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CAR T-CELL IMMUNOTHERAPY: A NEW FRONTIER IN CANCER TREATMENT

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ABSTRACT

Cancer remains the leading cause of death globally, accounting for one in every six deaths. Traditional cancer treatments include chemotherapy, radiation therapy, and targeted therapies, each with distinct advantages and limitations. Recent advancements in understanding cancer pathways have led to improved combination therapies that synergize various targeted treatments, including conventional chemotherapeutics such as taxanes and platinum compounds. Despite these advancements, novel strategies involving immune-mediated therapies, biological agents, and new drugs have yet to significantly reduce mortality rates or extend survival for patients with metastatic cancer. One promising innovation in this field is Chimeric Antigen Receptor (CAR) T-cell therapy, a type of personalized immunotherapy often described as a "living" drug with the potential to cure cancer. CAR T-cells are T cells genetically engineered to express chimeric antigen receptors that specifically target and destroy cancer cells expressing certain antigens. Over five generations of evolution, advancements in CAR structure-including the ectodomain, transmembrane domain, and endodomain-have led to the development of new therapeutic options. This therapy has achieved significant long-term success in treating blood cancers, revolutionizing the treatment of lymphoma, leukemia, and multiple myeloma. While CAR-T therapy has shown notable success, its application to solid tumors is still under investigation. Overall, CAR-T

cell therapy represents a significant advancement in cancer treatment, with ongoing research aimed at improving its efficacy and expanding its applicability to a broader range of cancers.

INTRODUCTION

In 2020, cancer was the leading cause of death globally, responsible for about 10 million fatalities, or nearly one-sixth of all deaths. The most common cancers include breast, lung, prostate and colorectal cancers. Approximately one-third of cancer cases are linked to lifestyle factors such as smoking, obesity, excessive alcohol consumption, poor diet, and lack of exercise. Cancers like cervical cancer are brought on by the human papillomavirus (HPV) account for around 30% of cancer incidences in low- and middle-income nations. Over time, cancer therapy has changed dramatically, with different strategies being used depending on the patient's overall health as well as the type, stage, and location of the cancer. A broad and conventional targeted treatment is appropriate for a variety of malignancies, including solid tumors and blood cancers. It is commonly used in conjunction with other treatments, and they often cause significant side effects due to their lack of selectivity. Additionally, cancer cells can develop resistance to these treatments over time, which can limit their long-term effectiveness. On the other hand, targeted therapy targets the precise biochemical pathways that are necessary for cancer cells to survive. It is more precise and generally associated with fewer side effects, however resistance can still develop, and it can only be used to tumors that express the targeted targets.[1]

Another popular treatment that works well for treating localized cancers is radiation therapy, which is frequently combined with chemotherapy or surgery. Nevertheless, it is less efficient against metastatic illness and can harm neighbouring healthy tissues.[2] Checkpoint inhibitors are an example of immunotherapy strategy that has demonstrated the potential for long-lasting responses against a variety of malignancies; however, not all patients respond well to these treatments and they come with an autoimmune reaction risk. CAR T-cell therapy shows great promise for cancer treatment, but it faces several challenges that need to be addressed before it can be more widely and effectively used. Cancer develops when the immune system's ability to remove toxins surpassed the rate of cell development. High rates of DNA and RNA mutation can be caused by a combination of environmental factors, genetic predispositions, and radioactive exposure. Most people with localized cancer eventually develop metastases, and successful systemic therapy remains uncommon. The effectiveness of checkpoint inhibitor-based immunotherapy is often limited by the immunosuppressive

nature of the tumor microenvironment (TME) and the lack of neoantigens, despite its novelty and potential for treating various malignancies.[3] Chimeric antigen receptor (CAR)-T cells are immune cells engineered to mount cytotoxic responses against tumor-associated antigens (TAAs) expressed on cancerous cells. In contrast to conventional T cell receptors (TCRs), CARs do not require the major histocompatibility complex (MHC) in order to identify tumor antigens.[4] The fourth generation of CARs, referred to as TRUCKs or armored CARs[4], secretes inflammatory cytokines including IL-12 and IL-15. The first generation of CARs featured a CD3 signaling domain. There are presently two authorized CD19-specific CAR-T cells for B cell malignancies. Numerous studies have demonstrated that CAR-T cells effectively target cancer stem cells (CSCs) through their ability to recognize and attach to TAAs.[4] Side effects, such as cytokine release syndrome and neurotoxicity, as well as difficulties in applying the therapy to solid tumors, are areas of active research. Despite these challenges, CAR T-cell therapy remains a promising frontier in cancer treatment, offering hope for more effective and personalized cancer care.

Structure of Chimeric Antigen Receptor

The ectodomain, transmembrane domain, and endodomain are the three main domains that make up chimeric antigen receptors (CARs) (Fig.1). The signal peptide, antigen recognition region, and spacer are the three crucial parts of the ectodomain, or the part of the CAR that interacts with the extracellular environment outside of the cell.[5] During synthesis, this section guides the developing CAR protein into the endoplasmic reticulum. This function is usually performed by a single-chain variable fragment (scFv) in CARs. The immunoglobulin heavy and light chains' variable regions are joined by a flexible linker to form the single-chain variable fragment, or scFv. An scFv, which is the antigen recognition domain, binds highly affinity and precisely to a target antigen. Although the most widely used version of this domain is the scFv, other recognition molecules could also be employed if they are able to bind the target antigen. The transmembrane domain and the antigen recognition domain are connected by the spacer. The IgG1 hinge region functions as the spacer in many scFv-based CAR designs, offering sufficient flexibility and the required separation between the antigen recognition domain and the cell membrane.[5] The CAR can traverse the lipid bilayer because the transmembrane domain keeps it attached to the cell membrane. It has an alpha helix that is hydrophobic and embeds in the membrane. The transmembrane domain that is chosen has a major influence on the stability of the CAR. As an example, the native CD3-zeta transmembrane domain may cause the artificial CAR to integrate into the native TCR

complex, whereas the CD28 transmembrane domain is frequently selected due to its stability.[6] An essential function of the endodomain, which is housed inside the cell, is to deliver activation signals to the T cell. Within the endodomain, the CD3ζ chain is a common element that harbors three immunoreceptor tyrosine-based activation motifs (ITAMs).[3,6] The CAR receptors clump together in response to antigen binding, starting a signaling cascade that stimulates the T cell. Furthermore, the endodomain may contain co-stimulatory signaling domains to improve CAR T cell activation and function.

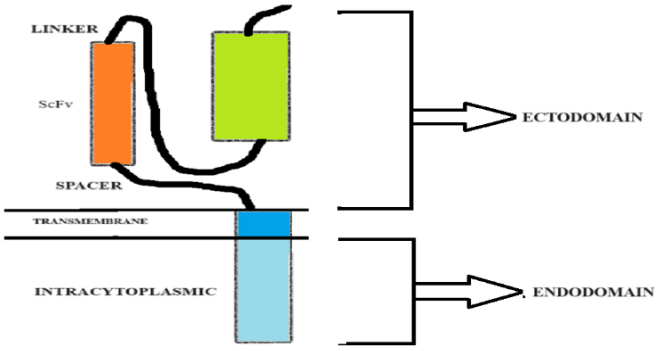

Fig.1: Domains of CAR-T cells.

Engineering of CAR T- cells for therapy

Leukapheresis, the first step of the procedure, involves taking a patient's blood, separating the leukocytes, and then putting the remaining blood back into the patient. Following thecollection of a sufficient quantity of leukocytes, the leukapheresis output is concentrated for T cells. This entails washing the cells to get rid of the anticoagulant-containing leukapheresis buffer. Next, the lymphocytes are enriched using a process called counterflow centrifugal elutriation, which maintains the survival of the cells while separating them according to size and density. Furthermore, T cell subsets can be distinguished based on the ratio of CD4 to CD8 by employing certain antibody bead conjugates or markers. Recuperated T cells must be able to respond to stimuli, successfully complete transduction (which includes integration, reverse transcription, and vector entrance), and perform as intended when they are refused. The age of the patient, the underlying condition, and the use of lymphotoxin drugs prior to therapy all have a substantial impact on the makeup of autologous beginning material from cancer patients.[6] For instance, memory T-cell concentrations decrease with each round of standard treatment for patients with non-Hodgkin lymphoma and ALL, which may result in a failure in the production or activity of CAR T cells. It is still difficult to predict a patient's immunophenotype or T-cell yield prior to collection. Cell quantity and

quality might potentially be affected by the cryopreservation of the apheresis product after collection.[7] Comparing frozen and thawed peripheral blood mononuclear cells (PBMC) to fresh apheresis products revealed that recovery and viability of PBMC were much lower. This was discovered by Panch and colleagues. However, the post-thaw recovery of mononuclear cells was sufficient for reliable CAR T cell production with negligible variations. However, post-thaw recovery of mononuclear cells was sufficient for reliable CAR T cell production, with no appreciable variations in subset composition, growth, or transduction effectiveness.

Freezing may also preferentially deplete immune cells including neutrophils and myeloid-derived suppressor cells (MDSCs) that inhibit T-cell proliferation in vivo. On the other hand, fresh products have logistical challenges such as a limited window of opportunity for generating CAR T cells, the requirement to schedule collections according to patient condition, and the scarcity of apheresis and manufacturing slots.[6] It can be detrimental to T-cell activation and expansion to have specific cellular subsets present at the beginning of the culture.[7] For example, MDSCs and monocytes can prevent ex vivo T-cell activation and proliferation. Red blood cells and granulocytes are examples of other pollutants that can inhibit T-cell growth. However, after thawing, the mononuclear cell recovery was sufficient for reliable CAR T cell production, with no appreciable variations in subset composition, growth, or transduction efficiency. Additionally, certain cell types, such as neutrophils and myeloid-derived suppressor cells (MDSCs), that inhibit ex vivo T-cell proliferation may be preferentially depleted by freezing.[7]

The term "domain" also refers to T lymphocytes that have been altered by the addition of extracellular antibodies such as single chain variable fragments (scFv), or CAR-T cells (chimeric antigen receptor). The intracellular signaling domain and the transmembrane domain are the domains. There are four generations in the genetically modified domain, and each generation has improved anti-cancerous properties.[8] There is only one intracellular domain, CD3, in the first generation; no costimulatory domains are present. To increase the anticancer activity, interleukin must be applied separately since this type of CAR-T cell cannot manufacture interleukin (IL-2) However, in the second and third cases, the effectiveness and durability of CAR-T cells are increased through genetic engineering with one or more intracellular signaling domains.[9]

The fourth generation of CAR-T cells, also referred to as TRUCK (T cell redirected for antigen-unrestricted cytokine-initiated killing), have an extra cassette coding for a transgenic

protein, which is released by lymphocytes that have undergone genetic engineering and modifies the anti-cancer response.[9] TRUCK CAR T-cells and other armored CAR T-cells are designed to release cytokines that alter the immunosuppressive milieu found in solid tumors. These modified CAR T-cells seek to augment the anti-cancer properties of both resident immune cells and CAR T-cells by inducing activation of the tumor microenvironment (TME) through manipulation of the cytokine milieu. A cytokine that is generated in response to infections by monocytes, macrophages, and dendritic cells is called IL-12. NK cells are activated by IL-12, which also enc ourages naïve T-cells to differentiate into immune-stimulating Th1 cells rather than immunosuppressive Th2 cells. Through the induction of a persistent immune response and immunological memory against cancer antigens, studies have demonstrated that CAR T-cells modified to release IL-12 can considerably improve anti-tumor efficacy when compared to regular CAR T-cells, both in laboratory trials and animal models. On the other hand, systemic IL-12 administration at therapeutic dosages has been linked to serious toxicities, including in some cases mortality.[10] Researchers have created CAR T-cells that only release IL-12 when they come into contact with the tumor, limiting its effects to the tumor site and possibly lowering these hazards. This strategy produces antigen-independent anti-tumor effects by activating immune cells like macrophages and enhancing CAR T-cell cytotoxicity against malignancies.[11] Analogous approaches have been investigated concerning IL-18, an additional cytokine that stimulates Th1 and NK cells without causing appreciable systemic damage as shown in experimental investigations. In preclinical models, CAR T-cells modified to release IL-18 have demonstrated enhanced tumor suppression and extended longevity, indicating that it could be a more secure and potent substitute for IL-12. The potential of IL-15 and IL-7 to improve CAR T-cell activity in solid tumors is also being studied. While IL-7, in contrast to IL-2, enhances CAR T-cell survival and activity without aggravating the immunosuppressive effects induced by Tregs, IL-15 encourages the proliferation and cytotoxicity of CD8+ T-cells and NK cells.[11] (Fig.2).

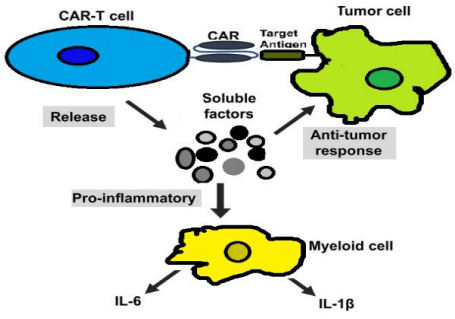

Fig.2: Mechanism of CAR-T cells.

Challenges in CAR T cell therapy

Regulatory channels known as immunological checkpoints stop the immune system from attacking healthy cells. They serve as the brakes that regulate immunological responses and preserve tolerance. T cells and NK cells are the primary, though not exclusive, locations of ICs, which are cell-surface proteins. They may play a beneficial or detrimental role in lymphocyte recruitment depending on whether the right ligands are found on target cells or APCs. ICs can strengthen stimulatory or inhibitory signals by facilitating interactions between ligands and the receptors that correspond to them on the effector and target cells. In order to maintain immunological homeostasis and avoid autoimmunity, ICs are crucial.[12,13] Via interactions between immune receptors and ligands, also referred to as immune checkpoints, T cells receive immunological signals that are either costimulatory or inhibitory. The primary costimulatory immune checkpoints are CD80, CD86 ligands and CD28 receptor; CD70 ligand and CD27 receptor; OX40 ligand and OX40 receptor; CD137 or 41BB ligand and CD137 (4-1BB) receptor; ICOS ligand and ICOS receptors. These checkpoints also influence the signaling pathways and interactions between tumor and immune cells. VISTA, B7H3, B7H4 ligands/receptors, PD-L1/PD-L2/PD-1, CD80, CD86/CTLA-4, CD112/CD155/TIGIT, Gal-9/TIM3, and MHC-peptide/LAG-3/KIR are the primary inhibitory immunological checkpoints. Under normal circumstances, tumors exploit the checkpoint pathways to evade autoimmunity. The tumor infiltrating T cells' (TILs') interaction with its ligands, PD-L1 and PD-L2 (on tumor cells or APCs, resulting in decreased T cell proliferation and cytokine) on the surface of antigen-presenting cells and malignant cells, inhibits TIL potency checks the TILs' ability to proliferate in the tumor microenvironment. Immune checkpoint blockade, such as anti-PD-1 (such as pembrolizumab, nivolumab) and anti-PD-L1 (such as durvalumab, atezolizumab): inhibit cancers from evading the immune system by blocking the PD-1/PD-L1 interaction. /PD-L1 with anti-CTLA-4 (Ipilimumab, for example, Cytotoxic T-Lymphocyte Antigen 4): increases T cell activation and anti-tumor responses by blocking CTLA-4): stops checkpoint molecule-triggered fatigue, which has revolutionized the therapy of several forms of advanced solid malignancies.[19] It does this by inhibiting T cell activation by binding to CD80/CD86 on antigen-presenting cells (APCs). Consequently, the T cells are a potent weapon in the anti-tumor therapeutic arsenal. usually obtained from an antibody's single-chain variable fragment (scFv), which binds to a particular cancer antigen. The CAR is anchored to the T cell membrane by the transmembrane domain. Signaling Domain: Usually derived from CD3ζ, it activates T cells upon antigen identification. The signaling domain, which is frequently

formed from CD3ζ and co-stimulatory molecules like 4-1BB or CD28, activates T cells upon identification of antigen. Modern cancer immunotherapy has undergone a revolution thanks to PD1 findings.[14] Several drugs that target PD1, PD-L1, or CTLA-4 are frequently employed as immune checkpoint inhibitors (ICIs) to reduce immune system suppression and induce immunoablation in cancer cells that were previously extremely resistant to treatment.[18,19] New insights into the immunomodulatory properties of gut microbiota provide fresh perspectives on how to improve cancer immunotherapy. T-cell activation is a demanding process that is controlled by two signals: the first is produced when the T cell receptor (TCR) interacts with peptide/major histocompatibility complex (MHC); the second signal is produced when T cells' CD28 interacts with its ligand B7-1 (CD80)/B7-2. New insights into the immunomodulatory properties of gut microbiota provide fresh perspectives on how to improve cancer immunotherapy.[20,21] T-cell activation is a complex process that is controlled by two signals: the first is produced when the T cell receptor (TCR) interacts with peptide/major histocompatibility complex (MHC); the second signal is produced when T cells' CD28 interacts with its ligand B7-1 (CD80)/B7-2 (CD86) on antigen-presenting cells (APC), which stimulates T cells. T lymphocytes from individuals with hematologic malignancies have demonstrated aberrant phenotypic and compromised function in both peripheral blood and bone marrow.[15,16]

Targeted therapy of CAR-T cells

The single-chain variable fragment (scFv) of a monoclonal antibody, which serves as the extracellular domain for target recognition, is combined with signaling domains typically derived from the T-cell receptor complex to create CARs. T cells can be genetically engineered to express CAR molecules on their surface, enabling them to kill target cells upon antigen binding.[17,18] It has been demonstrated that CAR T cells' killing and proliferation are driven by the inclusion of a CD28 CD3-ζ signaling domain; however, adding a TNFα receptor-like costimulatory component, specifically 41BB, has enhanced their persistence in vivo. Based on the scFv of the TEM8 antibody L2, we developed second-generation (CD28.CD3-ζ) and third-generation (CD28.41BB.CD3-ζ) TEM8-specific CAR molecules, referred to as L2 2G and L2 3G, respectively. Primary human T cells from three healthy donors were transduced with L2 2G or L2 3G CAR transgenes, achieving similar transduction rates. While CAR T cell therapy has shown remarkable success against hematologic malignancies, applying this treatment to solid tumors has proven challenging. This difficulty has led to significant efforts to identify biomarkers for solid tumors, and

currently, 17 such biomarkers are being investigated in clinical trials. Mesothelin (MSLN), a glycoprotein present on the cell surface and in the serum of cancer patients as soluble MSLN-related peptide (SMRP), has emerged as a promising target for cancer immunotherapy, becoming the second most commonly targeted biomarker after CD19 [19,18,20]. MSLN expression in normal tissues is limited to mesothelial cells lining the pericardium, peritoneum, and pleura. For CAR-T therapy to minimize side effects associated with the destruction of healthy cells, it is crucial that target antigens are only found on the surface of cancer cells. Research has identified several effective antigens for CAR-T immunotherapy, including HER2, CEA, MUC1, EpCAM, CLDN 18.2, MSLN, NKG2D, and FOLR1. These modified T cells are engineered to recognize these antigens on tumor cells. The abbreviations for these antigens are as follows: HER2 (human epidermal growth factor receptor 2), CEA (carcinoembryonic antigen), MUC1 (mucin 1), EpCAM (epithelial cell adhesion molecule), CLDN 18.2 (claudin 18.2), MSLN (mesothelin), NKG2D (natural-killer receptor group 2, member D), and FOLR1 (folate receptor).[19] Cytotoxicity assays showed that L2 2G and 3G CAR T cells effectively targeted and eliminated triple-negative breast cancer (TNBC) cell lines, including Hs578T, MDA-MB-231, MDA-MB-436, and MDA-MB-468, as well as the human breast tumor endothelial line HC 6020 and murine tumor endothelial cell lines 2H11 and bEND.3. Importantly, TEM8-negative Raji cells were unaffected. Further analysis of cytokine release from CAR T cells in response to TNBC and tumor endothelial cell lines revealed that L2 3G CAR T cells produced significantly higher levels of IFNγ and IL2 in response to all four TNBC cell lines and 2H11 compared to L2 2G CAR T cells. In co-culture with bEND.3, only IFNγ levels were elevated in L2 3G cells, while L2 2G cells exclusively produced IL2 [20]. The modest expression of TEM8 in bEND.3 cells, combined with the lower activation threshold of L2 2G cells, may explain why L2 2G, but not L2 3G, cells were activated by bEND.3. Notably, NT T cells did not release any detectable cytokines.

Clinical utilization of CAR-T cell therapy

The CAR gene is introduced into T cells through genetic modification in the lab, allowing the T cells to identify and target particular tumor cells. A sufficient number of CAR-T cells can be generated for use in therapy by expanding and cultivating the transformed T cells *in vitro*. Patients may need to have treatment preparatory procedures including lymphodepletion and bridging therapy before receiving CAR-T cell therapy. The conditioning procedure needed for CAR-T cell therapy is lymphodepletion.[21] The therapy focusses to lower the patient's natural killer cells, macrophages, and normal T cells as well as to boost the CAR-T cells' ability to

survive and carry out their therapeutic function. The patient is given an intravenous infusion of CAR-T cells by the physician after the cells have grown to a suitable quantity and they are ready for therapy. Following CAR-T cell therapy, patients are continuously watched and monitored; this includes keeping an eye out for any negative responses, assessing the tumor's response, and tracking the activity and survival of CAR-T cells within the body. Notable application outcomes in hematological cancers have been attained by CAR-T cell treatment.[22] As an illustration, CAR-T cells made to target the CD19 antigen have been shown to have therapeutic effects by destroying CD19+ leukemia cells. CAR-T cell therapy has also demonstrated remarkable effectiveness in treating B-cell acute lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia, and relapsed/refractory B-cell non-Hodgkin's lymphoma (B-NHL). After receiving CAR-T cell therapy, approximately 40–60% of B-NHL patients experienced a durable remission and survived, while approximately 80–90% of B-ALL patients experienced a complete remission and survival.[23] Positive advancements have been accomplished despite several obstacles and restrictions in the investigation of CAR-T cell therapy's applicability to solid tumor treatment, as opposed to hematological cancers.[23] Target antigens on the cell surface of neuroblastoma cells, such as GD2, have been created and administered by CAR-T cells. Patients with high-risk and refractory neuroblastoma have showed some treatment success using CAR-T cells, according to preliminary results from clinical trials. Prostate-specific memory acid phosphatase-producing CAR-T cells have also shown some efficacy against prostate cancer, and clinical trials including CAR-T cell therapy for soft-tissue sarcoma have hinted at some potential.[23,24] Several obstacles must be overcome for CAR-T cell therapies to be effective in solid tumors, including antigenic variety, immune evasion because of the tumor microenvironment, and obtaining enough proliferation and infiltration.

CONCLUSION

CAR T-cell immunotherapy has revolutionized cancer treatment, particularly for blood cancers, by leveraging the immune system to target and eradicate cancer cells. Despite significant advancements in CAR T-cell therapy for hematologic malignancies, ongoing research aims to further optimize its specificity and effectiveness while reducing side effects. Additionally, efforts are underway to extend CAR T cell therapies to treat other cancers, including solid tumors, marking the beginning of a notable success story in cancer treatment by redirecting antitumor immunity. The clinical development of technologies that stimulate the immune system to target and eliminate cancer cells has become a central goal of

translational research, with ongoing studies focusing on the mechanisms that drive early and sustained immune responses against tumors. Although CAR T-cell therapy has demonstrated remarkable outcomes and is rapidly transforming the treatment of hematologic cancers, but challenges persist in enhancing survival rates and achieving long-lasting benefits. As the field progresses, CAR T-cell therapy holds the promise of revolutionizing cancer care and providing new hope for patients worldwide.

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