specific tumors, a variety of new treatment means have gradually emerged. For example, using pharmaceutical means to modify the drug delivery system and targeting the tumor site via parallel photothermal therapy. Furthermore, adoptive cell therapy(ACT),such as CAR-T and TCR-T , through cellular and molecular biology methods to tackle both non-solid tumors and solid tumors [2]. T cells from the patient's blood are cultured and modified in vitro to express artificial receptors for specific Tumor antigens, which directly recognize tumor antigens (TA) and do not involve Major Histocompatibility Complex (MHC). The emergence of cell therapies such as CAR-T have achieved clinical success, especially for Acute lymphoblastic leukemia (ALL). For specific tumor antigens, the development of new cell therapies, such as anti-CD19 CAR therapy, will be applied in the field of tumor therapy singly or combined with other technologies in the future, which will Lead to achieving' greater success and further development in the future.

Cell therapy is the use of specific cells which usually are immune cells. Modifying or engineering these cells to treat specific diseases that are difficult to tackle with conventional drugs or methods. In

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this article, the author bases on the investigation of several cutting-edge literature in the field of cell therapy, combined with the personal research experience. In the first part, the principle, development and clinical application of cell therapy are discussed. In the second part, the author compares unmarketed cell therapy products at different clinical stages with marketed cell therapy products through a specific clinical research database, analyzes the differences in safety and expected therapeutic effect, and finally performs a simple economic analysis to evaluate the problem of drug accessibility. In the end, based on the above content, the author puts forward insight into future improvement and the key research directions at the technical level. In addition, joint research should be carried out in combination with oncology, chemistry, physiology, physics and other disciplines to jointly build a new cell therapy with wider applicability under the background of multiple heterogeneity of the human body, and discuss its importance in personalized medicine.

2. Basic principles and development of cell therapy in tumor

2.1. Cell therapy Overview and technical principles

In terms of ACT for the treatment of tumors, the basic principle is to culture and transform immune cells in vitro, and then inject them back into the patient. Consequently, the improved immune cells will have higher targeting and therapeutic ability to the tumor, promoting the recovery expectation for some patients. Compared with lymphocytes in vivo, ACT not only improves the ability to target accurately, but also the number of lymphocytes transfused back into the patients also had an overwhelming advantage over the number of lymphocytes in the body. Mainstream cell therapy includes tumor infiltrating lymphocyte therapy (TIL), TCR-T and CAR-T therapy. This article mainly relates to TCR-T. TCR on T cells plays an important role in killing tumor cells. When the TCR on T cells recognizes the HLA antigen peptide complex on tumor cells, the intracellular immune receptor tyrosine activation motif (ITAM) will be phosphorylated [3], realizing intracellular signal transduction and transmitting specific signals to activate the killing of specific tumor cells. After four generations of technological innovation in TCR-T therapy, the latest TCR-T therapy not only has industrial production capacity [4] (obtained after the second TCR-T therapy technological innovation) and high affinity [5] (obtained after the third generation of technological innovation), but also has a high specificity for tumor antigens and a higher safety ability for patients [6] (obtained after the fourth generation of innovation).

There are two types of antigens targeted by TCR-T: tumor-specific antigens (TSA) and tumor-associated antigens (TAA). Although TCR-T can directly select any tumor antigen to target, it remains a challenge to select reliable and highly specific antigens ,ensuring therapy's effectiveness, avoiding off-target events, and the down-regulation of tumor autoantigens.

In order to solve such problems, we can first obtain the mutant neoantigens present in the tumor tissue by genomic sequencing even single cell sequencing of the patient's tumor tissue and cells, so as to improve the specificity of TCR-T and reduce the negative effects on other tissues. Secondly, different TSAs or TAAs can be added to multiple T cell clones to obtain T cell clones with different tumor gene targets.

Just as mentioned above, the theoretical basis of TCR-T is that TCR recognizes the HLA antigen peptide complex on the tumor to complete the binding and mutual recognition steps, so the affinity between TCR and HLA is a crucial point. The screening and adaptation of HLA and TCR on the tumor cells of specific cancer patients are now in clinical practice. If the affinity between TCR and HLA is too low, on the one hand, the killing effect of tumor and the recurrence after healing will be overshadowed, and there will be a potential threat to healthy tissues. However, when the affinity between TCR and HLA is too high, it may cause the overactivation of the immune system in the patient, causing the disorder of the immune system with the potential risk of causing cytokine storm.

2.2. Establishment of initial exploration, breakthrough and development milestone

In 2002, Yee et al. carried out ACT for melanoma patients, using the first-generation TCR-T treatment mode. In vitro, T cell clones extracted from patients are first stimulated with specific tumor antigens to

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produce TCR-T with high affinity to tumor antigens. This step is obtained through the participation of specific dendritic cells. After the Phase I clinical trial, the results show that TCR-T under this method has a good safety. Although the sample volume of patients was limited, the median survival was also increased from 4 months to 11 months, showing a good application prospect, but there was also a phenomenon of antigen loss, which became a potential obstacle in treatment.

In order to have a better application in the clinical field, how to improve the mass production capacity of TCR-T has become the key. In 2006, Rosenberg's group used a retrovirus to encode two polypeptide chains on a TCR with a potent anti-tumor MART-1. Transduction and response of the patient's primary lymphocytes are performed in vitro. The type of lymphocyte is transformed in this transduction, the immune capacity is significantly improved, and the transduction cells also have a strong proliferation ability, which solves the shortcomings of the original insufficient industrial production of TCR-T.

In the third major innovation of TCR-T, Rosenberg's team first proposed the influence of TCR affinity with tumor antigens on therapeutic efficacy in 2013, determined the TCR affinity threshold, and defined the optimal balance between effective antitumor activity and autoimmunity. A year later, in 2014, the team used a structure-based design to predict point mutations in TCR(DMF5) that enhance the binding affinity of TCR(DMF5) to the agonist tumor antigen Major histocompatibility complex (PMHC) MART-1 (27L)-HLA-A2, MART-1(27L)-HLA-A2 induces complete T cell activation to trigger an immune response, allowing the atomic detail contact interface of the TCR-pMHC complex to be used to predict mutations, thereby improving functional affinity without increased cross-reactivity.

In the fourth and most recent major technological revolution in TCR-T, researchers have used the concept and technology of targeting tumor neoantigens to improve the specificity and safety of treatment. A neoantigen is a polypeptide-human leukocyte antigen complex on the cell surface, in which the polypeptide component, the neopeptide, is the degradation product of the altered mutant protein. Neoantigens are expressed only in diseased tissues, are not suppressed by immune tolerance, and can induce specific anti-tumor responses by binding to TCR, so they are ideal therapeutic targets [7].

3. Current status and challenges of cell therapy in cancer

3.1. Approved tumor cell therapy products

As of May 2024, the only TCR-T therapy currently approved was the first product, Kimmtrak (tebentafusp-tebn, IMCgp100), which was approved by the FDA on January 25, 2022. For the treatment of adult patients with HLA-A*02:01 positive uveal melanoma (mUM). According to a search on clinicaltrail.gov, as of May 2024, there are currently two products in Phase III trials, both for previously untreated patients with advanced melanoma who are HLA-A*02:01 positive. The remaining products are concentrated in clinical phase II and clinical phase I, of which 107 clinical phase II products are currently under study, and 173 clinical phase I products. Tebentafusp is a bi-specific gp100 peptide-HLA-A *02:01 directed T cell receptor CD3 T cell binder. It consists of the fusion of the TCR-targeting domain or the TCR arm with the single chain variable fragment (scFv) anti-CD3 effect domain and the TCR arm binds to the HLA-A binding gp100 peptide on the surface of uveal melanoma cells.

3.2. Clinical application case analysis

This section analyzes Kimmtrak, the first TCR-T therapy approved by the FDA. The uveal melanoma treated by Kimmtrak is a rare ocular tumor in clinic. Surgical resection was the main treatment before Kimmtrak was listed, but the adverse events such as tumor recurrence and metastasis made the traditional treatment unsatisfactory and new treatment methods were urgently needed. Therefore, after the market on January 25, 2022, Kimmtrak was put into use in the patient group of unresectable or metastatic uveal melanoma, and in April of the same year, it was also approved by the relevant authorities of the European Union and put into clinical use [8].

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3.3. Evaluation of therapeutic effect and safety

Kimmtrak patients treated with tebentafusp showed better overall survival compared with pembrolizumab, ipilimumab or dacarbazine, based on data from the Phase III clinical trial.

In the first human study of the safety and efficacy of tebentafusp (IMCgp100-01), two partial responses were observed in patients with non-metastatic uveal melanoma (14%;n=14 evaluable), 8 patients (57%) achieved tumor control at ≥16 weeks. In patients with metastatic uveal melanoma (n=33 evaluable), two partial responses (6%) and six stable (18%) were observed, showing promising therapeutic potential.

IMCgp100-01 was consistent with the safety results of tebentafusp in both trials conducted simultaneously in the IMCgp100-102 (Phase 1 ARM) study. In both studies, the most common treatment-related adverse events (AEs) occurred in the skin or may have been mediated by cytokines. Common adverse events include rash, itching, dry skin, fever, hypotension, periorbital edema, fatigue, nausea, and chills. These adverse effects can be controlled with standard clinical interventions - intravenous fluids and corticosteroids are used to treat hypotension; Paracetamol and antihistamines are used to relieve skin toxicity and fever. Adverse reactions associated with treatment with tebentafusp usually develop within 2-12 hours after the end of infusion and usually resolve within 48-72 hours after onset, regardless of whether treatment is performed. These adverse reactions were also more common in the first three vaccinations, with side effects slowing down from the fourth vaccination.

3.4. Production cost and technical threshold

As more TCR-T therapies enter the research stage in clinical practice, the technical threshold of the current version is gradually decreasing with the maturity of TCR-T technology [9,10]. However, the production and family financial burden at the current level, as well as the iterative update of TCR-T technology in the future are all aspects worth improving and thinking about. CAR-T and TCR-T share significant market difficulties, such as Kite Pharma's Yescarta (Axicabtagene ciloleucel) priced at $373,000 per course, which is a huge financial burden for most families in the United States and other countries.

According to the disclosure and public data of relevant companies, the production cost of TCR-T products accounts for 80% of the current total price, so it is difficult to further reduce the price under the objective circumstances of existing productivity and production levels. Therefore, in the future, TCR-T related market prices can be reduced from the following aspects to improve the accessibility of products. The first is to reduce the production cost of the product, considering the change of auxiliary materials and the optimization of large-scale production process; Secondly, with the expansion of the market scale, the price will continue to decrease from the perspective of the development trend of economics. Finally, a certain amount of insurance compensation can be paid for this major disease from the perspective of social medical insurance and commercial medical insurance to improve the accessibility of drugs and products.

4. Future development trend and prospect

4.1. Direction of technological innovation and improvement

From the perspective of technological innovation and improvement direction, it is necessary to start with the existing problems and challenges of TCR-T. The main problem and challenge is that, as mentioned above, in order to improve the targeting and specificity of tumor sites, it is necessary to search for related molecules that are specifically highly expressed on the surface of tumor tissues compared to normal tissues. Therefore, it is necessary to search for highly specific molecules that have core functions and constitute core structures at tumor sites. In order to prevent the selective pressure of a single molecular target from weakening the effect on tumor killing ability, multi-molecular targeted polyclonal T cells should be constructed.

In TCR-T treatment, heterodimers formed from endogenous chains (alpha and beta) and exogenous chains (alpha and beta), receptors with new specificity, or non-functional complexes causes autoimmune

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response to treatment, leading to fatal destruction of hematopoietic cell banks. Additional disulfide bonds can be introduced through the TCR constant region, single-stranded TCR, and TCR/CD3 fusion products can be applied. Because the a/b and g/d chains of TCR do not match each other; For some patients with high tumor load or multi -tumor sites, the effective persistence of TCR-T in vivo needs to be improved, as well as their ability to expand [11].

Furthermore, considering the important relationship between the affinity of TCR structure and the anti-tumor activity described above. For example, selective modification of CDR3 region of TCR (alpha and beta) chains can improve selectivity and binding ability. Reduce the glycosylation level of TCR and improve the binding ability of TCR by deglycosylation. The transmembrane structure of TCR can also be modified, for example, the three transmembrane residues of the TCR a chain can be modified into hydrophobic amino acids, and the affinity can be enhanced through structural changes, thus enhancing the anti-tumor ability

4.2. Multidisciplinary cooperation and collaborative research

In order to improve the effectiveness, safety and accessibility of TCR-T, multidisciplinary cooperation is urgently needed to solve the problems encountered in TCR-T therapy.

In terms of effectiveness, the therapeutic effectiveness of TCR-T is affected by factors such as the structure of TCR itself, selectivity and affinity of interaction with other molecules. Therefore, it is necessary to further study and explain the relationship between TCR structure and function in the field of structural biology, so as to find the most suitable TCR structure for molecular affinity of different targets. In addition, oncology and molecular biology should discover other TAA or TSA in tumors. As mentioned above, cell types in tumor tissues of patients are not the same, so it is extremely important to identify and analyze the abundance of various tumor cell surface antigens and the difference in expression of this type of antigen from normal tissues. As well as the side effects and clinical efficacy and safety data for patients in the field of pharmacy and clinical medicine, further improvements should be made to the dosage form and the mode of administration. For example, the pharmaceutical modification of reinjected T cells can enhance the specific targeting of tumor sites, and the tumor eliminating and immune response ability can be enhanced by specific membrane protein modification. Finally, we should also collaborate with the field of pharmacoeconomics, medical insurance companies and large pharmaceutical companies to improve the product process which are based in the marketing price, improving the accessibility of drugs in patient groups, making drugs play a greater medical value, enhancing the vitality of the medical market, and empowering the renewal of the next generation of TCR-T cell therapy.

5. Conclusion

In this passage, the development history, mechanism of action, clinical application, future development trend and existing problems of TCR-T therapy are comprehensively discussed through literature research and market research methods. TCR-T technology was gradually born in 2002, after four changes, in the tumor specificity, mass production capacity has been greatly improved. As an emerging cell therapy technology, the mechanism of action of TCR-T at the molecular and cellular levels has been constantly updated in the scientific research community in recent years, which has played an important role in the transformation of TCR structure and the change of affinity after the transformation. However, due to certain deficiencies in the cognition of TCR structure on the surface of T cells and multiple tumor antigens on the surface of different tumor cells in the same tumor tissue in patients, the mechanism of action and optimization plan of TCR-T at some levels are still questionable. However, as more TCR-T projects have been put into clinical trials in recent years, more problems will be resolved and more clinical problems will be improved in the process of clinical trials and scientific research. At present, the main market problem is that the price of a single course of treatment is such high because of the high research and development cost and production cost in the early stage, which is difficult for patients and families to bear. This requires multi-party cooperation in the future in the scientific research community, the clinical community, and the market industry represented by pharmaceutical companies and insurance

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industries to explore a better future for the accessibility and sustainable innovation and development of TCR-T. In general, TCR-T has been a good way to cure solid tumors (such as melanoma), and the future treatment of non-solid tumors is also worth looking forward to. As an emerging cell therapy, when the price, effectiveness and safety steadily improve in the future, it will usher in a wide range of applications, and will continue to empower related fields.

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