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Review Article

CAR-T cells: prospective genetic engineering approach to orchestrate solid tumor in lung cancer

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Abstract

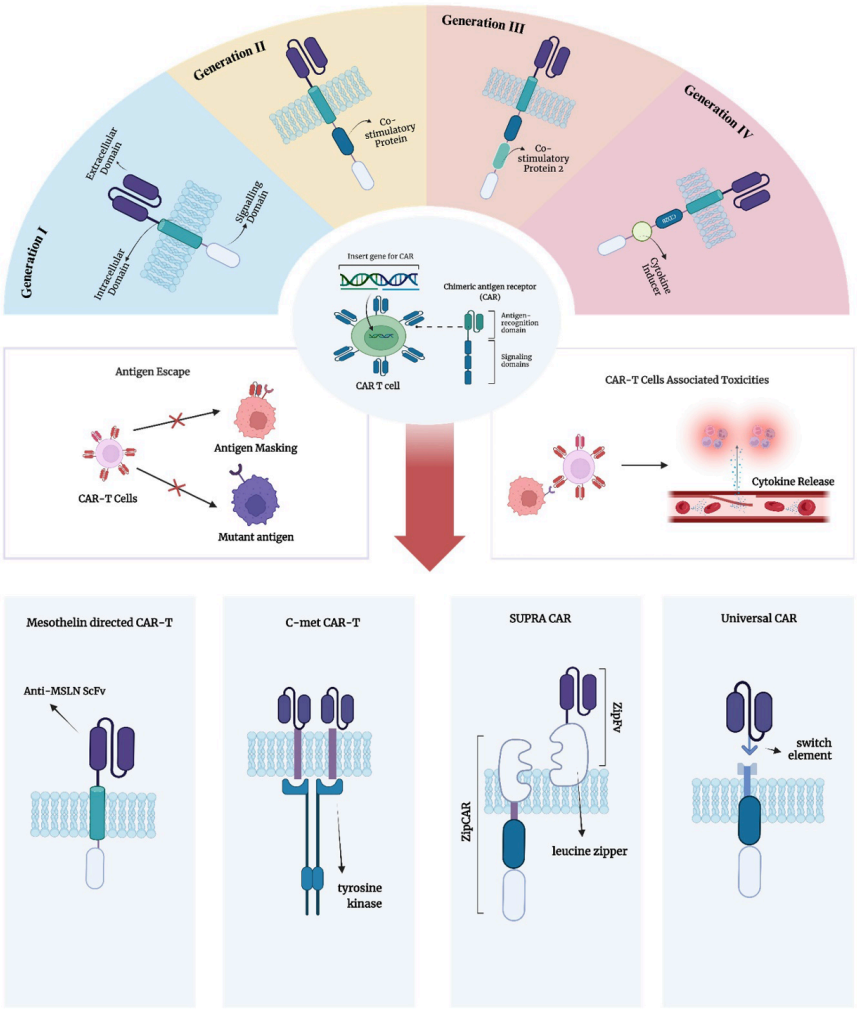
Introduction: Various strategies, starting with surgery, systemic radiation therapy with cytotoxic chemotherapy, and immunotherapy, have been carried out to address mortality from lung cancer. None of these therapies has showed remarkably successful treatments for lung cancer. Developing technology leads to innovation of cancer-targeted therapy as an ideal strategy. Chimeric antigen receptor T cells (CAR-T cells) are one of the novel immunotherapy approaches in genetic engineering. CAR-T therapy has showed promising results as the cancer-targeted therapy.

Methods: This review identifies relevant research by the keywords “Lung Cancer”, “CAR-T for Lung Cancer”, “CAR-T for solid tumor”, “CAR-T for SCLC” or “CAR-T for NSCLC”. The articles are extracted from Pubmed, Web of Science, Scopus, Science Direct, and Google Scholar. Data are shown based on discussions of the modification receptor, co-stimulator, and CAR-T cells.

Results: CAR-T acts to overcome lung cancer by targeting several receptors, such as mesothelin and c-Met. Several generations have also evolved to more specific and effective therapy. CAR-T modifications like BBIR, SUPRA CAR, and UIR have also been developed to minimize side effects.

Conclusion: CAR-T developments are not limited to CAR modification, but include its components and structure.

Graphical abstract



Keywords

cancer, lung cancer, solid tumor, chimeric antigen receptor, CAR-T modification, genetic engineering

Introduction

In 2020, the International Organization for Research on Cancer reported that around 19.3 million new cases of cancer were identified globally, leading to 10 million deaths (Sung et al. 2021). In addition, lung cancer ranks second among the 36 forms of cancer that have been recognized, with an incidence of 2.2 million cases (11.4%) in 2020 and 2.5 million cases (12.4%) in 2022, leading to 1.8 million deaths overall (18.7%) until 2022 (Bray et al. 2022; Li et al. 2023). Among other cancer varieties, lung cancer is suggested as the leading cause of mortality. Based on this finding, lung cancer is one of the non-communicable diseases that requires special attention as a serious global health problem.

Lung cancer is a progressive disease marked by abnormal alteration in healthy cells, resulting in unchecked growth and the potential for invasion and uncontrolled spread within the lung organ (metastasis) that enable tumor cells movement to a distant location and establishment a new cancer growth (Liu et al. 2012; Popper 2016). The survival rate for patients with lung cancer is an average of 7-17 months, varying according to their lung cancer type (Allemani et al. 2018; Soerjomataram et al. 2023). Numerous variables, including genetics, lifestyles, and environmental factors, contribute to the risk of lung cancer. Smoking, along with exposure to cigarette smoke (passive smoking), emerges as a risk factor for lung cancer development, with approximately 80-90% of cases being linked to smoking (Sung et al. 2021). According to survey findings, men are more likely than women to get lung cancer, with ratios of 1:16 and 1:17, respectively, for both smokers and non-smokers (Wolf et al. 2023). Moreover, exposure to ambient air pollution, dietary ingestion of heavy metal contaminants, and the consumption of alcoholic beverages are other variables that raise the risk of lung cancer (Sung et al. 2021).

Different treatment approaches are now undergoing significant improvements and are continuously evolving. These include surgery, systemic radiation therapy coupled with cytotoxic chemotherapy, and immunotherapy (Debela et al. 2019). Surgical intervention is usually advised for patients with early-stage NSCLC (Non-small Cell Lung Cancer); however, because about 70% of NSCLC patients are diagnosed at an advanced stage, surgery is often not the most effective treatment option (Baker et al. 2016). Conversely, chemotherapy exhibits limited therapeutic efficacy, with success rates of 6% and 35% for early and late-stage NSCLC that are administered by radiotherapy and without surgical intervention, respectively. Even so, chemotherapy's 5-year relative survival rate remains below 0-26% (Stage IIIB-IV) (Godoy et al. 2023).

Scientific study and technological advancement led to the creation of more advanced targeted medicines mainly aimed at cancer cells. Chimeric antigen receptors (CAR), often referred to as chimeric antigen receptor T-cells (CAR-T cells), use modified T cells as an immunotherapy agent (Zhang and Zhang 2020). Naturally, T cells function as part of the immune system to recognize and fight pathogens, playing an essential role in the body's immune system. They protect the body by identifying antigens on infected cells and initiating immune response through their T cell receptors (TCRs) interacting with the Major Histocompatibility Complex (MHC) on the surface of these cells. This interaction is highly selective, ensuring that T cells only bind to the appropriate MHC, leading to the activation and subsequent destruction of the infected cells. This selective mechanism is the basis for developing CAR-T therapy (Wu et al. 2021). An innovative therapy involves genetically altering T cells to express CAR, allowing them to identify tumor antigens selectively. Upon activation, these engineered T cells exhibit potent anti-tumor effects and undergo multiplication, contributing to the targeted elimination of cancerous cells. Interestingly, this therapy operates independently of the major histocompatibility complex defense, allowing for a more versatile and effective immune response against cancer (Xiao et al. 2021). In 2017, the FDA gave the first approval to this therapy, namely Tisagenlecleucel (Kymriah). It is used for the treatment of Acute Lymphoblastic Leukemia (ALL). Furthermore, three additional CD19-specific CAR-T cell therapies – Axicabtagene Ciloleucel (Yescarta), Brexucabtagene Autoleucel (Tecartus), and Lisocabtagene Maraleucel (Breyanzi) – have also received FDA approval for treating B-cell malignancies (Maude et al. 2018; Locke et al. 2019; Abramson et al. 2020).

The design of CAR-T cells has advanced beyond novel variants, undergoing several alterations to improve therapeutic efficacy (Moreno et al. 2022). In this study, some of the modifications of CAR-T are further discussed. CAR-T therapy is a specialized T cell immunotherapy, emerging as a strong replacement. Extracting patients' T cells and genetically modifying these cells using CARs to identify specific antigen tumor cells allows targeted and effective killing of tumor cells (Zhang and Zhang 2020). The deliberate advancement of CAR to enhance its effectiveness depends on innovative engineering and genetic manipulation techniques. These strategies seek to introduce innovative CAR-T design, increase anti-tumor efficaciousness, improve clinical efficacy, reduce toxicity, and find biomarkers of therapeutic response (Sterner and Sterner 2021). Focusing on recent advancements in lung cancer, this article explores several developments in T cell therapy and various research on modifying CAR and T cells.

Methods

Search strategy and study selection

Relevant articles were searched such as Pubmed, Web of Science, Scopus, Science Direct, and Google Scholar using keywords such as "Lung Cancer", "CAR-T for Lung Cancer", "CAR-T for solid tumor", "Generation of CAR-T", "CAR-T structure", "CAR-T for SCLC", or " CAR-T for NSCLC". Follow-up keywords such as " Clinical Trials of CAR-T", and "CAR-T modifications" were also used. The studies selected and evaluated all published studies until 31 December 2023.

The abstracts of all articles were downloaded. Simultaneously, the authors investigated the abstracts to identify potential articles that include relevant information according to the proposed topic of discussion. The authors emphasize CAR-T for lung cancer and its impact on various factors that influence its effectiveness. The abstracts that did not mention lung cancer or solid tumors with target antigens were excluded.

In the identification step, the authors thoroughly examined original articles in full text to uncover references potentially overlooked by the authors' initial search strategy. Then, the review process is meticulously refined to incorporate pertinent references not initially captured. During the screening process, the authors simultaneously read all abstracts for inclusion. The primary focus of this study is the specific modification of CAR or CAR-T itself that targets receptors to kill aberrant cells, especially those CAR-T cells approved by the FDA. If the abstract needs clarity, the authors will retrieve and carefully review the full publications to determine their relevancy. Preclinical and clinical studies were incorporated into the review to provide comprehensive insight into the current research status.

Data extraction

The studies are systematically categorized based on the CAR-T therapy modification model, which involves changes to the receptors, co-stimulators, or CAR-T cells. This categorization considers their efficacy and selectivity in eradicating aberrant cells by targeting the receptor, especially those CAR-T cells that have received FDA approval. When conducting *in vivo* or preclinical studies, a lot of variables will be carefully taken into account, including the study design, number of mice, kind of CAR-T that is supplied, dose, administration technique, duration of therapy, experimental groups, molecular/condition assessment, and primary results. Similarly, for human studies, the type of CAR-T, dosage, administration method, duration of therapy, molecular/ condition assessment, and primary results will be thoroughly evaluated. The main focus of these investigations lies in assessing selectivity and effectiveness while establishing a connection with post-treatment conditions, encompassing physical and mental behavioral changes. Each author carefully reviewed every stage of the procedure.

Quality assessment and evaluation of findings

While evaluating the quality of the articles utilized, they must offer a thorough description of the design and application of CAR-T in lung cancer and clarify the techniques used to get both behavioral and molecular evaluations. Articles would be significantly enhanced with the addition of comments on the observation of behavioral and physical changes in individuals. A visual depiction of the study methodology and conclusion for each subject matter should be provided by organizing the results in tables or figures. Every study of CAR-T should provide at least two data points about efficacy and selectivity, describing how CAR-T affects the molecular alterations of abnormal cells and the patient's conditions post-therapy stability.

The initial findings should concentrate on the design modification of CAR-T followed by their impact on lung cancer, alterations in aberrant cells, and patient circumstances. Finally, information on the immune system's involvements or molecular pathways should be included.

Results and Discussion

Lung cancer

Lung cancer is a solid tumor-forming malignancy. Therapeutic approaches become complicated as a result of these disparities. There are two primary types based on their growth characteristics: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC has a slower growth rate and is more commonly diagnosed in patients where 80% for NSCLC and 20% for SCLC (Liu et al. 2012; Grossman et al. 2021). On the other hand, SCLC has a faster growth rate but a lower prevalence in patients (Fig. 1) (Liu et al. 2012). Compared to SCLC, NSCLC is usually diagnosed at a higher rate and responds less well to radiation and chemotherapy (Schiller et al. 2002). On the other hand, because of SCLC's aggressive spreading tendency, even if chemotherapy and radiation therapy are sensitive to the disease, they are not able to completely cure it (Wang et al. 2017).

Another differentiating factor between the two lung cancer types is their array of cancer markers. The cancer marker also referred to as the Tumor-associated antigens (TAAs), examples include Carcinoembryonic antigen (CEA), EGFR, human epidermal growth factor receptor 2 (HER2), mesothelin (MSLN), prostate stem cell antigen (PSCA), mucin 1 (MUC1), tyrosine kinase-like orphan receptor 1 (ROR1), programmed death ligand 1 (PD-L1), CTLA4, and CD80/CD86 (Kandra et al. 2022). These TAAs are commonly expressed by both tumor and normal cells, making them a potential target in developing CAR-T cells. In contrast to SCLC, Thyroid transcription factor-1 (TTF1) is highly expressed in nearly 90% of SCLC cases. The distinct expression of every TAA highlights how important target selection is to CAR-T therapy and impacts the overall efficacy of treatment. This justification propels scientists' continuous advancements and developments of various methods toward more precise and potent tailored treatment.

Development of CAR-T therapy

CAR-T therapy was developed in 1989 by two researchers named Zelig Eshhar and Gideon Gross (Styczyński 2020). They were the first researchers to establish a chimeric molecule that combines an antigen-binding region and a monoclonal antibody (mAb) with a T cell receptor transmembrane domain and the intracellular signaling domain of the CD3 zeta chain. The binding domain recognizes and binds the target antigen, activating the signaling domain. The transmembrane domain is necessary to ensure that the binding and signaling domains remain flexible when interacting with the antigen (Lipowska-Bhalla et al. 2012). This structure was then introduced to the world for the first time in 2008 as the first generation of CAR-T cell therapy (Zhao et al. 2018). However, the CAR-T structure generations present advantages and disadvantages (Table 1).

Due to the limitations found in generation 1 CAR-T, scientists began developing new generations of CAR-T to reduce these limitations. The second generation of CAR-T started integrating several intracellular signaling domains from various co-stimulatory receptor proteins to provide additional signals to T cells (Fig. 2).

Apart from providing additional signals, other functions of the co-stimulator are to increase CAR-T proliferation and prevent T cell exhaustion (Holstein and Lunning 2020; Marofi et al. 2021). Some co-stimulators commonly used include CD28, 4-1BB, or OX-40. Each co-stimulator used has advantages, which can be an option in NSCLC and SCLC therapies (Table 1). The biggest challenges faced by this second generation are the antigen escape phenomenon and the limited response duration of treatment (Sterner and Sterner 2021).

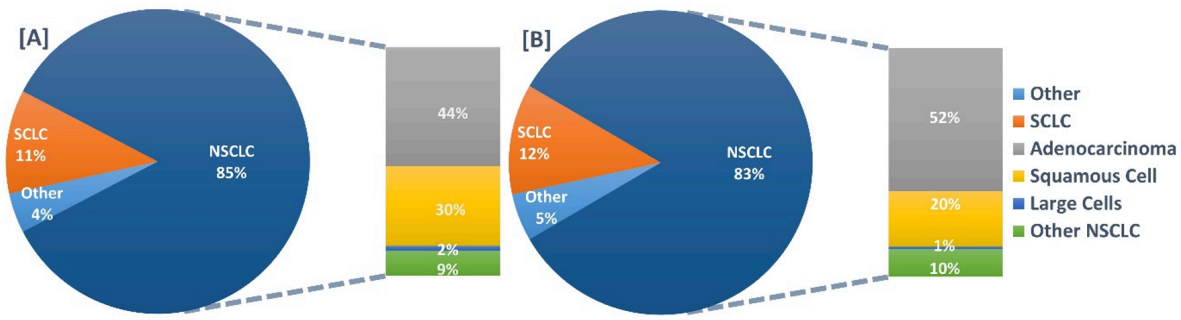


Figure 1. Types of lung cancer prevalence in [**A**] males and [**B**] females.

Although this second generation showed promising clinical responses, many patients using this therapy suffer relapse and partially or wholly lose expression of the target antigen in their cancer cells. When the target antigen is wholly or partially lost, cancer cells gain an opportunity to evade immune cells as those modified with CARs from attacking them. Therefore, the development of the third generation of CAR-T was carried out to overcome and increase the effectiveness and the challenges still faced by the previous generation.

According to Table 1, different types of co-stimulators have various ways of action mechanisms in complete CAR-T signaling. This third-gen of CAR-T utilizes different co-stimulator working mechanisms and tries to combine two types of co-stimulators into T cells.

Table 1. Advantages and disadvantages of CAR-T generations

Generations	Advantages	Disadvantages
First	The potential of CAR-T in mimicking antigen recognition carried out by endogenous TCR. The CAR structure in this generation allows T cells to recognize specific tumor antigens directly, without requiring antigen presentation via MHC as in the endogenous T cell receptor (TCR).	• Low proliferation capacity and short survival time (Zhao et al. 2018). • Inability to produce IL-2 (Brocker 2000).
Second	• Does not require exogenous IL-1 signals (Park et al. 2015; Lee III et al. 2015). • Increasing proliferation, cytotoxicity, and sustainable fiber response prolongs cell life (Ramachandran et al. 2017).	• The emergence of severe cytokine release syndrome (sCRS) in the first week of administration (Park et al. 2015). • Acute toxicity such as fever, hypotension, delirium, and other neurological toxicities (Neelapu et al. 2018). • Partial or complete loss of target antigen expression in cancer cells leading to premature CAR-T cell exhaustion (Sterner and Sterner 2021). • Signaling that is not strong enough (Tomasik et al. 2022).
Third	• Improves CAR-T cells' effector function, growth, and survival (Tomasik et al. 2022). • More successful in generating functional CAR-CD19 T cells with increased cytotoxicity against control cells.	• Increases cytotoxicity against control cells • More complex to produce, increasing costs and time to produce. • third-gen CAR-T therapy still has many disadvantages compared to previous generations, such as CRS, neurotoxicity, manufacturing challenges, or inadequate efficacy, and no improvement in efficacy compared to 2nd generation.
Fourth	• Changing tumor-driven immune suppression to an immunologically permissive environment and avoiding systemic toxicity (Chmielewski and Abken 2020). • Stimulates more tumor clearance by bystander NK cells and conventional T cells and opposes the tendency of T-reg cells to promote tumor growth (Tokarew et al. 2019).	There is a risk of very physiological levels of IFN, resulting in uncontrolled activation of NK cells and macrophages and, ultimately, hematological, intestinal, liver, and lung failure (Car et al. 1999).

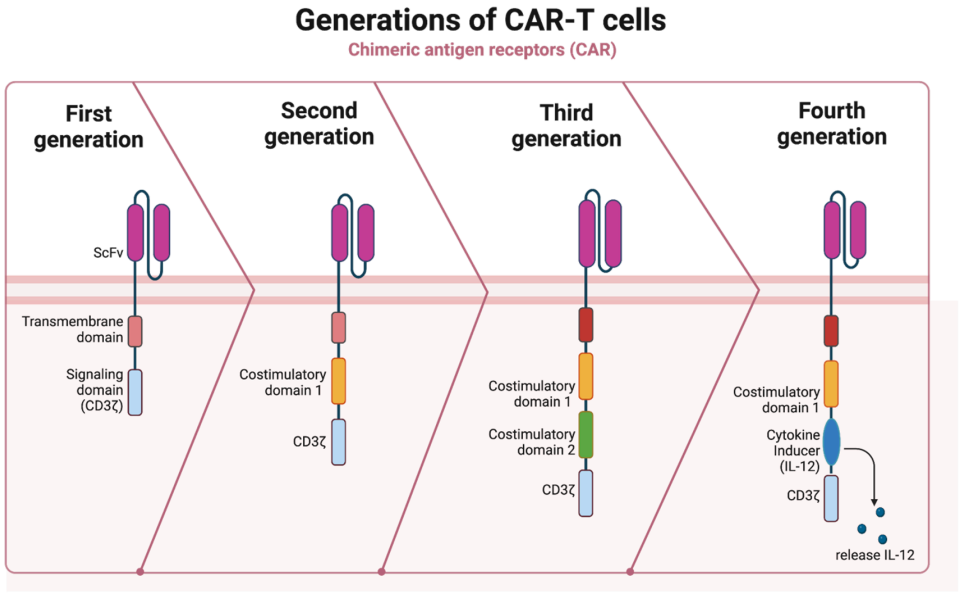


Figure 2. Structure of CAR-T generations.

The advantage of combining these two co-stimulators is a more robust signaling system (Table 1). However, it should be noted that different combinations of 2 co-stimulators can provide various effects. More research is still needed to examine the most practical combination of co-stimulators for NSCLC and SCLC. However, the co-stimulator position also dramatically influences the CAR-T signaling pathway. Despite the promising research results, the main problem with generation 3 CAR-T is related to side effects and efficacy compared to 2nd generation. Cytokine Release Syndrome (CRS), characterized by a systemic inflammatory reaction, is one of the main side effects experienced by third-gen CAR-T users (Fajgenbaum and June 2020). Because it combines more signaling molecules, the release of cytokines as a communication medium will increase, resulting in more cytokines. Excess in the body results in a systemic inflammatory reaction.

The development of three generations of CAR-T has shown impressive results. Researchers discovered new components of CAR-T to improve the previous generations. T cells redirected for universal cytokine-mediated killing (TRUCK) are known as fourth generation of CAR-T. One of the most stunning advantages of the fourth-gen CAR-T is the ability to change the immune suppressive environment driven by tumors into an immune-permissive environment. As tumors progress, some cancer cells within tumor lesions frequently lose antigen and MHC expression on their surfaces, so these cells are not detected by natural cytotoxic T cells or engineered CARs (Chmielewski and Abken 2020). Stimulating the innate immune response is an optimal approach to target antigen-deficient cancer cells and achieve sustained tumor reduction. IL-12 is one possibility, as it significantly enhances the response of innate and adaptive immune cells against cancer cells (Gun et al. 2019). T cells and NK cells secrete more interferon (IFN) and express more granzyme B and perforin, but tumor-induced T-reg cells are suppressed (Hodge et al. 2014). T cells are engineered with tumor-specific chimeric antigen receptors (CARs) and NFAT expression cassettes that are either constitutive or inducible, encoding transgenic proteins, particularly, but not exclusively, cytokines. When CAR-T cells attach to the CAR-specific antigen on tumor cells, CAR signaling triggers the phosphorylation of NFAT, which then moves to the nucleus and activates an NFAT/IL-2-responsive minimal promoter to drive the expression of transgenes. Conversely, NFAT phosphorylation can also be triggered by TCR/CD28 signals, allowing the concept to be applied to T cells with transgenic TCRs. When cytokines are used as transgenic products in cells, they can function in a cis-autocrine manner to support the survival and proliferation of CAR-T cells or in a trans manner to influence the immune cell environment. For instance, they can activate NK cells and help polarize macrophages (Chmielewski and Abken 2020). As a result, this process stimulates more tumor clearance by NK cells and conventional T cells and counters the tendency of T-reg cells to promote tumor growth.

The next generations of CAR-T continue to develop to minimize various side effects and increase the specificity of this therapy (Fig. 3). Recently, a fifth-generation CAR-T was created, which is still the interest of research and is entering the clinical trial stage.

Mesothelin-targeted CAR-T

Mesothelin (MSLN) is a glycoprotein that plays a role in cell adhesion and is associated with cancer invasion and metastasis. Elevated MSLN expression (approximately 69%) of lung adenocarcinoma may heighten the risk of recurrence and reduce overall survival in NSCLC (Morello et al. 2016). It activates intracellular pathways directly through its GPI domain or interacting with its receptor, CA125/MUC16. MSLN activates intracellular NF-κB, MAPK, and PI3-kinase pathways involved in cell

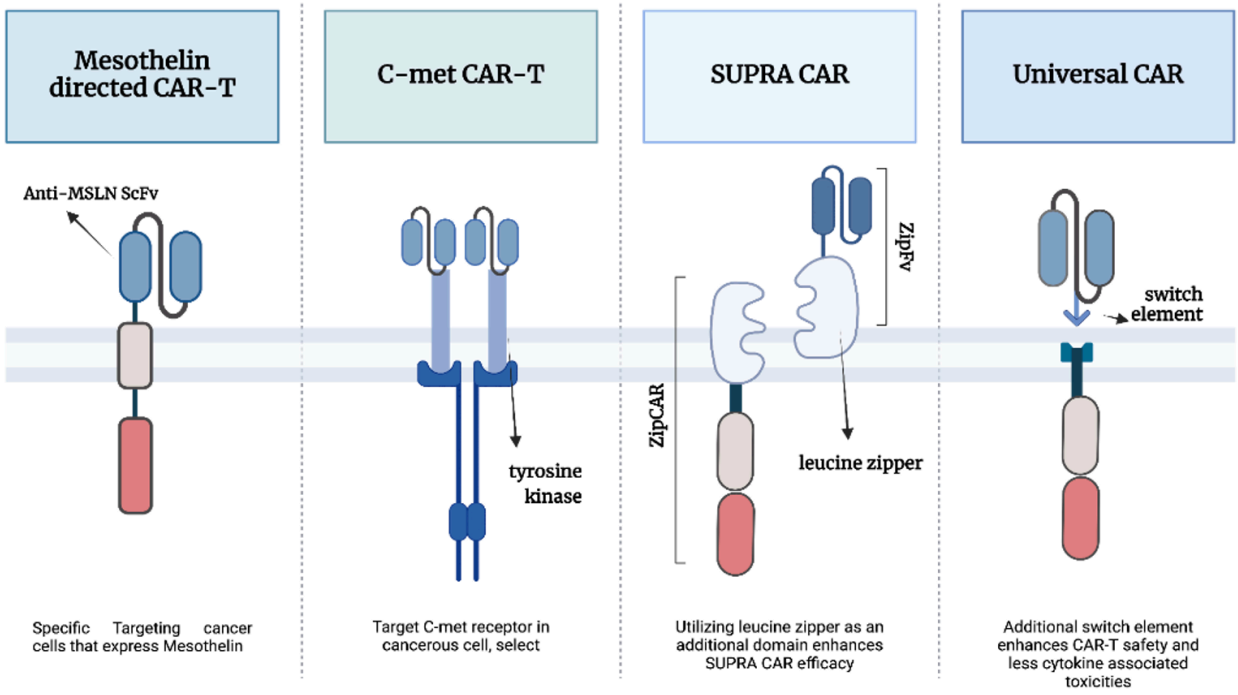


Figure 3. Modification of CAR-T.

proliferation and apoptosis resistance. Overexpression of MSLN is positively associated with greater tumor aggressiveness and poorer prognosis in lung cancer patients (Kachala et al. 2014). MSLN is becoming a more desirable TAA for CAR-T therapy in solid tumors. MSLN is highly expressed in solid tumors and low in normal mesothelial cells and is reported to support a favorable safety profile with potential targeting in MSLN-expressing solid cancers. The extracellular domain of MSLN comprises (1) region I (N-terminal region; residues 296–390), which is the membrane-distal region (MDR) and binds to mucin MUC16 (also known as CA125), a protein frequently expressed in malignant mesothelioma cells and linked to tumor aggressiveness; (2) region II (residues 391–486); and (3) region III (the C-terminal region; residues 487–598), which enhances T cell activation and cytotoxicity, making it a more effective target (Castelletti et al. 2021).

CAR-T cells targeting mesothelin have shown effective cytotoxicity against tumor cells expressing mesothelin and successfully inhibited tumor growth in preclinical models. Several clinical trials are investigating anti-MSLN CAR-T cells for lung cancer treatment (NCT02414269 and NCT02580747). *In vivo* studies demonstrated that MLSN-CAR-T cells inhibited xenograft growth and exhibited a greater capacity to kill cancer cells than standard T cells in NSCLC (Ye et al. 2019). In preclinical studies, combining mesothelin-targeted CAR-T cells with checkpoint inhibitors or chemotherapeutic agents showed enhanced anti-tumor effects. Various CAR designs have been used to target mesothelin: (1) first-generation CAR with the CD3z signaling domain and (2) second-gen CAR including additional costimulatory domains such as CD28 or 4-1BB and CAR bi-specific targeting mesothelin and PD-L1 (Adusumilli et al. 2014; Sotoudeh et al. 2019; Fajgenbaum and June 2020).

c-Met CAR-T

NSCLCs with a mutation in MET exon 14 and its surrounding introns might be responsive to c-Met inhibitors. C-Met, a transmembrane receptor encoded by the Met gene with inherent phosphatase activity, is expressed in epithelial cells. When activated, C-Met drives cell proliferation, angiogenesis, migration, invasion, and survival (Kim and Kim 2017; Liang and Wang 2020). Mutation in MET exon 14 represents a distinct molecular subtype of NSCLC. Prospective clinical trials involving C-met inhibitors are required to confirm MET exon 14 mutations as a critical therapeutic target for NSCLC (Awad et al. 2016). Previous research employed a modified approach for NSCLC therapy targeting c-Met, where the anti-c-Met ScFv structure is fused with transmembrane and intracellular domains. This approach uses a lentiviral vector to introduce the c-Met CAR gene into human T cells for transfusion (Kachala et al. 2014). The c-Met gene fragment consists of a CD8α signal peptide, c-Met ScFv, liked via CD8α to the CD8α transmembrane region, along with 4–1BB and CD3ζ (Min et al. 2022). The experiment found that the CAR sequence expression was stable and effectively targeted c-Met fiber-positive NSCLC cells, leading to increased proliferation and the release of high cytokine levels, accompanied by specific cancer cell-killing activity against cancer cells. C-Met CAR-T cells' tumor suppression is stronger than non-transduced T cells and shows enhanced cytotoxicity against NSCLC. It reduced subcutaneous graft tumor growth from A549 cells, but no off-target toxicity was observed in healthy organs.

Biotin binding immune receptor (BBIR) CAR and split, universal and programmable (SUPRA) CAR

BBIR CAR system and SUPRA CAR are some of the CAR-T structure modifications that add additional ligand binding domains, namely biotinylated ligands such as antibodies and leucine zippers. Specifically, SUPRA CAR is designed with a split structure that incorporates a two-compartment receptor system: a universal receptor (ZipCAR) expressed on T cells and a tumor-targeting ScFv adaptor (ZipFv) (Cho et al. 2018). The advantage of this modification is that it simultaneously targets more than 1 TAA (generally 2 TAA) in solid tumors due to the biotinylated ligand recognizing TAA (Urbanska et al. 2012; Cho et al. 2018). SUPRA CAR-T cells employ a similar approach, using leucine-zipper oligomerization to link scFv with the transmembrane and intracellular activation domain of the CAR. As the name programmable CAR, SUPRA CAR can be programmed using AND and OR logic to enhance the therapy's safety. This design is versatile because it targets several ligands and is also more specific as it can be customized to kill cells that express both or only one of the TAA introduced to the cell. However, its application in the clinical environment still needs to be improved and further investigated due to several significant limitations (Cho et al. 2018). In addition, leucine-zipper's potential immunogenicity is generally higher than standard scFV-CARs, leading to more undesirable effects (Gorovits and Koren 2019).

Universal immune receptor (UIR)

Understanding the shortcomings of BBIR and SUPRA CAR, researchers have developed another CAR-T design called UIR, which similarly targets multiple TAAs simultaneously or subsequently with a single receptor. There are three types of UIR: specific, bispecific, and Fc-binding tags. The two well-known types of UIR are ADCC and anti-tag CAR. In ADCC, effector cells with Fc receptors can actively destroy selected cells with surface antigens attached by specific antibodies, which act as an immunological link between the Fc receptor and the target antigen. A previous study demonstrated that a CAR-T design that incorporates the fundamental principles of ADCC by adding a CD16VV chimeric protein to the co-stimulator protein region drives cancer cell destruction in a preclinical model of human subcutaneous HER2-positive breast cancer *in vivo*. This was accomplished after the intraperitoneal injection of HER2-specific trastuzumab and following administration of NK cells engineered CD16(VV), NK-92CD16 (Clémenceau et al. 2015).

HER2 is a tumor marker often found in NSCLC lung cancer, amplifying 2-4% (Yu et al. 2022). The HER2 protein belongs to the HER/ErbB, the receptor tyrosine kinase family. It includes an extracellular region, a transmembrane domain, and a tyrosine kinase domain with a regulatory region at the C-terminal end (Roskoski 2014). HER2 lacks known soluble ligands; its downstream signaling is activated through dimerization with other HER family members bound by ligands. HER2 is also less prone to internalization and degradation, allowing it to remain active on cell membranes longer

(Roskoski 2014). The usual result of alterations in the HER2 gene/protein is the hyperactivation of the receptor due to increased homo- or heterodimerization and autophosphorylation. This activates multiple signaling pathways, leading to unchecked cell proliferation (Roskoski 2014).

On the other hand, Anti-tag CAR is a UIR that utilizes a conventional scFv-based CAR receptor, where the target antigen is a peptide tag or small molecule. Such tags are either genetically incorporated or chemically bound to a range of target ligands, including small molecules to antibodies. The tag-labeled target ligands connect anti-tag CAR T cells with antigen-expressing tumor cells, facilitating the engagement of adjustable effector functions (Minutolo et al. 2019). The development of CAR-T designs that can target multiple TAAs simultaneously or subsequently adds to the specificity and accuracy of this therapy.

Future prospect

In recent years, CAR-T cell therapy has undergone a transformative revolution, offering hope and promising prospects for enhancing more effective therapeutic options and serving as evidence of scientific advancement. While it has been successful in the treatment of hematologic malignancy, challenges such as toxicity, resistance, and limited efficacy against solid tumors remain. Therefore, investigating the future direction of CAR-T therapy is essential to improve therapy effectiveness and expand its use across different types of cancer. Incorporating co-stimulator combinations in CAR-T cells' structure could address existing challenges, particularly resistance and T cell exhaustion.

CAR-T cell persistence and exhaustion are associated with relapse in patients who have received CAR-T cell therapy. Resistance to CAR-T cell therapy is caused by an inhibitory protein CTLA-4. CTLA-4, a negative regulatory protein, regulates T cell proliferation. The binding of CTLA-4 to the B7 molecule prevents T cells from killing cancer cells. Recent advancements in genetic engineering and synthetic biology have enabled the development of several modifications of CAR-T cell structure to address CAR-T cell persistence and exhaustion. For instance, combining co-stimulator ICOS and CD28 could provide satisfactory synergistic effects regarding T-cell proliferation, persistence, and rapid response due to their association with antibodies. When ICOS is activated by its ligand, it will activate the PI3K pathway in T cells. T cells activated by ICOS specifically activate TFH (T follicular helper) and Th17, essential in fighting extracellular pathogens. Th17 activation will cause inflammation. CD28 will provide amplification signals and act as an inhibitor of CTLA-4 (Lownik et al. 2020). Nevertheless, the various arrangements and alternative choices of co-stimulatory molecules require further investigation to identify the most effective and safe CAR-T therapy.

Conclusion

In summary, new CAR-T innovation strategies featuring efficient toxicity reduction have great potential for safer and more practical applications in various types of lung cancer. This study highlights the potential ways to improve CAR-T therapies. It highlights modifying CAR-T cells as an ideal strategy for achieving more specific, efficient, and safe patient therapies. These modifications aim to achieve several particular targets in lung cancer cells, such as mesothelin and c-Met. In addition, structure modification such as BBIR & SUPRA CAR, UIR, and the co-stimulatory combination is also a potential option to obtain better signaling strength between T-cells. This collective effort makes CAR-T therapy a potential and promising lung cancer targeted therapy, leveraging specific lung cancer markers and offering increased hope for recovery in cancer patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

All of the data that support the findings of this study are available in the main text.

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