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Optimizing Chimeric Artificial T Cell Receptor Therapy for Solid Tumour Targeting by Manipulating the Tumour Microenvironment: A Literature Review

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Abstract

Introduction: Chimeric antigen receptor (CAR)-T cell therapy represents a breakthrough in cancer treatment by harnessing the power of genetically engineered T cells to target and eliminate tumour cells. This approach involves modifying a patient's T cells to express CARs that recognize and bind to specific cancer antigens, bypassing conventional antigen presentation mechanisms. While CAR-T therapy has achieved notable success in treating 'blood,' or 'liquid' cancers, its application to solid tumours remains problematic due to the immunosuppressive tumour microenvironment (TME), which impairs T cell function and promotes tumour escape.

Methods: A comprehensive review was conducted using PubMed and Google Scholar, focusing on publications from March 2002 to March 2024. The search criteria included terms related to CAR-T therapy, solid tumours and TME modulation. Studies were selected based on their relevance to CAR-T therapy challenges, advancements in TME modulation and clinical applications. Research focusing exclusively on liquid tumours was excluded to ensure the review's focus on solid tumour contexts.

Results: Analysis of lymphocyte densities revealed that hot tumours, characterized by high densities of CD3+ and CD8+ lymphocytes at both the tumour periphery and core, demonstrated the most favorable prognostic outcomes. Checkpoint blockades targeting CTLA-4 and PD-1/PD-L1 have been shown to prevent tumour escape. Additionally, engineering CAR-T cells to express immune checkpoint (IC) inhibitors counteracts the expression of IC ligands by immunosuppressive cells. T cells engineered to express IL-12 or IL-18 cytokines also allowed for better infiltration into the TME.

Discussion: Targeting inhibitory immune checkpoints and suppressive cells, as well as manipulating CAR-T cytokine expression, have all shown to be promising ways in which the TME can be modulated to improve patient outcomes. Future research may include looking into the development of strategies to ensure long-term immunological memory in CAR-T cells, particularly for chronic or recurring solid tumours.

Conclusion: Modulating the TME through various molecular and cellular avenues is crucial in improving the effectiveness of CAR-T cell therapy and therefore, optimizing antitumour immunity.

Keywords: CAR-T cell therapy; CAR-T therapy; tumour microenvironment; TME; solid tumour; immunosuppressive TME; immune checkpoints; immune checkpoint inhibitors; proinflammatory cytokines; anti-tumour efficacy

Introduction

Chimeric antigen receptor (CAR)-T cell therapy is a rapidly evolving cancer-targeting strategy that has revolutionized the way we find and kill tumour cells [1, 2]. This approach involves isolating a patient's own T cells and altering their genetic material so that these cells can produce a synthetic chimeric antigen receptor. This CAR structure provides T cells with the ability to identify cancer cells and ignore inhibitory signaling from cancer cells, and therefore better tumour-killing efficacy, after they are infused back into the patient's bloodstream [1, 2]. Although this strategy has illustrated significant success with hematological malignancies, solid tumour targeting is a significant hurdle for CAR-T cells [1–4]. One of the most pressing issues that hinders effective cytotoxic T-cell responses to solid tumour is the immunosuppressive tumour microenvironment (TME), which inhibits proper T-cell infiltration and promotes tumour-cell escape from immune response, as well as T-cell exhaustion due to chronic antigen stimulation [1, 3, 4].

CAR-T cells are T cells that are engineered to express a synthetic CAR that enhances their ability to identify and bind tumour-associated antigens (TAAs) [1–3, 5, 6]. Unlike conventional T cells which identify antigens presented on major histocompatibility complex (MHC) molecules, CAR-T cells can identify antigens on target cells directly without the need for MHC. These receptor proteins typically express 4 domains, including an antigen-binding,

transmembrane, costimulatory and activation domain. The antigen-binding domain is the extracellular region of the receptor which recognizes TAAs and is composed of a monoclonal antibody-derived single-variable fragment (ScFv). The co-stimulatory and activation domains enhance a variety of responses via extracellular signalling transduction, including the proliferation of T cells and inflammatory cytokine secretion [1, 2, 6]. With a deeper understanding of co-stimulatory signalling during T cell activation, later generations of CARs were designed with a stronger co-stimulatory signalling to enhance the tumour-killing efficacy compared with the first generation CAR structure which has lower efficacy caused by the lack of co-stimulatory domain [1, 2, 6].

The development of second, third and fourth-generation receptors involved the addition of more co-stimulatory domains to the CAR structure, in order to improve cytotoxicity and cell expansion. Unlike the first-generation CAR which only had a CD3ζ activation domain within its intracellular region, second and third-generation CARs were engineered to carry one or two costimulatory domains, respectively, typically derived from either CD28 or 4-1BB [1, 2, 4–6]. Studies have shown that these signalling moieties not only enhance CAR-T cell cytokine secretion, but also promote T-cell expansion and persistence, therefore increasing tumour-killing efficacy. To date, there have been six FDA-approved CAR-T cell products since 2017, four of which target the CD19 antigen and two of which target B-cell maturation antigen (BCMA) [7]. Due to the high relapse rate (60%) seen with previous CAR-T cell therapy patients, focusing on the development of next-generation CARs and altering CAR-T administration is vital in improving patient outcomes [7]. Due to its limited approval for solely liquid cancers such as acute lymphoblastic leukemia and diffuse large B-cell lymphoma (DLBCL), as well as its reflection of a high insufficient therapy response in solid tumour patients, expanding its clinical applications is vital in preventing disease recurrence and treating a wider range of cancers [7, 8].

In order for cancer development and progression to occur, immune evasion and suppression must take place [8]. This cancer-favourable niche is sustained by the powerful TME and is characterized by both anti-tumour response suppression and pro-tumour response promotion [9]. The TME has been shown to have low oxygen levels and high oxygen-reactive species, as well as containing cell populations that express immune checkpoints to evade immune recognition and suppress CAR-T cell expansion via the expression of anti-inflammatory cytokines [9, 10]. It is also characterized by multiple physiological abnormalities, including vasculature that inhibits immune cell extravasation, as well as a denser extracellular matrix (ECM) when compared to normal tissues [11, 12]. This paper aims to investigate various aspects of TME modulation, to elucidate how the TME can be regulated in order to decrease its immunosuppressive characteristics and allow for better CAR-T cell infiltration and maintenance to extend the application of CAR-T therapy to solid tumour patients. Here we will discuss the targeting of immune checkpoints and suppressive cells, as well as the manipulation of cytokine receptor expression.

Methods

To conduct this review, Web of Science, Pubmed and Google Scholar databases were used to search for various articles relating to CAR-T cell therapy that covered a range of topics, including but not limited to: current challenges with the therapy, advancements regarding tumour microenvironment modulation, the therapy's clinication application and signaling strategies for CAR structures. The terms that were used to perform the search were ("CAR-T therapy" OR "CAR-T cell therapy") AND ("solid tumours" OR "tumour microenvironment" OR "checkpoint signalling" OR "advancements" OR "techniques"). The search was limited to papers published in the English language from March 2002 to March 2024. Articles that focused solely on liquid tumours were excluded, and relevant literature was included.

Results

Lymphocyte Densities Influence Patient Outcome

Various tumour subtypes have been classified based on their immune microenvironment status with a classification method based on CD3 protein as well as cytotoxic (CD8) and CD45RO lymphocyte populations [14, 15]. By quantifying CD3/CD45RO or CD3/CD8 or CD8/CD45RO cell populations in the tumour area, the designated tumour can be assigned an immunoscore between 0 and 4, wherein a high score signifies a high density of cell types mentioned above both at the periphery and centre of the tumour. This has led to identifying three main tumour classes, known as hot, altered and cold tumours. Cold tumours are characterized by a low immunoscore and low CD3+ and CD8 populations at both the tumour centre and invasive margin, wherein hot tumours possess a high immunoscore and high lymphocyte populations at both tumour sites [14, 15]. Several studies have illustrated that this immune-classification has prognostic value and is a good predictor of cancer relapse and patient survival. In one study, immunohistochemical analyses were used to quantify the cytotoxic (CD8) and memory (CD45RO) T cells from colorectal cancer patient tumour tissue microarrays [16]. Patients with high CD8 and CD45RO populations exhibited a 86.2% survival rate with 4.8% tumour recurrence, compared to a 27.5% survival rate and 75% tumour recurrence of cancer patients with a low level of these cells populations, five years after their diagnosis [15, 16]. Strong CD45RO cell infiltration normally accompanies an increase in the expression of genes involved in the cytotoxic response [16]. The strength of CD3+ cell response in tumour areas has additionally been shown to be a more reliable predictor of clinical outcomes in colon carcinoma,

as well as in head and neck cancers [17, 18]. An analysis of stage II colon carcinomas investigated the correlation between intraepithelial CD3+ cell densities and disease-free survival (DFS) [17]. CD3+ cells infiltrating the tumour microenvironment were quantified and compared to those infiltrating the peritumoural stroma. CD3+ cell density in tumours of colon carcinoma patients was found to be higher than in non-tumourigenical colonic mucosa of the same patients, wherein a lower density of intraepithelial CD3+ tumour-infiltrating lymphocytes (TILs) led to a significant decrease in patients' DFS [17]. The importance of the CD3+ response in patient outcomes has further been illustrated in head and neck cancers [18]. By stimulating lymph node cells from cancer patients with anti-CD3 monoclonal antibodies, researchers were able to elucidate that an unresponsive CD3 receptor in patients led to a much higher neuroblastoma recurrence rate within the first 24 months after treatment, suggesting that CD3 plays an important role in tumour recurrence [18].

Targeting Inhibitory Immune Checkpoints and Suppressive Cells

As "gatekeepers" of immune responses, inhibitory immune checkpoints (ICs) and suppressive cells act as regulatory mechanisms promoting immune suppression preventing excessive immune responses, which tumour cells exploit via inhibitory checkpoint upregulation [19]. This upregulation is one of many factors related to the immunosuppressive nature of the TME and escape from anti-tumour immune responses [20]. ICs and suppressive cells within solid TMEs have remained a persistent issue for CAR-T cell therapies as their application has moved towards solid tumour treatment. Current CAR-T therapies have suffered from a lack of tumour infiltration, tumour killing efficiency and T cell exhaustion. IC inhibitors (ICIs) have shown extensive promise in the treatment of solid cancers. Previously ICIs were approved only as a salvage therapy to be used alongside or after chemotherapy to treat metastatic and advanced cancers [21]. Recently, ICIs have become the preferred treatment for patients with early-stage cancers before considering conventional chemotherapy [21]. ICIs initiate a blockade within solid TMEs, hindering further tumour escape by inhibiting key ICs, including cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) [22]. FDA-approved ICIs include nivolumab (Opdivo) and pembrolizumab (Keytruda), both checkpoint inhibitors targeting PD-1; atezolizumab, avelumab, and durvalumab, which block PD-L1; and ipilimumab (Yervoy), a checkpoint inhibitor that targets CTLA-4 [23]. Several different strategies of CAR-T cell therapy in combination with ICIs have been explored clinically. These include exogenous ICIs combined with CAR-T cell therapy and CAR-T therapy with additional auto endocrine immune checkpoint antibodies [22]. The first strategy involves administering CAR-T cell therapy prior to ICI injections [22, 24, 25]. Advancements in ICIs using combined PD-1/CTLA-4 antibodies, a dual checkpoint blockade alongside CAR-T therapy saw the treatment of malignant brain tumours increasing anti-tumour efficacy compared to conventional CAR-T therapy [22, 26]. While this form of combination therapy has shown improvement in the objective remission rate in advanced patients unfortunately this strategy has drawbacks including the need for repeated ICI injections, ICIs are captured by tumour-associated macrophages (TAMs) before reaching CAR-T cells preventing PD-1/PD-L1 blockade, and systemics side effects and immune complications [22, 27, 28]. The second strategy involves engineering CAR-T cells to express PD-1/PD-L1 antibody scFv [22]. Recent studies have shown promise with results suggesting this strategy allows for CAR-T cells to kill tumour cells directly but also enhance the local immune response within the tumour, thereby improving solid TME infiltration [22, 29]. Another factor associated with the immunosuppressive nature of solid TMEs are the immune suppressive cells that are upregulated preventing anti-tumour immunity. Regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and TAMs are suppressive cells that are present within the TME at various upregulated levels [30]. These cells secrete various inhibitory cytokines and growth factors, engage in metabolic competition, and express IC ligands themselves preventing the effective use of CAR-T cell therapy and ICIs [30]. By depleting these immune suppressive cell types, researchers have been able to enhance the anti-tumour immune response along with the infiltration, and efficiency of CAR-T therapies and ICIs preventing further T-cell exhaustion [30-32].

Manipulating CAR-T Cytokine Expression

The expression of proinflammatory cytokines on CAR-T cells to improve immune stimulation and tumour cell targeting is another potential strategy that improves T cell infiltration into the TME [1, 3, 4]. Researchers have engineered CAR-T cells to express the IL-2 cytokine, in order to improve the therapy's anti-tumour efficacy [33, 34]. Second-generation CD19 CAR-T cell constructs possessing either a CD18 or 41BB co-stimulatory domain and secreting IL-2 (CD19-CD28z-IL-12 and CD19-41BBz-IL-12, respectively) have been shown to produce higher interferon γ (IFNγ) levels when compared to those that have no IL-2 secretion modification [33]. Mice treated with either the CD19-CD28z-IL-12 or CD19-41BBz-IL-12 constructs, displayed decreased tumour growth after 3 weeks, in addition to lymphoma eradication in 26% of mice with the CD28-containing construct and 22% with the 41BB-containing construct. CAR constructs that did not encode IL-2 not only exhibited poorer cytotoxicity when compared to their IL-2-expressing counterparts, but they were also unable to maintain long-term survival in the mouse models [33]. IL-12 is another potent inflammatory cytokine that has been utilized in tumour microenvironment

infiltration, via the modification of IL-12 armoured CAR-T cells [34, 35]. When compared to non-IL-12-secreting cells, IL-12-secreting CD19-targeted CAR-T cells in mice were able to eradicate CD19 expressing tumours without the need for prior cyclophosphamide conditioning therapy [35]. Cyclophosphamide, an alkalizing agent that has been used to treat malignancies in a variety of cancers, can enhance CAR-T cell anti-tumour efficacy [36]. Pegram et al. utilized cyclophosphamide to induce cytotoxic activity against CD19-positive B-cell lymphoma tumours, as prior conditioning was found to be necessary for a better antitumour response post-infusion of CAR-modified T cells specific to CD19 (19mz+ T cells) [35]. The infusion of 19mz+ T cells into nontumour-bearing mice did not induce any B cell aplasia (marked tumour regression) and the infusion of 19mz+ T cells into tumour-bearing mice did not increase mice survival when compared to control mice treated with cells that were not targeted to CD19 (Pmz+ T cells). Treating both nontumour-bearing and tumour-bearing mice with cyclophosphamide treatment before 19mz+ T cell infusion illustrated hCD19+ B cell aplasia and tumour eradication, respectively, when compared to the control group. Genetically modified 19mz+ T cells that additionally secrete IL-12 (19mz/IL-12+), were shown to have enhanced in vitro toxicity and higher expression of the T cells activation marker, CD25, when compared to 19mz+ T cells that are not IL-12-secreting. In the absence of cyclophosphamide, 19mz/IL-12+ cells (but not 19mz+ or control cells) were able to induce B cell aplasia in tumour-bearing mice, as well as their long-term survival, illustrating that IL-12 secretion overcomes the necessity for prior conditioning in vivo to eradicate tumours [35]. Further research has suggested that other pro-inflammatory cytokines possess similar T cell enhancement abilities, including CAR-T cells engineered to express IL-18, a, IL-12-related cytokine, in a melanoma model [35, 37]. CAR-T cells secreting IL-18 (CD19-IL-18 cells) exhibit enhanced proliferation and engraftment in vivo, with increased tumour elimination ability and B cell aphasia induction, suggesting that IL-18 secretion improves T cell on-target effects [37].

Discussion

The immunosuppressive nature of the TME in solid tumours is a major barrier to effective CAR-T cell therapy. Our review examined strategies to overcome these obstacles, focusing on enhancing tumour infiltration, persistence, and overall efficacy of CAR-T cells. One key finding was that solid tumours classified as "hot" tumours, which have high densities of CD3+ and CD8+ T cells, are more responsive to CAR-T therapy and exhibit better clinical outcomes. In contrast, "cold" tumours, which lack significant immune cell infiltration, are less responsive, underscoring the need for TME modulation to make these tumours more treatable.

Targeting inhibitory immune checkpoints such as CTLA-4, PD-1, and PD-L1 emerged as a promising strategy. These checkpoints play a critical role in suppressing immune responses, and tumours exploit these mechanisms to avoid immune detection. ICIs like nivolumab and pembrolizumab have shown potential in reactivating T cells within the TME, enabling better tumour control when combined with CAR-T cell therapy. This approach can reduce T-cell exhaustion and improve tumour infiltration, particularly in solid tumours where immune suppression is a significant hurdle. Additionally, the depletion of immunosuppressive cells within the TME, such as Tregs, MDSCs, and TAMs, has been shown to enhance CAR-T cell efficacy. These cells contribute to immune suppression by secreting inhibitory cytokines and promoting tumour escape. Reducing their presence can improve CAR-T cell persistence and tumour-killing capacity. Cytokine modulation represents another effective strategy. Engineering CAR-T cells to express pro-inflammatory cytokines like IL-12 and IL-18 has demonstrated improved tumour infiltration and enhanced anti-tumour activity. Preclinical models show that these cytokine-modified CAR-T cells can eradicate tumours more efficiently, even in the absence of additional conditioning treatments.

Conclusions

This review underscores the potential to enhance CAR-T cell therapies by targeting and modulating the TME through a range of molecular and cellular strategies. While CAR-T therapies have shown remarkable success against hematological malignancies, their application to solid tumours remains a significant challenge, largely due to the immunosuppressive nature of solid TMEs. Our goal was to bring attention to the current literature that addresses these challenges, emphasizing the need to optimize anti-tumour immunity in solid tumours through novel approaches. The complexity of interactions between the immune system and the solid TME remains a critical area for future investigation. Understanding these interactions more comprehensively will provide a foundation for the development of new therapeutic strategies that can overcome the limitations of current CAR-T therapies. Notably, modulating immune checkpoints, suppressive cell populations, and cytokine expression within the TME could unlock new ways to enhance can the efficacy of CAR-T cells against solid tumours. Additionally, engineering CAR-T cells with improved infiltration and persistence capabilities will be vital to their success in a solid tumour context. Future research must focus on identifying specific molecular targets within the TME that either promote or inhibit immune responses. By dissecting the mechanisms that lead to immune evasion, such as the dense extracellular matrix or the presence of inhibitory immune checkpoints, researchers can pave the way for more tailored approaches. These might include the use of combination therapies with

ICIs, or the depletion of immunosuppressive cell populations like Tregs and MDSCs. Furthermore, fine-tuning cytokine expression in CAR-T cells holds promise for enhancing their potency and longevity in solid tumour environments. While CAR-T cell therapy has already revolutionized cancer treatment, there remains vast untapped potential in expanding its efficacy to solid tumours. The future of CAR-T therapy will rely on an integrated understanding of the TME, allowing for the development of next-generation CARs that are equipped to thrive in these hostile environments. By doing so, CAR-T therapies could become as effective against solid tumours as they currently are against liquid tumours, significantly broadening their clinical utility and improving patient outcomes across a wider spectrum of cancers. Continued research in this field will be essential to overcoming the remaining hurdles and unlocking the full potential of CAR-T therapy.

List of Abbreviation
BCMA: B-cell maturation antigen
CAR: chimeric antigen receptor
CD45RO: memory T cells
CD8: cytotoxic T cells
CTLA-4: cytotoxic T-lymphocyte-associated antigen 4
DFS: disease-free survival
DFS: disease-free survival
DLBCL: diffuse large B-cell lymphoma
ECM: extracellular matrix
IC: immune checkpoint
ICI: immune checkpoint inhibitor
IFNγ: interferon γ
MDSC: myeloid-derived suppressor cell
PD-1: programmed cell death protein 1
PD-L1: programmed death-ligand 1
ScFv: single-variable fragment
TAA: tumour-associated antigens TME: tumour microenvironment MHC: major histocompatibility complex
TAM: tumour-associated macrophage
TIL: tumour-infiltrating lymphocytes
TILs: tumour-infiltrating lymphocytes
Treg: regulatory T cell

Conflicts of Interest
The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent
The study did not require any ethics approval and/or participant consent because this was a literature review.

Authors' Contributions
AK: made substantial contributions to drafting the manuscript, reviewing data and gave approval for the final version to be published.
QG: made substantial contributions to drafting the manuscript, reviewing data and gave approval for the final version to be published.

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