Chapter

Targeting Tumor Microenvironment for Advanced Cancer Therapy

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Abstract

The tumor microenvironment (TME) has emerged as a pivotal determinant in the progression of cancer and the development of resistance to therapeutic interventions. The heterogeneous cellular composition of the TME not only facilitates tumor proliferation but also poses formidable obstacles to the efficacy of conventional treatments. This chapter delves into an examination of the distinctive attributes of the TME, exploring both established and innovative approaches designed to target the TME. Through a thorough analysis of the intricate involvement of the TME in cancer biology, we underscore the imperative for a comprehensive understanding and specific modulation of the TME to enhance the efficacy of cancer treatments. This elucidation provides novel insights for further research endeavors and clinical applications.

Keywords: tumor microenvironment (TME), cancer immunotherapy, tumor-associated macrophage (TAM), myeloid-derived suppressor cells (MDSC), cancer-associated fibroblasts (CAFs), extracellular matrix, therapy resistance, cancer progression, checkpoint blockade, chimeric antigen receptor (CAR)-engineered T (CAR-T) cell, innate T cell

1. Introduction

Contrary to the traditional view of cancer as a simple disease, cancer is now recognized as a complex ecosystem [1]. Besides cancer cells, the tumor microenvironment (TME), comprising a varied assortment of immune cells, cancer-associated fibroblasts (CAFs), endothelial cells (ECs), pericytes, and other cell types unique to tissue, plays a vital role in the development and treatment of cancer [2]. The cellular composition and functional condition of the TME may vary based on the tumor locations, the intrinsic traits of the cancer cells, the stage of the tumor, and patient-specific factors; within the TME, different cells could either inhibit or promote tumor

development [2]. Through heterotypic intercellular interactions between cancer and non-cancerous cells, TME diminishes the effectiveness of immune checkpoint blockade and adoptive cell therapies, underscoring the necessity of new treatments specifically designed to rectify the TME [3–5]. Given that TME contributes to the development and preservation of cancer hallmarks, including sustained proliferative signaling, resistance to cell death, angiogenesis induction, activation of invasion and metastasis, initiation of tumor-promoting inflammation, and evasion of immune destruction, to different extents, strategies targeting the TME have become a significant focus in antitumor therapy, which includes targeting tumor-infiltrating T-cells, confronting cancer-associated fibroblasts, modulating the extracellular matrix, and so on [6–9].

This chapter offers a thorough introduction to the major composition and corresponding dynamic interactions within the TME, which subsequently affects cancer progression and antitumor therapy resistance. Current techniques targeting the TME along with their effectiveness and clinical applications are discussed. Moreover, this chapter explores innovative approaches in advanced cancer therapy that incorporate TME considerations. Finally, this chapter evaluates the synergistic effects of combining TME targeting with conventional cancer treatments, providing a comprehensive overview of the strategies to improve cancer therapy through TME modulation.

2. Key components in the TME

Cancerous cells are not the only ones involved in the development and progression of the disease [1]. In fact, the TME is made up of a wide variety of cell types and other components that function to both support and resist cancer progression [4, 6, 10, 11]. Of these components, the most important ones include immune cells, stromal cells, vascular cells, as well as the extracellular matrix [2]. It is the interaction between these cells and tumor cells that make the TME a rich ecosystem for cancer development and resistance against the immune system [12]. The section below outlines the key elements that comprise the TME and highlights how they function in the scope of tumorigenesis.

Among the most diverse subset of cells in the TME are cells of the innate and adaptive immune systems [3]. The innate immune cells—macrophages, neutrophils, invariant natural killer T cells—present the body's first line of defense and utilize non-specific mechanisms to fight pathogens, including cancer [13]. On the other hand, adaptive immune cells, such as B cells, T cells, and natural killer cells, are highly specific in their targeting of pathogens [13]. While some of these cells possess potent antitumor properties, such as the highly cytotoxic natural killer cells and CD8-positive T cells, others like the immunosuppressive regulatory T cells and M2-like macrophages actually support the growth of the tumor by preventing inflammation and participating in the formation of new blood vessels [2].

Adding to the complexity of the constantly evolving TME are stromal cells and vascular cells [8, 14, 15]. Typically, stromal cells are found surrounding organs and act as structural tissue to protect and support them [14]. Depending on their origin, stromal cells can be identified as cancer associated fibroblasts, adipocytes, and stellate cells [13]. In the context of tumorigenesis, cancer cells recruit the stromal cells of their surrounding tissue and incorporate the plasticity and regulatory signaling of these cells to the advantage of the tumor [14]. For example, cancer-associated fibroblasts are a major component of the TME that exhibit enhanced

proliferative and extracellular matrix formation upon activation [14]. They can be formed from a variety of stromal cells, including adipocytes and stellate cells of the liver, as well as mesenchymal stem cells derived from the bone marrow [13]. Due to their ability to model the extracellular matrix, cancer-associated fibroblasts can influence the mode of interaction among the subtypes of cells in the TME and directly change the mechanical properties of the tumor as a whole [13, 16]. Additionally, stromal cells contribute to the growth of cancer through the secretion of pro-inflammatory cytokines and growth factors for the promotion of blood vessel formation [14]. Since most solid tumors tend to develop hypoxic conditions, blood vessel formation, also known as angiogenesis, is essential for the progression of cancer [2]. Therefore, it is not surprising that vascular cells such as endothelial cells contribute largely to the TME. In an otherwise nutrient-deprived setting, tumors utilize vascular endothelial cells to form new blood vessels that can deliver them essential nourishment [13].

Apart from the multiple cell types present in the TME, an important factor of the ecosystem is the extracellular matrix [14]. Comprised of proteins, glycoproteins, and collagen, the extracellular matrix not only provides structure to the TME but also forms the space in which cancer cells interact with all the other cell types [2]. This includes facilitating contact-dependent communication between cells and acting as a reservoir for secreted cytokines and signaling molecules to be detected by cells in the vicinity [2]. For example, in the latter case, the extracellular matrix may sequester growth factors such as vascular endothelial growth factor (VEGF) that promotes angiogenesis, which can bind to endothelial cells and initiate blood vessel formation in the tumor [13].

The TME is a highly dynamic phenomenon, with all of the components—cellular or molecular—functioning together for the cancer to survive and grow [17]. Cancer cells recruit their surrounding cells to develop defenses and to utilize the host system for their benefit [17]. Immune cells are polarized to become immunosuppressive, as is the case of M2-like macrophages [17]. These macrophages promote angiogenesis in the tumor through the secretion of the VEGF and suppress antitumor immune cells such as T helper cells by secreting anti-inflammatory cytokines like IL-10 [12]. In addition to interactions between cancer cells and the other cells of the TME, the interplay between the non-tumor components is another crucial factor that drives the tumor progression as well as resistance [14]. As stromal cells can be transformed into proliferative cancer-associated fibroblasts, which in turn drive the formation of the tumor extracellular matrix, they also signal to vascular endothelial cells to form new blood vessels [12]. On another level, the same cancer-associated fibroblasts involved in the structural formation of the tumor also suppress cytotoxic T cells through the secretion of the anti-inflammatory cytokine TGF-β [18]. This way, the cancer delegates its own development to the cells of the TME and utilizes intrinsic mechanisms found in them to confer resistance against the antitumor immune response and therapies in development [12].

Currently, there is a lack of treatments targeting the TME in standard clinical use [13]. The TME then arises as a critical barrier to effective treatment, due to the TME milieu being central to several pathways responsible for drug resistance, tumor metastasis, growth, and immune evasion [17]. Therefore, surmounting the obstacles posed by the TME presents a promising therapeutic strategy that could substantially enhance the success of solid tumor therapies [13]. Outlined below are the various therapy strategies that concurrently target the TME and tumors and demonstrate synergistic effects with enhanced efficacy (**Figure 1**).

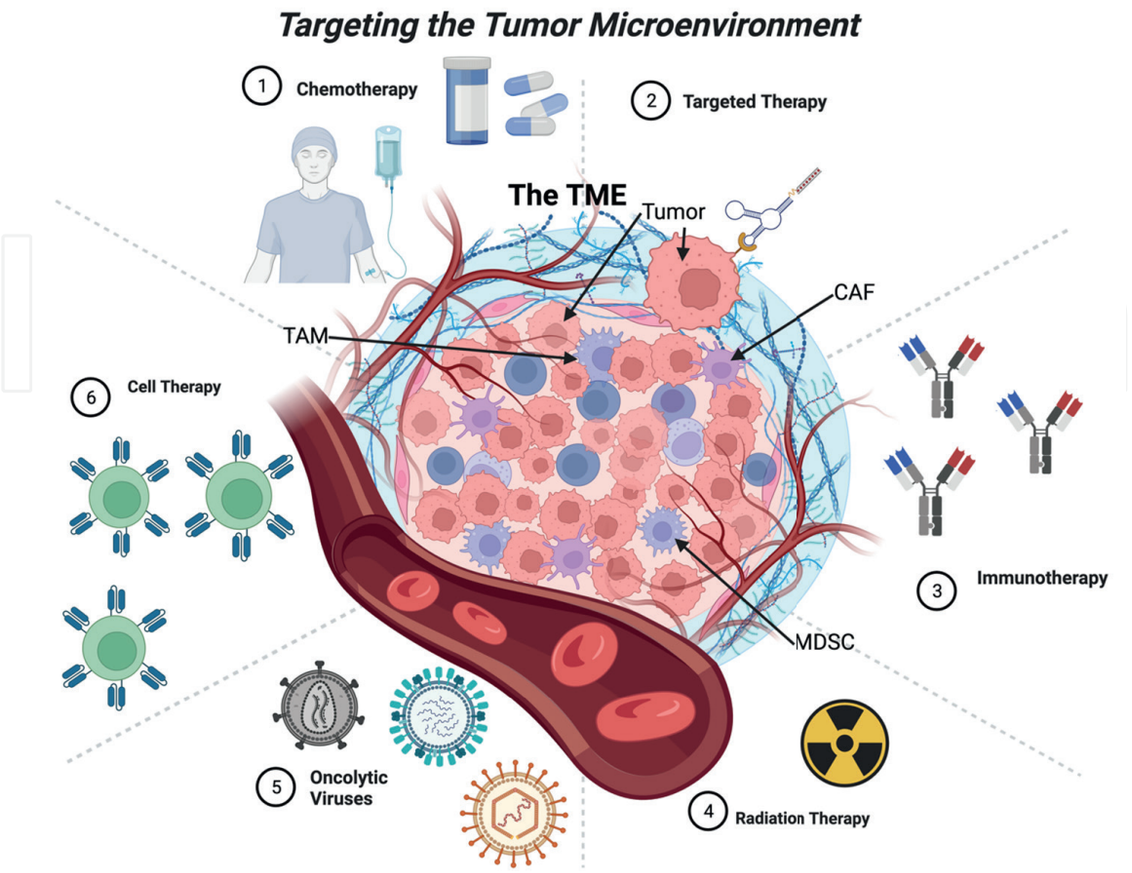

Figure 1.
Multiple strategies to target the tumor microenvironment.

3. Chemotherapy, targeted therapy, and immunotherapy to target the TME

Cytotoxic agents such as Taxols, cisplatin, and 5-fluorouracil are the cornerstones of cancer therapy due to their ability to disrupt essential physiological processes such as cell division, metabolic processes, and DNA replication in rapidly proliferating cells [19]. Despite their demonstrated effectiveness, chemotherapies face a significant hurdle in the form of the TME, which limits their cytotoxic potential [17]. Thus, most current strategies employed to minimize the effects of the TME combine chemotherapy, targeted therapy, and immunotherapy, specifically targeting immunosuppressive components within the TME to enhance the overall efficacy of cancer treatments [17].

3.1 Depletion of TAMs

Tumor-associated macrophages (TAMs) exhibit the capability to rescue and promote the survival of cancer cells post-exposure to antimitotic agents, such as Taxols, which disrupt microtubule dynamics crucial for successful cell division [20]. By curtailing the duration of Taxol-induced mitotic arrest and mitigating the activation of apoptosis pathways prompted by Taxols, TAMs play a pivotal role in preventing cancer cell death *via* the secretion of specific factors [20]. Therefore, blocking the CSF-1/CSF1R axis to prevent M2-like polarization and TAM recruitment emerges as a strategy to counteract the effects of TAMs [21]. Investigations of breast cancer

focusing on depleting TAMs within the TME through CSF-1R inhibition have demonstrated increased DNA damage and amplified cancer cell death when combined with Taxol treatment compared to Taxol treatment alone [20].

The blocking of PD-1/PD-L1 with monoclonal antibodies is well established as a potent therapy for a diversity of cancers [22–26]. TAM expression of PD-1 in the TME has been shown to inhibit macrophage phagocytosis and tumor immunity [27]. However, TAM infiltration is also associated with PD-1/PD-L1 checkpoint inhibitor (CI) immunotherapy drug resistance by secreting immunosuppressive cytokines and metabolic products and increasing the surface expression of PD-L1 on tumor cells [28, 29]. Given these caveats in the context of TAM activity in PD-1/PD-L1 therapy, combination therapy targeting TAM depletion offers an innovative alternative. In fact, using both CSF-1R inhibitors and PD-L1/PD-1 CI immunotherapy has shown promise in treating brain cancers [28, 30, 31]. Likewise, clinical trials implementing a combined regimen of chemotherapy and antibodies that obstruct signals involved in TAM recruitment, such as CCR2, have observed synergistic effects [32]. Another immunotherapy currently in several clinical trials includes a CD40 agonist, also known as mitazalimab, which aims to reprogram TAMs toward an antitumor M1-like state and away from an M2-like immunosuppressive state, thereby increasing penetration of cytotoxic T cells and chemotherapeutic agents into the tumor stroma [33, 34]. Finally, V domain Ig suppressor of T cell activation (VISTA), an Ig superfamily protein primarily found in the hematopoietic compartment, has been investigated for its involvement in negatively regulating T cell responses [35, 36]. VISTA knockout on macrophages and myeloid-derived suppressor cells (MDSCs) resulted in a reduced ability to locate to the TME [37]. VISTA CI immunotherapy has shown promise alone and in conjunction with PD-1/PD-L1 CI immunotherapy [38]. These studies underscore the active role the TME plays in facilitating tumor progression and survival and emphasize the need to target both the TME and tumor.

3.2 Depletion of MDSCs

MDSCs are a heterogeneous population of immature myeloid cells known to rapidly proliferate in the TME [39]. MDSCs are further defined into two subsets based on their phenotype, morphology, and activity: polymorphonuclear (PMN)-MDSCs and monocytic (M)-MDSCs [39, 40]. The proliferation of MDSCs is driven by tumor-derived growth factors, including GM-CSF, G-CSF, M-CSF, VEGF, and IL-6 [41]. The most notable and unique characteristic of MDSCs is their plasticity [42]. MDSCs can act on many cell types at once, including by differentiating into TAMs, suppressive DCs, and M2-like suppressive macrophages [42]. Strategies for targeting MDSCs include depletion by chemotherapy and CD33-targeted antibody-drug conjugate therapy, differentiation by TLR agonists such as CpG oligonucleotides, blocking accumulation by chemokine inhibitors and STAT3 inhibitors, and directly blocking immunosuppression through PDE5 inhibitors and COX2 inhibitors [42]. Moreover, combinations of several of these therapies can provide new effective therapies for testing in clinical trials. One such clinical trial involves the use of a TLR agonist known as MGN1703 in conjunction with a CTLA-4 monoclonal antibody in late-stage solid tumor malignancies [43]. Another study sought to treat metastatic triple-negative breast cancer by delivering a combinational therapy of a TLR3 ligand called rintatolimod, IFN-a2b, and a COX-2 inhibitor called celecoxib, which resulted in a significant increase in cytotoxic T lymphocyte infiltration into the TME and clinical and stable disease responses in patients [44]. As more clinical trials are

undertaken, one case study highlights the unique promise offered by combination therapies. A patient who had experienced hepatic metastases of metastatic sinonasal undifferentiated carcinoma progression following treatment with pembrolizumab (PD-1 inhibitor) was treated with an additional combined regimen of ipilimumab (CTLA-4 inhibitor) and COX-2 inhibitor, resulting in a clinical response in target liver metastases [45].

3.3 Modulation of regulatory T cells

Regulatory T cells are the primary T cells (Tregs) responsible for immunosuppression in the TME [46]. They have been identified as major obstacles to the immune response in the TME because they secrete inhibitory cytokines and directly inhibit antitumor immune cells such as cytotoxic $CD8^+$ T lymphocytes [46]. The most common immunotherapy targeting tumor-infiltrating lymphocytes (TILs) is immune checkpoint inhibitors (ICIs) (CTLA-4, TIGIT, and PD-1), which have achieved success [47]. Notably, 60-70% of patients receiving PD-1 ICI therapy do not experience an objective response, with 20-30% of patients experiencing eventual tumor relapse [47–50]. At the same time, depletion of Tregs is associated with a number of autoimmune diseases [51]. Thus, some scientists have called for a combination therapy of Treg depletion by CD25 and CCR8 and ICI therapy to improve outcome and prevent complete organism-wide depletion of Tregs [50]. In addition to these therapies, the development of the GITR agonist is of note. GITR has been identified as a possible co-stimulator on Tregs and is highly expressed on the surface of Tregs [50, 52]. When stimulated by its ligand, DTA-1, Tregs become apoptotic [50, 52]. Recent clinical trials have shown anti-GITR products are not effective in reducing cancer burdens, but new PD-1, anti-GITR multimers have shown promise in *in vivo* mouse models [50, 52].

3.4 Blocking of dysfunctional angiogenesis

Abnormal angiogenesis fosters a vascular network designed to bolster tumor development, metastasis, and the sustenance of the tumor *via* nutrient supply [53]. Among the major drivers of this process lies the vascular endothelial growth factor (VEGF) pathway [53]. Tumor cells commonly overexpress VEGF and engage this pathway as VEGF binds to its respective receptor on endothelial cells, thereby stimulating their proliferation and formation of erratic blood vessels [54]. The aberrant vasculature within tumors diminishes the effects of chemotherapeutic drugs *via* two modalities: 1. Reduction of cellular apoptosis and 2. Impairment of drug delivery into tumor sites [54]. Consequently, blocking the VEGF pathway offers a strategy to potentiate the efficacy of chemotherapeutic drugs [54]. Notably, in a phase III trial for colorectal cancer, combining antibodies against VEGF, like bevacizumab, with chemotherapy (irinotecan, 5-FU, and leucovorin), yielded significantly improved overall survival and progression-free survival compared to treatments without bevacizumab [54]. Multiple clinical trials for other indications including breast cancer and non-small cell lung cancer have also replicated these similar synergistic effects and overall highlight the impact of concurrently targeting the TME alongside the tumor itself [54].

3.5 Targeting hypoxia and metabolites

A hypoxic TME is an intrinsic characteristic of solid malignant tumors. As cancer cells proliferate, they rapidly consume oxygen [55]. Moreover, abnormal vasculature

further contributes to a hypoxic environment, increasing the likelihood of metastasis, resistance to traditional cancer therapies, and a poor prognosis [42]. Tumor cells can survive in such an environment by switching to anerobic metabolism, producing erythropoietin, and upregulating proto-oncogenes [56]. Additionally, hypoxia has been shown to contribute to the function and accumulation of intra-tumoral Tregs and tumor-associated macrophages, further suppressing the immune response [57]. Specifically, unlike activated effector T cells, Tregs primarily rely on oxidative phosphorylation and fatty acid oxidation, metabolic processes favored by the hypoxic, low pH, and nutrient-depleted TME [58]. Cancer immunotherapies target this difference in metabolism using checkpoint blockades (CTLA-4, PD-1) and lactate neutralizers (MCT inhibitors or pH-selective antibodies) [58]. Numerous hypoxia-inducible factor targeting drugs interfere with hypoxia-inducible factors during various stages of their production [16, 59]. Some approaches include inhibiting HIF-1α mRNA expression, preventing HIF-1α translation, degrading HIF-1α protein, and interfering with HIF-1α and HIF-2α heterodimerization with HIF-1β to impair hypoxic tumor growth [60]. Another therapy exploits the hypoxic environment to deliver cytotoxins. Hypoxia-activated prodrugs are reduced by cellular oxidoreductases to form DNA-reactive cytotoxins through a process irreversible only in hypoxic conditions [61, 62]. These DNA-reactive cytotoxins then proceed to kill hypoxic cancer cells [16, 59]. Although some hypoxia-activated prodrugs showed promise in Phase I and II clinical trials, there has been limited success in Phase III trials. TH-302, a prodrug that releases isophosphoramide mustard, which alkylates DNA under hypoxia, has shown considerable promise among hypoxia-activated prodrugs and is under combinational therapy clinical trials [61]. Furthermore, hyperoxia therapy aims to increase oxygen content to reverse tumor hypoxia through various methods, including hyperbaric oxygen therapy, normobaric oxygen therapy, carbogen inhalation, and oxygen-generating nanoparticles, among others [16, 59]. Supplementing oxygen to reduce hypoxia is still in its nascent stages of investigation and is being explored for combinational therapies [59].

4. Radiation therapy to target the TME

The use of high doses of radiation to irreparably damage the DNA of cancer cells is a common therapy that approximately 50% of all cancer patients receive and contribute toward 40% of cured cancers [63]. However, the benefits of radiation therapy are offset by the concomitant remodeling of the TME into a more immunosuppressive one, as exemplified by the indirect boost of tumor-promoting TAM infiltration during radiation [64]. One promising way to address this challenge is by combining radiation therapy with TME-specific treatments. For instance, blocking immunosuppressive pathways during radiation can significantly enhance antitumor activity while attenuating radiotherapy side effects such as tissue scarring [65]. Additionally, tumor cells can be further sensitized to irradiation through the use of nanoparticles [66]. Manganese dioxide (MnO2) has been shown to increase the pH of the TME and reduce hypoxic conditions, thus inhibiting tumor autophagy [66, 67]. Indeed, subsequent *in vivo* studies combining MnO2 nanoparticles with radiation therapy demonstrated a significant decrease in tumor growth compared to radiation alone [66]. These recent developments in radiation therapy illustrate how combining it with TME-specific treatments could greatly improve tumor-eradicating efficacy while diminishing radiation's undesired side effects.

5. Oncolytic viruses to target the TME

The effectiveness of oncolytic viruses (OVs) relies on their ability to selectively target tumor cells. For instance, HSV-based oncolytics such as T-VEC (Imlygic) and Delytact achieve tumor specificity through the deletion of specific genes to prevent antiviral pathways and inhibit virus-mediated inhibition, proving clinically successful [68]. Another example is Vaccinia virus (VV)-based oncolytics, exemplified by JX594 and derivatives, which have shown varying degrees of efficacy in late-phase clinical trials [69, 70]. Their natural tropism toward tumor cells, coupled with genetic modifications such as thymidine kinase (TK) gene deletion, enhances tumor selectivity [68]. OVs play a crucial role in transforming the immunologically cold TME into an immunologically hot environment [71]. This shift promotes long-term tumor-specific immunity, providing surveillance against relapse [71]. OV therapy influences the dendritic cell-T cell axis by inducing immunogenic cell death, releasing damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and cytokines [72]. Dendritic cells (DCs) are potent antigen-presenting cells that bridge the innate and adaptive immune systems [73]. OV therapy enhances DC infiltration, maturation, and antigen presentation, promoting T cell activation [74]. CAFs within the TME impede the spread of viruses within the ECM, limiting the effectiveness of oncolytic viruses alone [75]. To address this challenge, an oncolytic adenovirus with a modified gene (Rb-binding-deleted E1A), controlled by a promoter derived from the stroma-related SPARC gene, successfully infected and destroyed both tumor and stromal cells in experiments involving human ovarian cancer and stroma-containing tumors in mice, without causing harm to non-malignant tissues [75]. In addition to CAFs, immunosuppressive cells in the TME, such as Tregs and TAMs, can limit the efficacy of oncolytic viruses [76]. Scientists are addressing this challenge by targeting these cells using oncolytic viruses engineered to express immunomodulatory agents [76]. An illustrative study identified Folate Receptor B (FRb) as a marker on M2-like macrophages *in vitro* [76]. FRb-targeted oncolytic viruses demonstrated the ability to activate the body's own T cells and reduce the number of M2-like macrophages in samples taken from cancer patients with malignant ascites, thus preserving the more pro-inflammatory M1-like macrophages [77]. The combination of tumor-selective replication and immunomodulation by oncolytic viruses offers a flexible approach to combating cancer [78]. Their combination to overcome the TME shows promise, underscoring the changing field of oncolytic viral therapy for more potent cancer treatments.

6. Cell-based therapies to target the TME

The use of chimeric antigen receptor (CAR)-engineered T (CAR-T) cell therapy has emerged as a groundbreaking approach to treat blood cancers and is now rising as a potential therapy for solid tumors [11, 79]. The therapy entails the extraction of T cells from cancer patients, subsequent enhancement of these T cells through the induction of CAR molecules, and the autologous re-infusion of the enhanced T cells [11, 79]. Despite demonstrating substantial promise in addressing solid tumors, akin to numerous therapies, cell-based therapies are met with challenges posed by the TME. Major obstacles inhibiting the efficacy of cell-based therapies include the immunosuppressive nature and hindered infiltration of the TME [3, 17, 80, 81]. Physical barriers within the TME, such as TAMs, ECM, and irregular vasculature,

restrict the ability of cell-based therapies to infiltrate this milieu [3, 17, 80, 81]. Moreover, a multitude of immunosuppressive elements, including immunosuppressive cells such as TAMs, MDSCs, and Tregs, alongside inhibitory molecules such as PD-L1, CTLA-4, adenosine, TGFB, and IL-10, among others, are ubiquitous within the TME [82]. These immunosuppressive components facilitate T cell exhaustion and dampen the immune response [5]. Innovative strategies have emerged to disrupt the TME, representing the next generation of cell products designed to treat solid tumors.

6.1 TAM targeting innate-like T cells

TAMs constitute a substantial portion of the TME, often comprising up to 50% of the tumor mass in some tumors [13]. These TAMs play a dual role: 1. Act as a physical barrier that hinders immune cell infiltration and 2. Express high levels of PD-L1, inducing T cell exhaustion, contributing significantly to maintaining an immunosuppressive TME [3, 17]. Traditional CAR-T cell therapy relies on conventional αβ T cells sourced from cancer patients due to their intrinsic cytotoxic properties [83]. However, these T cells pose the risk of graft versus host disease (GvHD) and lack the capacity to remodel the TME [84]. To address these limitations, an innovative strategy involves leveraging unconventional T cells equipped with CARs. These unconventional T cells, including invariant natural killer (iNKT), mucosal-associated invariant T (MAIT), and gamma-delta T (γδT) cells, are MHC-I independent and possess TCRs that recognize distinct antigen-presenting molecules CD1d, MR1, and BTN3A1 (CD277), respectively [3–5]. Importantly, these antigen-presenting molecules are highly conserved and ubiquitously expressed on TAMs [5]. Unconventional T cells engage in a TCR-dependent mechanism that enables them to target and eliminate TAMs effectively, remodeling the TME toward a more proinflammatory state [3–5]. Through engineering with CARs, these unconventional T cells can simultaneously modulate the TME and target the tumor itself, potentially enhancing the efficacy of solid tumor therapies [5].

6.2 MDSC targeting CAR-T cells

Another challenge to CAR-T therapy lies in MDSCs, a heterogeneous immune cell population recruited to the TME of most solid tumors [3–5]. MDSCs inhibit effector T cell activity through multiple mechanisms, such as promoting Treg expansion, secreting immunosuppressive cytokines, and sequestering essential amino acids for T cell proliferation [3–5]. One approach to rescue CAR-T cytotoxicity could be in the engineering of a chimeric receptor targeting both MDSCs and tumor cells. As agonists of TRAIL Receptor 2 (TR2) selectively induce apoptosis in MDSCs, engineering CAR-T cells with TR2 is a promising strategy [85]. *In vitro* studies demonstrated that adding TR2 and co-stimulatory receptor 41BB on CAR-T cells decreased the numbers of MDSCs while significantly enhancing CAR-T cell potency against tumor cells [85]. In comparison, CAR-T cells targeting either MDSCs or tumor cells alone did not prove as effective [85]. This synergistic approach to CAR-T cell engineering emphasizes the benefits of simultaneously targeting cancer cells and their microenvironment.

6.3 ECM degrading CAR-T cells

Cell-based therapies targeting tumor cells are limited by the extent of their infiltration into the TME [5]. The ECM plays a major role in shaping the TME, influencing its histopathology, behavior, and governing biochemical and biophysical aspects

regulating TME processes [5]. Besides facilitating cancer progression and metastasis, the ECM acts as a physical barrier impeding immune cell infiltration, thereby diminishing the effectiveness of various cell-based therapies [86]. To address this obstacle, innovative engineering approaches have emerged to overexpress heparanase (HPSE), an enzyme that degrades heparan sulfate proteoglycans (HSPGs), a key ECM constituent [86]. Disrupting the ECM *via* HPSE overexpression promotes immune cell infiltration [86]. This modification, incorporated alongside CAR engineering in T cells, demonstrated enhanced infiltration and antitumor efficacy in preclinical xenograft models of neuroblastoma for GD2-specific CAR-T cells with HPSE engineering [86]. This engineering approach highlights the significance of concurrently targeting the TME and tumor cells, perpetuating synergistic effects overcoming TME limitations.

6.4 Blocking immunosuppressive molecules with ICB

In the TME, cell-based therapies encounter challenges from immunosuppressive molecules inducing cellular exhaustion and diminished cytotoxicity, reducing the effectiveness of therapies for solid tumors [5]. Among these molecules, PD-L1 stands out as a prominent checkpoint ligand ubiquitously expressed within the TME by macrophages, DCs, MDSCs, B and T cells, fibroblasts, and tumor cells [87, 88]. The binding of PD-L1 with PD1 expressed on therapeutic cells deactivates the immune response and cellular activation by inhibiting proliferation, inducing cell death, diminishing persistence, and decreasing effector function [23, 88, 89]. Blocking the immunosuppressive interaction between PD-1 of immune cells and PD-L1 within the TME offers synergistic effects with cell-based therapies against solid tumors [4]. Preclinical models of $Her2^+$ sarcoma and breast cancer demonstrated synergistic effects where combining anti-PD-1 and Her2-targeting T cells resulted in enhanced CAR-T cell function and tumor killing [87]. The combination of immune checkpoint blockade and CAR-T cell therapy synergizes by blocking the immunosuppressive PD-1 axis between the therapeutic cells and TME, improving therapeutic outcomes compared to CAR-T cell therapy alone [4].

7. Conclusion

In this chapter, we conduct a thorough examination of the TME in the progression and treatment of cancer. Far from being a bystander, the TME is characterized by its complex and dynamic interactions, actively participating in the context of cancer. TME exerts a significant influence on tumor development, metastasis, and the efficacy of therapeutic interventions. The intricate relationship between the TME and cancer cells introduces distinct challenges while also unveiling new opportunities for enhancing cancer treatment strategies.

Despite the variety, numerous cancer therapies such as radiation, chemotherapy, and cell-based treatments are commonly limited by the TME. By significantly contributing to cancer growth and survival, the TME often reduces the efficacy of cancer-targeting therapies. Strategies that simultaneously address both cancer cells themselves and the TME have shown promise in effectively treating solid tumors. The development of innovative methods to target the TME offers the potential for enhancing cancer treatments. Such advancements could enhance patient outcomes and overcome the challenges presented by the TME in cancer therapy.

Overall, this chapter highlights the critical role of TME in cancer. Integrating a comprehensive understanding of the TME is necessary for the development of cancer treatment strategies. The multifaceted consideration offers insights for further research and clinical applications that could bolster the efficacy of cancer therapies.

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Competing interests

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