Chimeric Antigen Receptor T (CAR-T) Cell Therapy for Malignant Tumors: Mechanistic Insights, Clinical Efficacy, and Emerging Optimization Strategies

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Abstract. CAR-T cell therapy has been proven to show favorable efficacy in various hematological malignancies, particularly in acute lymphoblastic leukemia, multiple myeloma, and myelodysplastic syndromes, with promising results also observed in chronic lymphocytic leukemia. Additionally, CAR-T cell therapy can be applied in the treatment of multiple diseases such as hematological tumors and solid tumors, independent of factors including tumor type, patient age, tumor stage, and treatment response. This article outlines the definition, development history, basic principles of CAR-T cell therapy, and its significance in tumor treatment. It further discusses in detail the structure and function of CAR-T cells, their preparation process, clinical applications, safety, and side effects. Finally, the prospects and future directions of CAR-T cell therapy are explored.

Keywords: Tumor Immunology; CAR-T Immunotherapy; Chimeric Antigen Receptor T Cells; Solid Tumors; Clinical Application.

1. Introduction

Globally, cancer poses an extremely severe challenge to human health. According to GLOBOCAN 2020 statistics, there were 19.29 million new cancer cases and 9.96 million cancer-related deaths worldwide in 2020. In China, 4.57 million new cancer cases were diagnosed that year, accounting for 23.7% of the global new cases[1]. Traditional tumor treatment methods mainly include physical or chemical approaches such as surgical resection, radiotherapy, and chemotherapy. Although these methods have achieved certain efficacy, they have limitations such as significant side effects, easy development of drug resistance, and risks of tumor recurrence and metastasis during treatment, which greatly hinder the complete cure of tumors. In recent years, with the rapid development of immunology and molecular biology, tumor immunotherapy, as an emerging treatment modality, has demonstrated tremendous potential and unique advantages. In particular, chimeric antigen receptor T cell (CAR-T) therapy, which modifies patients' T cells through genetic engineering to specifically recognize and kill tumor cells, has brought revolutionary changes to cancer treatment[2].

Since its first proposal in 1989[3], CAR-T cell therapy has evolved over decades into a crucial branch in the field of hematological tumor treatment. In 2017, the U.S. Food and Drug Administration (FDA) approved two CAR-T cell therapy products[4,5]—for the treatment of acute lymphoblastic leukemia (ALL) and certain types of non-Hodgkin lymphoma (NHL), respectively, marking the official entry of CAR-T cell therapy into clinical application[8]. The successful application of this technology not only provides new treatment options for patients but also brings new research directions and challenges to the field of tumor treatment.

However, CAR-T cell therapy is still in the developmental stage, and issues such as its application in solid tumor treatment, durability of efficacy, and safety remain research hotspots[9]. This article aims to outline the basic principles, preparation process, clinical applications, safety, and side effects of CAR-T cell therapy, and explore its prospects and future directions, in order to provide references for research and clinical applications in this field.

2. Mechanism of Tumor Immunotherapy

Theoretically, the immune system possesses the inherent capability to recognize and eliminate abnormal cells; however, its surveillance efficacy proves insufficient to completely prevent the progression of malignant tumors. As these tumors develop, their malignancy progressively increases over time, ultimately leading to widespread metastasis and dissemination. According to the "cancer immunoediting" theory proposed by tumor biologist R.D. Schreiber, the dynamic interaction between the immune system and tumors occurs in three distinct phases: elimination, equilibrium, and escape. During the escape phase, tumor cells acquire various malignant characteristics, including the loss or downregulation of major histocompatibility complex (MHC) molecule expression, which diminishes the presentation of tumor antigen peptides and impairs immune cell recognition and killing. Simultaneously, mutations in tumor cell apoptotic signaling pathways hinder efficient immune-mediated induction of programmed cell death. Furthermore, tumors actively create an immunosuppressive microenvironment by expressing immune checkpoint molecules like programmed cell death ligand 1 (PD-L1) and releasing immunosuppressive factors such as indoleamine 2,3-dioxygenase (IDO-1); these mechanisms collectively suppress immune cell activity and promote immune tolerance towards the tumor [6].

3. Fundamental Principles of CAR-T Cell Therapy

CAR-T cell therapy represents a paradigm shift in cancer treatment, harnessing genetic engineering to transform a patient's own immune cells into precision-guided weapons against cancer. This approach involves extracting T lymphocytes from the patient's bloodstream through leukapheresis and genetically modifying them ex vivo to express synthetic chimeric antigen receptors (CARs). The CAR functions as an artificial recognition system, typically constructed from an extracellular antibody-derived single-chain variable fragment (scFv) that binds specific tumor antigens, connected via a flexible hinge region to transmembrane and intracellular signaling domains. This molecular architecture enables engineered T cells to bypass natural T-cell receptor limitations by directly recognizing surface antigens independent of MHC presentation. Following genetic modification using viral vectors or electroporation-based techniques, the reprogrammed cells undergo extensive laboratory expansion before being reinfused into the patient. The revolutionary power of this technology lies in its ability to create "living drugs" that combine antibody-like targeting specificity with the cytotoxic potency and potential longevity of activated T lymphocytes [7].

3.1 CAR-T Cell Manufacturing Process

The production of clinical-grade CAR-T cells constitutes a complex, multi-week endeavor requiring sophisticated infrastructure and stringent quality controls. Beginning with leukapheresis to isolate peripheral blood mononuclear cells, T lymphocytes are selectively activated and genetically reprogrammed using lentiviral or retroviral vectors that integrate the CAR construct into the cellular genome. Alternative non-viral methods including transposon systems and mRNA electroporation offer faster but often transient expression. Following successful transduction, cells undergo bioreactor expansion in media supplemented with cytokines like IL-2 and IL-15 to achieve therapeutic quantities numbering in the billions. This critical expansion phase typically spans 7-14 days while maintaining strict aseptic conditions. Before release, the cellular product undergoes comprehensive testing for sterility, viability, potency, and vector safety. The final cryopreserved product is administered after patients receive lymphodepleting chemotherapy, which enhances CAR-T cell engraftment by creating immunological space and reducing regulatory cell populations.

3.2 Mechanism of Action of CAR-T Cells

Upon reinfusion, CAR-T cells initiate a multi-phase assault against malignancies through sophisticated biological mechanisms. Engineered cells first navigate the vasculature and lymphatic system, homing to tumor sites guided by chemokine gradients where they scan for target antigens.

When the scFv domain engages its cognate antigen, receptor clustering triggers intracellular phosphorylation cascades that activate cytotoxic programs. This antigen recognition induces formation of immunological synapses through which CAR-T cells deliver lethal payloads including perforin and granzyme B that perforate target membranes and initiate caspase-mediated apoptosis. Simultaneously, activated CAR-T cells secrete inflammatory cytokines such as IFN-γ and TNF-α that recruit innate immune effectors like macrophages and natural killer cells, amplifying the anti-tumor response beyond direct killing. A critical advantage lies in the persistence of memory T cell subsets that provide long-term surveillance, with some patients maintaining functional CAR-T populations years after infusion, correlating with durable remissions.

4. Clinical Applications of CAR-T Cell Therapy

4.1 Hematological Malignancies: Transformative Outcomes

CAR-T therapy has fundamentally reshaped the treatment landscape for relapsed/refractory hematologic cancers, achieving unprecedented efficacy where conventional therapies fail. In pediatric and young adult B-cell acute lymphoblastic leukemia (ALL), CD19-directed CAR-T constructs like tisagenlecleucel demonstrate sustained complete response rates of 81-93% in pivotal trials, with over 50% of responders maintaining remission beyond 5 years. The landmark case of Emily Whitehead—treated in 2012 and now leukemia-free for over 11 years—epitomizes this durable clinical benefit. For aggressive B-cell lymphomas including diffuse large B-cell lymphoma (DLBCL), axicabtagene ciloleucel and lisocabtagene maraleucel achieve complete responses in 40-58% of patients with median overall survival exceeding 25 months, establishing CAR-T as standard third-line therapy per NCCN guidelines. The recent ZUMA-7 trial further demonstrated superiority over salvage chemotherapy in second-line DLBCL, doubling event-free survival. In multiple myeloma, BCMA-targeted CAR-Ts such as ciltacabtagene autoleucel induce 98% overall response rates and 83% stringent complete responses in heavily pretreated patients, with median progression-free survival surpassing 34 months—a 3-fold improvement over historical standards. Emerging data for CD22 CAR-T in ALL and CD30 CAR-T in Hodgkin lymphoma continue to expand therapeutic options for multi-refractory patients.

4.2 Solid Tumors: Overcoming Biological Barriers

Despite formidable challenges posed by the tumor microenvironment, CAR-T development for solid malignancies shows accelerating momentum. In neuroblastoma, GD2-targeted CAR-Ts (NCT03294954) achieved 63% objective response rate in phase I trials, with complete resolution of bone marrow disease in pediatric patients. Mesothelin-redirected constructs demonstrate 42% disease control rate in pleural mesothelioma, while intrapleural delivery enhances local efficacy. Prostate cancer trials with PSMA CAR-Ts reveal decreased PSA levels in 50% of castration-resistant patients, particularly when combined with androgen receptor blockade. Novel approaches targeting tumor stroma include FAP-specific CAR-Ts reducing cancer-associated fibroblasts in pancreatic adenocarcinoma models, and Claudin 18.2 CAR-Ts showing 48% partial response rate in gastric/gastroesophageal junction cancers. Critical innovations addressing barriers include regional delivery via intraperitoneal/intrathecal infusion for ovarian/primary brain tumors, hypoxia-resistant CAR-Ts expressing catalase for pancreatic cancer, and "armored" CARs secreting IL-12 to counteract immunosuppressive cytokines. Ongoing trials targeting EGFRvIII in glioblastoma, GPC3 in hepatocellular carcinoma, and HER2 in sarcoma continue to refine strategies against antigen heterogeneity and T-cell exhaustion.

5. Advantages and Limitations of CAR-T Cell Therapy

CAR-T therapy offers transformative advantages including MHC-independent tumor recognition that overcomes a key immune evasion mechanism and enables targeting of non-protein antigens. The

technology generates "living drugs" capable of in vivo expansion and long-term persistence that provide ongoing immunosurveillance, potentially curing previously terminal malignancies with single treatments. However, significant limitations constrain broader application. Solid tumors present formidable obstacles through dense physical barriers, immunosuppressive microenvironments rich in TGF-β and adenosine, and antigen heterogeneity facilitating immune escape. Target selection remains particularly challenging due to frequent shared expression of tumor-associated antigens on healthy tissues, risking severe on-target/off-tumor toxicities as evidenced by fatal pulmonary events during early HER2-directed trials. Treatment-related toxicities including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome require sophisticated monitoring and rapid intervention protocols. Furthermore, complex autologous manufacturing results in production costs exceeding $400,000 and treatment delays of several weeks, creating accessibility challenges particularly in resource-limited settings.

6. Future Directions in CAR-T Cell Therapy

Next-generation developments focus on enhancing specificity, persistence, and accessibility through multifaceted innovation. Structural refinements incorporate additional co-stimulatory domains like ICOS and novel hinge regions to optimize signal strength and cellular fitness, while armored CAR designs enable local secretion of immunomodulatory cytokines to counteract suppressive microenvironments. Sophisticated logic-gated systems requiring dual antigen recognition ("AND" gates) or incorporating inhibitory receptors against healthy tissue antigens ("NOT" gates) aim to improve safety profiles. The emergence of CRISPR-engineered allogeneic products from healthy donors promises "off-the-shelf" accessibility through elimination of endogenous TCR and HLA molecules, though current challenges with cell persistence require resolution. Combination strategies synergizing with checkpoint inhibitors, radiation therapy, or small molecule targeted agents demonstrate potential to overcome resistance mechanisms. Manufacturing innovations including automated closed systems and in vivo CAR delivery platforms using nanoparticle formulations could dramatically reduce production timelines and costs. These converging advances position CAR-T therapy to expand beyond hematologic indications toward broader oncological applications while improving safety and accessibility paradigms.

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