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Review Article

Tumor microenvironment reprogramming by nanomedicine to enhance the effect of tumor immunotherapy

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ABSTRACT

With the rapid development of the fields of tumor biology and immunology, tumor immunotherapy has been used in clinical practice and has demonstrated significant therapeutic potential, particularly for treating tumors that do not respond to standard treatment options. Despite its advances, immunotherapy still has limitations, such as poor clinical response rates and differences in individual patient responses, largely because tumor tissues have strong immunosuppressive microenvironments. Many tumors have a tumor microenvironment (TME) that is characterized by hypoxia, low pH, and substantial numbers of immunosuppressive cells, and these are the main factors limiting the efficacy of antitumor immunotherapy. The TME is crucial to the occurrence, growth, and metastasis of tumors. Therefore, numerous studies have been devoted to improving the effects of immunotherapy by remodeling the TME. Effective regulation of the TME and reversal of immunosuppressive conditions are effective strategies for improving tumor immunotherapy. The use of multidrug combinations to improve the TME is an efficient way to enhance antitumor immune efficacy. However, the inability to effectively target drugs decreases therapeutic effects and causes toxic side effects. Nanodrug delivery carriers have the advantageous ability to enhance drug bioavailability and improve drug targeting. Importantly, they can also regulate the TME and deliver large or small therapeutic molecules to decrease the inhibitory effect of the TME on immune cells. Therefore, nanomedicine has great potential for reprogramming immunosuppressive microenvironments and represents a new immunotherapeutic strategy. Therefore, this article reviews strategies for improving the TME and summarizes research on synergistic nanomedicine approaches that enhance the efficacy of tumor immunotherapy.

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1. Introduction

Malignant tumors are among the most lethal conditions that threaten human life, so effective treatment strategies are desperately needed. In recent years, the development of tumor immunotherapy has advanced tumor treatment. Tumor immunotherapy involves overcoming the immunosuppressive conditions of the immune microenvironment and enhancing the responses of immune cells to tumor cells via the administration of antigens, checkpoint inhibitors, cytokines, or T cells to fulfill the purpose of tumor treatment [1,2]. However, the use of tumor immunotherapy in clinical practice still has certain drawbacks, including poor response rates and variations in patient responses, primarily due to the strongly immunosuppressive nature of the tumor microenvironment (TME). The TME refers to the local environment surrounding tumor cells and contains various elements, including the extracellular matrix (ECM), blood vessels, and immune cells. It plays a key role in the development and treatment of tumors. The TME is characterized by hypoxia, low pH, abnormal vascular proliferation, and large numbers of immunosuppressive cells, and these factors result in the development of an immunosuppressive microenvironment [3]. With continuous research on tumor progression, the TME has been confirmed to play a crucial role in the processes of tumor occurrence, invasion, and metastasis [4]. The TME is a unique biological environment that is formed by tumor cells, infiltrating immune cells, stromal cells, blood vessels, ECM, and secretory factors during tumor occurrence and development. These components of the TME affect tumor immunotherapy and the therapeutic effects of drugs on tumors.

The characteristics of the TME, including hypoxia, low pH, dense extracellular matrix, infiltration of large numbers of M2-tumor-associated macrophages (M2-TAMs), enrichment of cancer-associated fibroblasts (CAFs), enrichment of immunosuppressive cells and factors, and abnormal proliferation of blood vessels, result in immunosuppressive conditions in the TME, which reduce the effects of immunotherapy. Effective regulation of the TME and reversal of immunosuppressive conditions are effective strategies for improving the effects of tumor immunotherapy. The use of multidrug combinations to improve the TME is an efficient approach to boosting the effectiveness of antitumor immune responses. Therefore, researchers have studied TME reprogramming to enhance the effects of tumor immunotherapy. How to regulate the TME and reverse its immunosuppressive nature is an important topic that researchers should thoroughly explore and study. Researchers can regulate the microenvironment and reverse its immunosuppressive conditions through the administration of drugs or materials to improve the effectiveness of immunotherapy.

The inability to effectively target drugs reduces therapeutic effects and causes side effects, but nanodrugs have the advantages of improving drug bioavailability, promoting the targeting of drugs to tumors and reducing side effects [5]. For instance, Wang et al. [6] designed nanoparticles

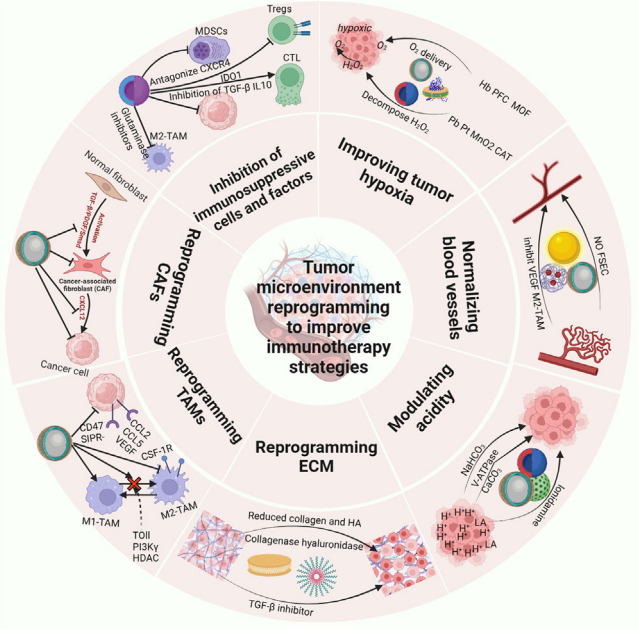

Fig. 1 – Overview of strategies for reshaping the TME and improving the efficacy of immunotherapy based on nanomedicine and nanodelivery systems. Created using Biorender.com.

that can efficiently penetrate the blood-brain barrier and specifically target tumor cells at the lesion site, thereby enhancing treatment efficacy. Importantly, nanodrug delivery carriers can also regulate the TME and deliver large or small therapeutic molecules to reduce the TME's suppressive effects on immunological cells [7]. In addition, some nanocarriers can also be used to enhance the efficacy of tumor immunotherapy due to their inherent properties (such as light, thermal effect, immunogenic cell death (ICD) induction, etc.) [8,9]. For example, drug delivery systems (DDSs) that are based on various nanomaterials (such as perfluorocarbons (PFCs), metal-organic framework materials (MOFs)) and delivery vehicles that are modified with collagenase, and anti-vascular drugs, have increasingly been shown to have potential and value for reprogramming the TME. Therefore, improving the TME by using nanomedicine and delivery systems is a reasonable strategy for improving immunotherapy. It can be seen that nanodrug carriers have great potential for reprogramming the immunosuppressive microenvironment, and it is necessary to conduct a comprehensive and in-depth review, and provide a new approach for enhancing tumor immunotherapy.

In this review, the relationship between the TME and immunosuppression, as well as strategies that involve nanodrug delivery carriers are summarized. The goal of this review is to support the development of strategies to reshape the TME, thus improving tumor immunotherapy and enhancing antitumor effects, this review may provide new ideas for enhancing the antitumor effects of immunotherapy. (Fig. 1)

2. Tumor immunotherapy

Tumor immunotherapy is a novel treatment strategy that targets the immune system, promoting precise, antigen-specific identification and killing of tumor cells. In various experimental and clinical studies, immunotherapy has been shown to have advantages over traditional antitumor therapies in prolonging progression-free survival and overall survival [10,11]. For instance, the application of chimeric antigen receptor T-cell (CAR-T) treatment has shown encouraging results in a clinical trial [12]. In this therapy, the patient's T-cells are designed to express a chimeric antigen receptor that recognizes and binds to specific antigens on tumor cells. This allows the CAR-T cells to precisely identify and attack the cancer cells in the patient's body, thus providing a targeted therapy for the treatment of cancer. CAR-T cell treatment has been applied to treat a number of hematologic tumors, like lymphoblastic leukemia and multiple myeloma. In one study [12], out of the 79 patients who received CD19 CAR T-cell infusions, 65 achieved complete remission, demonstrating a higher treatment success rate than conventional therapies. Moreover, immunotherapy is not only efficient and specific but can also achieve a long-term antitumor immune response through immune memory cells [13]. Traditional therapeutic strategies, such as surgery, chemotherapy, and radiotherapy, target the tumor itself, but the environment surrounding the tumor is rich and complex. Treatment focused solely on the tumor without addressing the TME may not achieve the desired results. Immunotherapy can reverse and ameliorate the immunosuppressive conditions of the TME, restoring the immune system's ability to attack the tumor. To date, immunotherapy has made significant advancements in cancer treatment. However, it still has some drawbacks and limitations, such as high individual variability, high expense, the potential development of immunotherapy resistance, and the occurrence of toxic side effects [14,15]. According to the different mechanisms of action, this review will describe different types of tumor immunotherapy, including tumor vaccines, adoptive cell therapy, immune checkpoint inhibitor therapy, nonspecific immunotherapy, neoantigen vaccine immunotherapy and monoclonal antibody immunotherapy in detail. (Table 1)

2.1. *Tumor vaccines*

Tumor vaccines introduce different forms of tumor antigens into a patient's body; these antigens are captured and processed by antigen presenting cells (APCs) and then presented to T cells to trigger innate and adaptive antitumor immune responses, which are the main mechanism by which the immune response is enhanced. In 2010, Provenge (sipuleucel-T), the first commercial therapeutic tumor vaccine based on dendritic cells (DCs), was given the green light by the US Food and Drug Administration (FDA) to treat metastatic or terminal prostate cancer; this was a milestone in tumor vaccine development. Tumor vaccines can be classified in a variety of ways. According to their tumor antigen components and properties, tumor vaccines can be divided into whole tumor cell vaccines, tumor protein/peptide vaccines and gene vaccines. According to their uses, tumor vaccines can be divided into preventive and therapeutic tumor vaccines [16]. Currently available prophylactic cancer vaccines include vaccines against human papillomavirus (HPV) and hepatitis B virus (HBV). In addition, personalized neoantigen tumor vaccines that use neoantigens to activate the immune system are currently being developed [17]. For example, on March 15, 2023, the LK101 injection, the first personalized neoantigen tumor vaccine approved by the National Medical Products Administration (NMPA) with acceptance number CXSL2200612, entered the clinical stage in China for the treatment of solid tumors. Certainly, tumor vaccines have limitations. For example, they are effective only against specific types of cancer and not for all cancer types. This limitation hinders their broad application [18].

2.2. *Adoptive cell therapy (ACT)*

ACT involves expanding and culturing tumor-killing immune cells *in vitro* and then returning them to patients to achieve the goal of tumor immunotherapy. Adoptive immunotherapy is a more direct approach to changing the established balance between tumor cells and immune cells [19,20]. At present, the immune cells that can be used for transfusion include T cells, macrophages, and natural killer (NK) cells; among these cell types, the adoptive T-cell therapy is widely applied. There are two main types of adoptive T-cell therapy. One type involves isolating and collecting tumor-infiltrating T cells, culturing and amplifying these cells, and then transfusing them back to the patient. The other type involves the use of genetic engineering to modify T cells to express chimeric antigen receptors (CARs) so that they can recognize target tumor antigens. These CAR-T cells are then injected back into the patient to specifically identify and kill target tumor cells. Currently, CAR-T immunotherapy has made remarkable progress in the treatment of hematologic tumors [21,22]. For instance, Kymriah (tisagenlecleucel), the first CAR-T therapy drug approved for marketing on August 30, 2017, exhibited a substantial ability to induce remission in the management of diffuse large B-cell lymphoma that has relapsed or is refractory. Furthermore, the global debut of the first fully human CAR-T therapy specifically targeting the B-cell maturation antigen (BCMA) on June 30, 2023, heralds fresh possibilities for patients with relapsed or refractory multiple myeloma (R/RMM). The adoptive transfer of autologous tumor-infiltrating T cells has also been shown to be very effective in treating metastatic melanoma [23].

ACT has shown certain therapeutic effects in the clinical treatment of some tumors; however, the therapeutic effect of this strategy on solid tumors needs further research and verification, and the approach has limitations, such as cytokine storms and off-target effects [24,25]. Moreover, the heterogeneity of solid tumors, which rarely express only one tumor-specific antigen [26], and signaling from intratumoral immunosuppressive checkpoints present major limitations of ACT in the clinical management of solid tumors.

Table 1 – Classification and summary of tumor immunotherapy.

Tumor immunotherapy	Principle	Representative drug	Characteristic	Ref.
Tumor vaccines	The presentation of tumor antigens induces anti-tumor antibodies and cellular immunity	Sipuleucel-T; HPV; HBV	It has a good prospect in combination with immunomodulatory antibody	[42]
ACT	The method of controlling the tumor by infusing the patient with specific immune cells that are specific to cancer cells *in vitro*	TIL; CAR-T; CAR-M; CAR-NK; TCR-T	Hematologic tumors have excellent efficacy, but solid tumors do not. TIL separation and amplification is difficult, and there is a bottleneck in industrial production	[25,43]
Immune checkpoint inhibitor therapy	Monoclonal antibodies target surface regulatory receptors on T lymphocytes to activate tumor-specific T lymphocytes	Anti-CTLA-4 (YERVOY); Anti-PD-1 (nivolumab); Anti-PD-L1 (atezolizumab)	Low toxicity, long - lasting, with traditional tumor targeting therapy and other immunotherapy, and a very good prospect of combination	[27]
Nonspecific immunotherapy	Stimulates T lymphocytes or antigen presenting cells to enhance the antigen presentation process, promotes the activation, proliferation or differentiation of anti-tumor immune cells	IL-2; G-CSF; Administration of cytokines IFN-γ and IL-2	Promotes the overall improvement of immune system function, can be used alone or in combination with other therapies to produce a stronger and more durable immune response, but its nonspecificity causes toxic side effects	[31]
Neoantigen vaccine immunotherapy	Promotes the proliferation of specific and protective T cells; its combination with PD-1 antibody can further promote the killing of specific T cells on tumors	The GEN-009 vaccine; mRNA-4157; RO7198457	Precise targeting of tumor cells and enhancement of the tumor-specific immune response. It can produce long-term immune memory and inhibit tumor recurrence and metastasis after treatment	[33,44,45]
Monoclonal antibody immunotherapy	Antibodies prepared by hybridoma cell technology against a specific epitope	Rituximab; Trastuzumab	High purity and strong specificity	[46]
Oncolytic virus	After intra - injection of oncolytic cancer, viral proliferation induces tumor lysis and triggers the generation of further anti-tumor immune mechanisms	T-VEC	It has a good prospect in combination with immunomodulatory antibody	[47]

2.3. *Immune checkpoint inhibitor therapy*

Immune checkpoints are inhibitory signaling networks of the immune system that perform key roles in preserving self-tolerance, modulating the magnitude of immune responses in peripheral tissues, and reducing tissue damage. In the TME, tumor cells and some immune cells can overexpress inhibitory immune checkpoints, thus inhibiting T cell activation. Therefore, checkpoint inhibitors can be used to reverse immunosuppression and promote immune system activation. At present, multiple tumor-inhibitory immune checkpoints, including programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), lymphocyte activation gene-3 (LAG3), and T-cell immunoglobulin domain and mucin domain-3 (TIM3), have been identified [27]. Among these checkpoints, anti-PD-1/PD-L1 therapies are the most effective immune checkpoint inhibitor therapies and have been approved for the treatment of a wide range of malignancies such as hematologic tumors, melanoma, lung, colorectal, liver, bladder, and kidney cancers [28]. The first anti-PD-1/PD-L1 immune checkpoint inhibitors to gain approval were nivolumab (Opdivo) and pembrolizumab (Keytruda), which obtained FDA approval for the treatment of certain cancer types in 2014. These anti-PD-1/PD-L1 drugs marked the dawn of a new era of cancer therapy. Recently, programmed cell death -ligand 2 (PD-L2) has also been found to have great potential in cancer treatment [29]. Immune checkpoint inhibitor therapy has shown some success, but the major bottleneck is the low response rate (only 10% to 30%) in the treatment of most cancers. For example, anti-PD-1/PD-L1 therapy has almost no effect on some types of cancer, such as colorectal cancer and pancreatic cancer with microsatellite stability (MSS CRC) [30]. Metastatic colorectal cancer is categorized into types with high microsatellite instability (MSI-H) and microsatellite stability (MSS). The majority of patients fall into the MSS category. From an immunological perspective, MSI-H CRC is primarily associated with an immune-inflamed phenotype, while MSS CRC often exhibits an immune-desert phenotype, characterized by a lower presence of immune cells. Immune checkpoint inhibitor therapy has significant drawbacks, including high individual variability [14]. At present, new immune checkpoint agents and their use in combination therapy are also being studied in

preclinical or clinical trials, with the aim of further improving the effects of tumor immunotherapy [27].

2.4. *Nonspecific immunotherapy*

Nonspecific immunotherapy stimulates the body's immune system in a nonspecific manner to enhance immune-mediated tumor inhibition. Some phagocytes, such as macrophages, secrete a variety of cytokines in addition to performing phagocytosis and antigen presentation functions. Some immune cells, such as B cells, T cells and APCs, can be activated by these cytokines. Therefore, immune cell activation can be achieved by the direct administration of relevant cytokines or by the administration of nonspecific immune stimulants [31]. Common nonspecific immune stimulants include interleukin (IL)−2, IL-12, and interferons. For instance, therapy involving lymphokine-activated killer (LAK) cells employs IL-2 to boost the immune activity of peripheral blood lymphocytes. These cells primarily comprise a mixed population of various lymphocytes, including NK cells and T lymphocytes. They exhibit cytotoxic effects on tumors *in vitro*. The mechanism of the LAK cell-mediated killing of target cells is analogous to that of NK cells, as LAK cells can recognize target cell surface structures through cell-to-cell contact and participate in tumor cell destruction by secreting cytokines. Nonspecific immunotherapy also exhibits certain limitations. For instance, due to its lack of specificity, it cannot directly target specific pathogens or abnormal cells, resulting in low selectivity [15]. Additionally, as it increases the overall activity of the immune system, it may lead to excessive immune responses or immune-related adverse events.

2.5. *Neoantigen vaccine immunotherapy*

Neoantigens are nonautologous proteins with individual specificity that are produced due to nonsynonymous mutations in the genomes of tumor cells [32]. Due to their strong immunogenicity and tumor-specific expression, neoantigens can induce tumor-specific T-cell responses, and prevent damage to normal tissues [33]. At present, neoantigen-based tumor vaccines stand out from many immunotherapies and have become a popular trend in the field of tumor immunotherapy. Neoantigen vaccine immunotherapy is a type of tumor immunotherapy that uses neoantigens present in tumor cells to activate the patient's immune system and thus fight the tumor. Neoantigen vaccines can precisely target tumor cells and enhance the tumor-specific immune response to promote targeted killing of tumors. In addition, tumor-specific immune responses that are induced by neoantigen vaccines persist, generate long-term immune memory, and prevent tumor recurrence and metastasis after treatment [34]. Recent research is also focused on combining this approach with immune checkpoint inhibitor therapy to enhance the efficacy of these neoantigen vaccines. Neoantigen vaccine immunotherapy represents a potentially innovative approach, but it also presents certain inherent challenges and drawbacks. For instance, the identification of appropriate neoantigens can be challenging because each tumor may exhibit a different antigen expression profile. Thus, meticulous screening and assessment are needed to determine the most suitable new antigens. Moreover, neoantigens may change during the course of tumor progression, further complicating vaccine design.

2.6. *Monoclonal antibody immunotherapy*

A monoclonal antibody is a type of antibody that has specificity for a single epitope region on an antigen, and it is usually prepared by the hybridoma technique [35,36]. Currently, monoclonal antibody drugs that are in clinical use can directly target tumor cells by recruiting T cells to the tumor site, and then binding to antigens on the tumor surface, thus contributing to the inhibition or even the elimination of tumors. The cancer types that can be treated with monoclonal antibody drugs mainly include breast cancer, colon cancer, lymphoma, etc. [37,38]. For instance, monoclonal antibodies like pembrolizumab (Keytruda) and nivolumab (Opdivo) have received approval for the treatment of different cancer types, such as non-small cell lung cancer, melanoma, and renal cell carcinoma. They function by inhibiting the immune checkpoint PD-1, thereby enhancing the immune system's response to tumors. Nearly 33 kinds of antibodies are in the late stages of clinical trials to treat cancer, such as multiple myeloma, melanoma, breast cancer, bladder cancer and other cancers [39]. Moreover, in recent years, monoclonal antibodies that target the CD39/CD73/A2AR pathway have been investigated in clinical trials and have shown good efficacy. The injection of JS019, the first monoclonal antibody against CD39, was approved in China for clinical trials on December 28, 2021, and has garnered significant attention [40]. Monoclonal antibody immunotherapy also has certain limitations, such as typically being specific to particular molecular targets. Therefore, it is suitable only for those tumor types that are associated with the target, which restricts its widespread application [41]. However, we believe that with continued improvement and development, monoclonal antibody therapy will become the preferred strategy for cancer treatment.

3. Tumor microenvironment (TME)

3.1. *Composition and characteristics of the TME*

The TME is a distinct and intricate tissue environment that arises during the occurrence and growth of tumors. It is widely acknowledged as a critical element influencing the development of tumors and the effects of immunotherapy.

The composition of the TME is complex, mainly comprising cellular and noncellular components (Fig. 2). The cellular components include endothelial cells (ECs), CAFs, and various types of immune cells, such as T lymphocytes, B lymphocytes, tumor-associated macrophages (TAMs), DCs, NK cells, neutrophils, and myeloid-derived suppressor cells (MDSCs), these cellular components interact within the TME, determining the outcomes of immune responses,

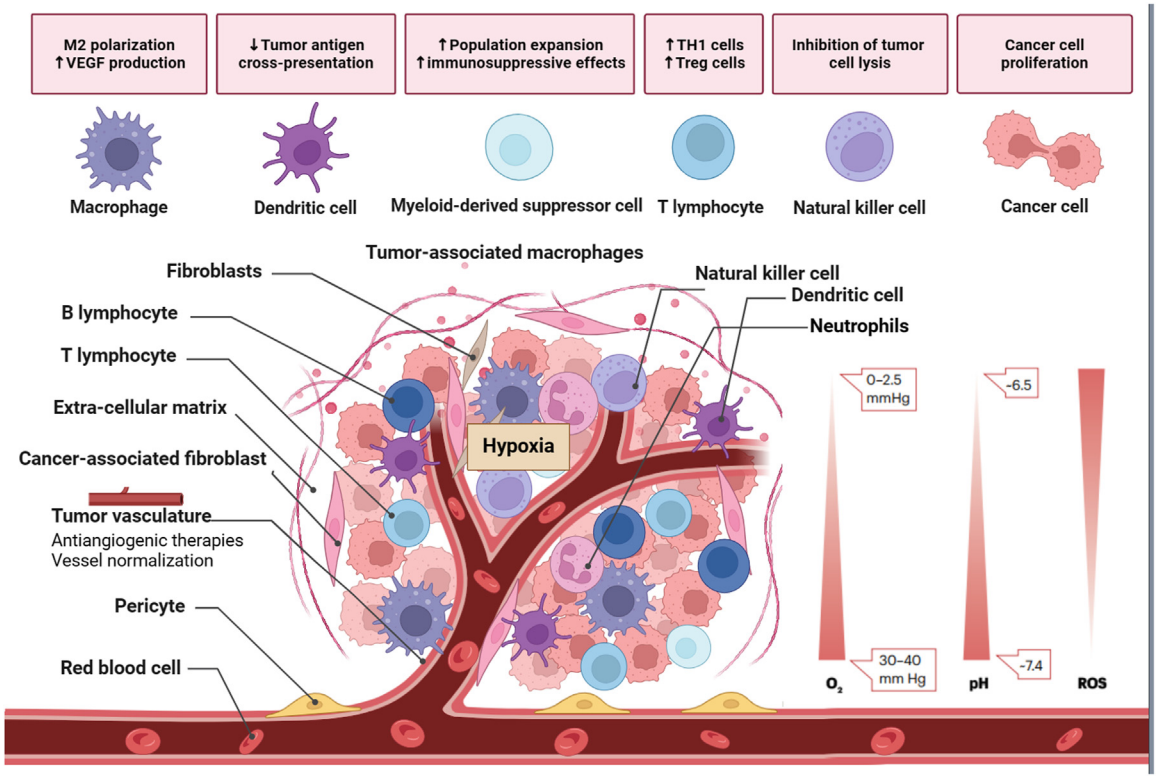

Fig. 2 – Major components and characteristics of the TME (including reactive oxygen species, pH and oxygen). Created using Biorender.com.

tumor growth, and treatment responses; The noncellular components include proteolytic enzymes, ECM proteins, growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and fibroblast growth factor (FGF), and inflammatory factors [48]. The unfavorable conditions in the TME allow the infinite proliferation of tumor cells, promote tumor development and metastasis, and constitute an immunosuppressive microenvironment.

The characteristics of the TME include the following: (1) Abnormal blood vessels: tumor blood vessels are significantly different from normal blood vessels and exhibit abnormal proliferation and malformation due to increased levels of VEGF [49]. (2) Hypoxia: during tumor cell growth, the excessive proliferation of malignant cells and abnormal blood vessels results in an insufficient supply of oxygen to tumor cells, so most solid tumors exhibit hypoxia [50]. (3) Lower pH: tumor cells use aerobic glycolysis as the main source of energy, and aerobic glycolysis preferentially utilizes acidic substances, such as lactic acid produced from glucose and CO_2 produced by intracellular aerobic metabolism. Thus, the tumor extracellular matrix has a lower pH than that of normal tissues. (4) High interstitial pressure: the increase in tumor mass and the high permeability of the vascular wall contribute to the characteristic high interstitial pressure of the TME. These characteristics promote tumor growth, invasion and treatment resistance and result in the formation of an immunosuppressive TME. Reprogramming the TME is a useful strategy for enhancing immunotherapy.

3.2. *Classification of the TME*

Tumor cells create an immunosuppressive TME by exploiting the immune system's negative regulatory mechanisms. The main cell types in tumor immune microenvironments (TIMEs) include T-regulatory cells (Tregs), CAFs, MDSCs, and TAMs. These cells, together with other cells, form complex regulatory networks and contribute to the formation of a tumor-promoting environment.

TIMEs are divided into three types: infiltrated-excluded (I-E), infiltrated-inflamed (IL-I), and infiltrated-TLS (TLS). I-E TIMEs are usually characterized by the presence of cytotoxic T lymphocytes (CTLs) in the tumor; these cells are located at the edge of the tumor or "stuck" in fibrotic nests (Fig. 3a), and it is difficult for these cells to infiltrate the core of the tumor. This type of tumor exhibits low immunogenicity and is referred to as a "cold" tumor; these tumors usually do not respond well to immune checkpoint therapy. This type of TIME is usually associated with various epithelial cancers, such as colorectal cancer and pancreatic ductal adenocarcinoma. IL-I TIMEs are characterized by the heightened expression of PD-L1 on tumor cells, accompanied by enhanced infiltration of CTLs and other white blood cells, along with elevated PD-1 expression within the tumor. (Fig. 3b). This type of tumor, such as microsatellite instability in colorectal cancer, usually responds well to immune checkpoint inhibitor therapy. Finally, TLS TIMEs have tertiary lymphoid structures (TLSs) that resemble lymph nodes (Fig. 3c). These TLSs are present at tumor margins and

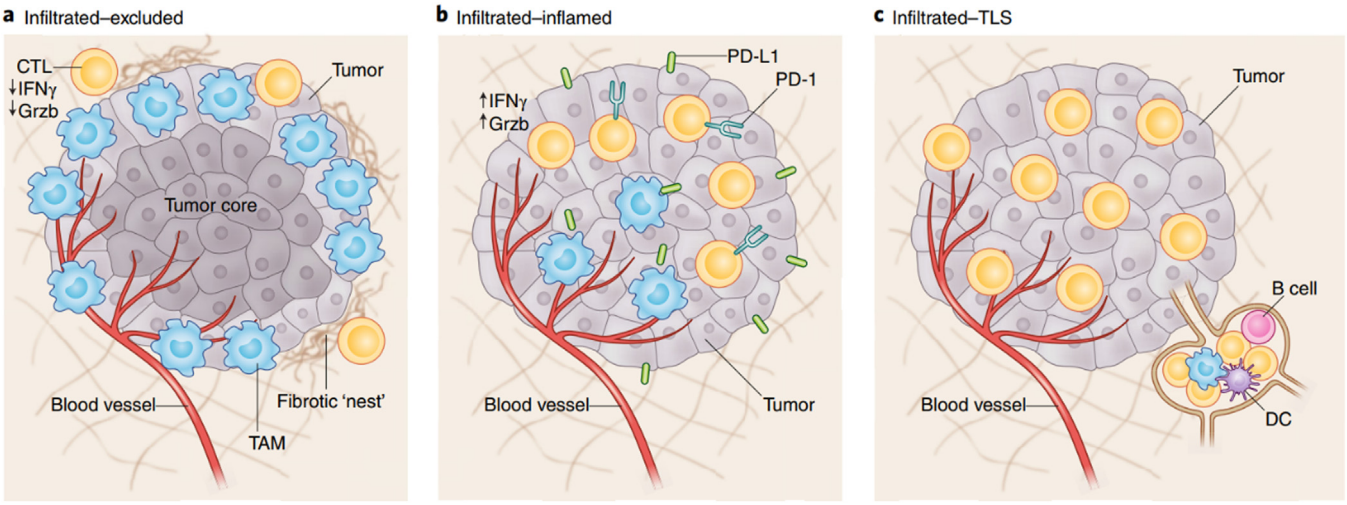

Fig. 3 – Classes of tumor immune microenvironments. Reproduced from [51] with permission from Springer Nature.

in the interstitium and usually are formed in response to increased inflammation, such as following vaccination [51].

3.3. *Immunosuppressive effects in the TME*

3.3.1. *Hypoxia*

Hypoxia is a classic physiological characteristic of TME and is an important driver of tumor growth in TME [52]. In contrast to the oxygen partial pressure in normal tissues (30–40 mmHg), the oxygen levels in tumor tissues progressively decrease towards the central regions of the tumor surface, reaching as low as 0–2.5 mmHg in certain core areas (Fig. 2). There are several causes of hypoxia-induced tumor immunosuppression: (1) Hypoxia upregulates hypoxia-inducing factor HIF1α, which regulates tumor angiogenesis and controls the expression of various vascular growth factors, leading to abnormal tumor angiogenesis and reducing the efficacy of immunotherapy. (2) Hypoxia can inhibit the expression of E-cadherin in epithelial cells and promote the metastasis of tumor cells [53]. (3) Tumor hypoxia promotes the formation of immunosuppressive TMEs by inducing the expression of chemokine ligand 28 (CCL28) and increasing the recruitment of regulatory T cells [54]. (4) The PI3K/AKT signaling pathway can be activated under hypoxic conditions [55]. In addition, hypoxia can increase reactive oxygen species (ROS) levels, leading to excessive malignant tumor cell proliferation and promoting tumor growth and metastasis.(5) Hypoxia can also affect key immune cell groups in the TME. For example, hypoxia supports the functions of immunosuppressive cells such as Tregs, MDSCs, and TAMs while interfering with the functions of effector T cells, NK-T cells, and NK cells, resulting in increased production of immunosuppressive cytokines and immunosuppression [56]. (6) Anoxia also leads to the polarization of TAMs toward the immunosuppressive M2 phenotype, inhibiting the recruitment of effector lymphocytes. In addition, hypoxia also affects the metabolic activity of cells in the TME, which affects the activity of proinflammatory immune cells and ultimately leads to the development of malignant tumors.

Hypoxia can result in immunosuppression by altering multiple metabolic processes in cancer cells, resulting in an accumulation of immunosuppressive metabolites like adenosine [57]. Hypoxia also substantially limits the effectiveness of treatments, including chemotherapy, photodynamic therapy and even immunotherapy [58]. Since an anoxic microenvironment can lead to immunosuppression, ameliorating the anoxic nature of the TME has great prospects for improving tumor immunotherapy.

3.3.2. *Abnormal vascular proliferation*

Abnormal vascular proliferation is a hallmark of solid tumors and tumor recurrence because it results in increased levels of factors, such as VEGF. Normal tumor blood vessels not only provide oxygen and nutrients to cells but also maintain the normal physiological cellular environment. In contrast, such abnormal blood vessels promote tumor progression through ischemia-reperfusion injury, resulting in tumor hypoxia and low pH [59]. Additionally, dysregulation of tumor vascular permeability and lymphatic drainage led to increased interstitial fluid pressure (IFP) in the TME [58]. Abnormal tumor angiogenesis leads to the establishment of an immunosuppressive TME through several mechanisms.

(1) Abnormal tumor blood vessel proliferation leads to hypoxia of the TME and low pH, which results in immunosuppression through various mechanisms [60]. First, the recruitment of immunosuppressive regulatory T cells is increased via the upregulation of the chemokines CCL17, CCL22 and CCL28. Second, colony stimulating factor (CSF)−1 and C–C-motif chemokine ligand (CCL)−2, which are secreted by tumor cells, recruit inflammatory monocytes and TAMs. TAMs are reprogrammed from the antitumor M1-like phenotype toward the immunosuppressive M2 phenotype. M2-like TAMs express Th2, IL4, IL10 and transforming growth factor (TGF-β) at high levels, thus inhibiting Th1 T cell-mediated immunity

[61,62]. Third, DCs maturation is inhibited, resulting in impaired antigen presentation and activation of tumor-specific CTLs. Fourth, endothelial cells (ECs) with an immunosuppressive phenotype undergo abnormal expansion. Fifth, the TME activates the PD-1/PD-L1 pathway, resulting in the upregulation of PD-L1 expression on CTLs, ECs, and tumor cells. The infiltration of CTLs into the tumor leads to PD-1 upregulation.

(2) The cells in the TME secrete VEGF, TGF-β, prostaglandin E2 (PGE2) and other factors to reduce the antitumor effects of effector T cells [59].

(3) VEGF is a critical group of growth factors playing a crucial role in angiogenesis and the upkeep of a normal vascular system. The abnormal proliferation of tumor blood vessels in the TME is induced by high levels of VEGF, which can also lead to immunosuppression. First, the increase in VEGF levels can directly inhibit the transport, proliferation and effector function of CTLs [63]. Second, high levels of VEGF reduce T cell activation by inhibiting DC maturation and antigen presentation, thus reducing T cell-mediated antitumor immune responses [64,65]. Third, excessive VEGF promotes the proliferation and accumulation of immunosuppressive cells, like MDSCs and Treg cells [66,67]. Fourth, VEGF regulates the migration of immune cells to malignant tumors by modifying the expression of adhesion molecules on ECs and immune cells, such as integrin ligand intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion protein 1 (VCAM1) [68–70]. Fifth, VEGF promotes angiogenesis, causes tumor vascular abnormalities, leads to TME hypoxia and low pH, and then promotes systemic or local immunosuppression [71–73].

(4) It has been demonstrated that angiogenin 2 (ANG2) signaling promotes immunosuppression in tumors via a variety of ways. First, ANG2 promotes the recruitment of MDSCs [74] and Treg cells [75] by increasing leukocyte-endothelial interactions through the upregulation of adhesion molecules. Second, ANG2 disrupts EC-pericyte contacts, thereby promoting the migration of immune cells from the vasculature to the TME [76,77]. Third, ANG2 can also regulate the function of monocytes by inhibiting the secretion of tumor necrosis factor (TNF), thus limiting the antitumor effects of these monocytes [78]. Finally, VEGF and ANG2 may work together to cause tumor immunosuppression [60].

In general, the abnormal proliferation of tumor vessels and its consequences result in the formation of an immunosuppressive TME, which reduces the capacity of immune cells to eradicate the tumor. Therefore, targeting vascular normalization is another strategy for reversing the immunosuppressive nature of the TME.

3.3.3. *Acidification*

Acidification is also a significant characteristic of the TME. The “Warburg effect” refers to the fact that, whereas normally differentiated cells primarily depend on mitochondrial oxidative phosphorylation to provide cellular energy, the majority of tumor cells typically preferentially utilize glucose for aerobic glycolysis to produce energy [79], which results in the accumulation of the product lactic acid in the extracellular tumor environment and the diffusion of hydrogen ions into the intercellular space [80]. In addition, carbon dioxide, which is produced by tumor respiration, is converted to H^+ and CO_3^{2-} by carbonic anhydrase IX (CAIX). Underperfusion of the tumor results in the inability of lactic acid and H^+ to be effectively transferred from the tumor, so carbonic acid and lactic acid become the direct causes of tumor acidification. This is why TMEs in most solid tumors are weakly acidic, with tumor pH values ranging from 6.5 to 6.8 [81].

The acidity and high levels of lactic acid in tumor TMEs can lead to immunosuppressive effects by recruiting immunosuppression-associated cells, such as Treg cells and MDSCs, to block the immune responses of effector T cells [82]. Acidosis in tumors further leads to immune tolerance of tumor-infiltrating lymphocytes (TILs) and induces TAMs to transit from an antitumor M1-like phenotype to a tumor-promoting M2-like phenotype [83]. Abnormal TAMs, along with Tregs, MDSCs, and cytokines, further lead to tumor immunosuppression [84–87].

Recently, a new study showed that lactic acid can also enhance the expression and inhibitory activity of PD-1 in Treg cells, which to some extent leads to poor efficacy of PD-1-inhibiting therapy [88]. Stearyl CoA desaturase 1 (SCD1) regulates the lipid metabolism within the TME, thereby influencing the interaction between tumor cells and immune cells. By modulating the lipid composition, SCD1 may weaken the cytotoxicity of immune cells against tumors while also enhancing the tolerance of tumor cells. Therefore, elucidating the role of SCD1 is crucial in understanding the mechanisms of resistance to tumor immunotherapy and in the development of novel therapeutic strategies. It has been shown that the hyperacidic nature of the TME can upregulate SCD1 by activating PI3K/AKT signaling. Additionally, hyperacidic conditions promote the binding of SCD1 to peroxisome proliferator-activated receptor A (PPARA), which triggers the synthesis of significant amounts of fatty acid and promotes tumorigenesis [89]. In addition, the acidic environment of the TME is often accompanied by hypoxia and abnormal vascular proliferation [90].

Among these factors, improving the low pH of TME by directly neutralizing acids in TME, inhibiting aerobic glycolysis, or inhibiting lactate efflux has been shown to have good effects on improving tumor immunotherapy. For example, in one trial (ChiCTR-IOR-14,005,319), sodium bicarbonate combined with transcatheter arterial chemoembolization (TACE) was found to have better antitumor efficacy than TACE alone [91]. Drugs that reduce lactate contents by inhibiting lactate dehydrogenase A (LDHA) have also shown good effects in the clinic [92]. Therefore, reversing acidosis in the TME by regulating lactate levels or directly neutralizing acidity is a new method to enhance tumor therapy, and this method also helps prevent the generation of aberrant tumor vasculature and enhances the immune response by restoring the activity of effector T-cells.

3.3.4. *Extracellular matrix (ECM)*

The ECM is a crucial constituent of the TME and can greatly influence the TME. It serves as a structural foundation that supports cell adhesion, growth, and migration. The interactions of tumor cells with proteins within the ECM can promote tumor growth and dissemination. The ECM consists of proteins that are secreted by cells, including collagen, fibronectin, integrin, elastin and proteoglycan, and structurally and biochemically support neighboring cells [93]. Among these proteins, collagen and hyaluronic acid (HA) have been demonstrated to display characteristic structures of three-dimensional macromolecular networks conducive to tumor growth [94]. ECMs are located in the stroma of the basement membrane and interstitial space. The dense ECMs and fibroblasts surrounding solid tumors form a physical barrier that prevents the entry of immune cells into the tumor tissue, providing a natural protective shield for tumor cell proliferation, differentiation, and metastasis. Additionally, the presence of the ECM significantly limits the infiltration of antitumor drugs into tumor tissues [95].

The hardening of the ECM plays a vital role in the growth and metastasis of solid tumors. This process promotes cancer cell expansion, epithelial stromal degeneration, tumor metastasis, and resistance to chemotherapy. Guo Wei and colleagues revealed the molecular mechanisms that regulate exosome secretion, providing new insights into how ECMs affect the control of tumor growth by TME. This study demonstrates that under conditions of ECM stiffening, the Akt protein is phosphorylated and further modified, leading to its interaction with Rabin8, a protein that activates the Rab family member Rab8. Once activated, Rab8 assists in exosome release, further promoting tumor growth. Additionally, tumor cells growing on stiff ECM secrete exosomes that activate the Notch signaling pathway, thereby promoting tumor growth [96]. Studies have shown that tumor cells secrete numerous growth factors and stimulating factors, including TGF-β, which also play an essential role in the process of ECM deposition. This can stimulate the production of proteases by CAFs, contributing to the synthesis and regulation of ECM proteins [97], thus leading to immune suppression. Therefore, regulating growth factors and stimulatory factors in the ECM is another approach for normalizing the TME [94,98].

In addition, the dense ECM in the tumor acts as a barrier, thus preventing drugs or other therapeutic agents from reaching the tumor and limiting the infiltration of antitumor drugs into tumor tissue; additionally, some factors that are secreted by tumor cells affect the ECM, resulting in a poor therapeutic effect of drugs on tumors. Therefore, components that degrade the ECM (such as collagen and hyaluronic acid) or inhibitors that target certain factors would be good tools for improving tumor therapy based on the ECM.

3.3.5. *Tumor-associated macrophages (TAMs)*

TAMs are essential for the development, progression, invasion, and metastasis of tumors, and they are more abundant than other types of immune cells in many solid tumors. Almost all stages of the tumor cell metastasis process are impacted by TAMs, including invasion, vascularization, intravasation, extravasation, and the promotion of tumor cell survival by cytokine release, including TGF-β and IL-10.

TAMs have the ability to trigger and sustain the TME's immunosuppressive condition through a variety of mechanisms, including immunological checkpoint molecule expression (PD-L1), the synthesis of immunosuppressive factors (TGF-β and IL-10), the release of chemokines (CCL17 and CCL22), and aberrant amino acid metabolism [99,100]. TAMs can also competitively bind to anti-PD-1 antibodies by expressing Fc segment receptors on their surface, resulting in immune resistance [101]. In addition, TAMs can affect the antigen presentation process, reducing the amount of tumor antigens that reach immune cells, thereby weakening the immune system's ability to recognize and attack the tumor. In conclusion, TAMs have a negative impact on immunotherapy, but their critical role in the TME makes them potential therapeutic targets. By modulating TAMs functions, the effectiveness of immunotherapy can be enhanced, leading to improved control of tumors.

There are generally two types of TAMs, namely, the M1 type and the M2 type. M1 TAMs have antitumor properties, while M2 TAMs are associated with characteristics that promote tumors [102]. M2 TAMs typically exhibit proinflammatory and immunosuppressive characteristics, contributing to the maintenance of immune evasion within the TME and tumor growth, while M1 TAMs tend to display anti-inflammatory and immune-activating characteristics, aiding in promoting immune responses and the destruction of tumor cells. M1 TAMs preferentially express proinflammatory cytokines, inducible nitric oxide synthase, IL-6, TNF-α and other factors. M2 TAMs express TGF-β1, platelet-derived growth factor (PDGF), arginase 1, CD206, CD163, and IL-4R [103]. M2 TAMs mediate immunosuppression by producing IL10, TGF-β, prostaglandin E2 (PGE2), and matrix metalloproteinase-7 (MMP7). However, most TAMs in the TME are M2 TAMs. Due to the influence of chemokines, M2-TAMs are regulated by HIF1α [104] and HIF2α and accumulate in the hypoxic zone of tumors due to the action of chemokines. Matrix metalloproteinase 7 (MMP7) can likewise have its expression increased by HIF2α [105]. MMP7 reduces the ability of T and NK cells to lyse tumor cells by separating FAS ligands from nearby cells. Furthermore, through the HIF1α signaling pathway, the lactic acid produced by tumor cells increases the production of VEGF and arginase 1, which further polarizes TAMs toward the M2 phenotype and encourages tumor growth [106].

In the early stages of tumor development, TAMs can inflict damage to DNA by generating substantial amounts of ROS and nitrogen. This process may lead to mutations in the surrounding cells, including epithelial cells, which directly result in the beginning and development of cancer. The ongoing generation of mutagenic substances intensifies the development of cancer [107]. In addition, by stimulating angiogenesis (such as via the expression of the factors ANG2, ANG1, and VEGF), TAMs recruit other hematopoietic cells (like neutrophils) and secrete tumor growth-promoting factors (like EGF) into the hypoxic region of the TME to promote tumor proliferation [106].

3.3.6. *Cancer-associated fibroblasts (CAFs)*

CAFs are the majority of cells in the peritumoral stroma. Their main function is to produce the ECM, which serves as a physical barrier to prevent the transport and penetration of immune effector cells. During the process of cancer cell migration and invasion, CAFs can induce surrounding stromal cells to undergo fibrosis by secreting cytokines and proteins, including TGF-β and basic fibroblast growth factor (bFGF). CAFs can also prompt tumor cells and other cells to secrete ECM proteases, such as metalloproteinases, especially matrix metalloproteinases (MMPs). These enzymes can degrade ECM components, including collagen and fibronectin. By secreting MMPs, CAFs assist tumor cells in traversing the ECM and entering surrounding tissues or blood vessels, thereby enabling tumor infiltration and metastasis [108,109]. Furthermore, the TME's intrinsic vascular anomalies and interstitial blood flow (IF) may encourage the conversion of CAFs, thereby accelerating tumor growth [110].

Studies have indicated that CAFs possess multiple immune regulatory mechanisms that help keep the immune system from attacking tumor cells. First, CAFs contribute to the differentiation of macrophage precursors into tumor-promoting macrophages (M2 TAMs) through various regulatory factors, thereby attenuating the tumor-killing ability of T cells [111,112]. Second, CAFs can also regulate neutrophil expression through the production of TGF-β and CXCL5, resulting in neutrophils adopting the characteristics of N2 cells, which in turn promote tumor growth [113]. Third, by creating an acidic microenvironment through glycolysis, CAFs produce significant amounts of lactic acid and H^+, suppressing the activation of immune cells [114,115]. Fourth, CAFs also reduce the bioavailability of drugs by inhibiting their diffusion through stiffening of the dense ECM and the formation of a hypoxic microenvironment in the TME, thus diminishing their antitumor effects [116,117]. Finally, CAFs can also contribute to the generation of an immunosuppressant environment by generating cytokines like IL6, growth factors like VEGF [118,119] and platelet-derived growth factors (PDGF), chemokines like CXCL12, and matrix metalloproteinases, TGF-β, and PGE2. Olumi et al. suggested that CAFs have the capacity to directly foster tumor progression [120]. Given the critical role of CAFs in tumor development, metastasis, and immunosuppression, targeting the inhibition of CAFs represents a pivotal direction in current tumor therapy research.

3.3.7. *T regulatory cells*

Tregs, which are the typical example of immunosuppressive cells, can effectively limit the immune response by inhibiting the activities of other anticancer T cells, such as CD4 helper cells and CD8 cytotoxic T cells [121–123]. $CD4^+$ T helper cells contain Th1, Th2, Th17, and Treg cells, with each subpopulation playing a distinct role in the antitumor immune response. Th1 cells produce interferon-gamma (IFN-γ) to enhance antigen presentation and promote the bactericidal function of macrophages, thereby acting as pivotal participants in cell-mediated immunity. Conversely, Th2 cells secrete IL-4, IL-5, and IL-13, with IL-4 participating in the stimulation of B-cell proliferation and immunoglobulin E (IgE) production. Therefore, Th2 cells are considered to mediate humoral immunity and control extracellular pathogens. On the other hand, Th17 cells generate IL-17 and other inflammatory mediators, inciting an inflammatory response that recruits leukocytes, such as neutrophils and monocytes, to the site of infection, thereby strengthening the immune response against certain infections [124]. Th1 cells suppress tumor development and are linked to favorable clinical outcomes [125]. Nonetheless, the presence of Th2, Th17, and Treg cells in tumors is frequently linked to an unfavorable prognosis [126]. Treg infiltration of tumor tissue effectively inhibits effector T-cell proliferation. The production of inhibitory cytokines like TGF-β restricts the immune response to the tumor, thus promoting immune evasion and accelerating tumor growth [127]. For example, Wang et al. [128] found that Tregs can suppress immune surveillance during the premalignant stages of nonalcoholic steatohepatitis (NASH), thereby promoting tumor development. Furthermore, Miller et al. [129] demonstrated higher numbers of intratumor Tregs and peripheral blood Tregs in prostate cancer compared to normal prostate tissues.

First, Tregs can drive tumor growth through the expression of immunomodulatory molecules like T-cell immunoglobulin and mucin domain 3 (TIM3), programmed cell death receptor 1, lymphocyte-activated gene 3 (LAG3), and the secretion of immunosuppressive factors like IL-10 and TGF-β. The lactic acid that accumulates in the TME can be used by Treg cells as an energy source and promote their ability to inhibit effector T cell functions [130]. Secondly, Tregs exert their immunosuppressive function through the production of potent cytokines, including IL-10, TGF-β, and IL-35. Additionally, they directly impact effector cells by releasing granzyme (GRZ) and perforin (PRF). Tregs modify the TME metabolic profile by expressing CD39 and CD73, leading to an increase in extracellular adenosine concentration and inhibition of the activation and proliferation of effector T cells. Furthermore, the immunosuppressive capacity of Tregs is not confined to effector T cells. For example, Tregs can block DC activity by inducing loss of MHC class II expression upon binding to LAG3 and down-regulating the key co-stimulatory molecule B7 upon interaction with CTLA4. Additionally, Tregs can promote MDSCs proliferation, skew macrophages toward a tumor-supportive M2 phenotype, and exhibit other capacities contributing to immunosuppression.

3.3.8. *Myeloid-derived suppressor cells*

MDSCs are another subpopulation of cells that suppress the immune system. They can suppress immune cells by secreting a number of immunosuppressive factors, such as decreasing the activity and proliferative capacity of efferent lymphocytes by releasing nitric oxide, arginase, and ROS [131]. MDSCs can be categorized into two broad categories: mononuclear MDSCs (M-MDSCs) and polymorphonuclear MDSCs (PMN-MDSCs) [132]; M-MDSCs accumulate in tumors, generate elevated levels of arginase-1 and nitric oxide, hinder both antigen-specific and nonspecific T cell responses, exert higher inhibitory effects than PMN-MDSCs, and play a major role in the immunosuppressive conditions of the TME [133].

Previous research has shown that MDSCs can effectively suppress the function of antigen-specific CD8 T cells by reducing the production of cytokines such as IL-2 and IFN-γ. Furthermore, MDSCs can dampen the activity of NK cells by producing inhibitory factors, like arginase-1 and TGF-β, thereby weakening their immune surveillance against tumors [134,135]. MDSCs strongly suppress the activity of output T cells and NK cells and stimulate Tregs by limiting cysteine necessary for T-cell activation, catabolizing arginine essential for T-cell protein synthesis, secreting the immunosuppressive factor TGF-β, and increasing VEGF expression to boost angiogenesis. MDSCs can also regulate the numbers of Th1, Th2, and Th17 cells and increase IL-4, thus mediating tumor immune escape and leading to tumor progression [136,137].

4. Nanomedicine improves immunotherapy by regulating the TME

4.1. *The advantages of nanomedicine*

With the rapid development of nanotechnology and nanomedicine, nanomaterials have received widespread attention in the areas of drug delivery, targeted therapy, tumor diagnosis, etc. [138]. Utilizing nanomaterials as carriers improves drug solubility, enhances drug bioavailability, increases drug biocompatibility, prolongs the time of circulation of drugs in the body, and prevents the recognition and clearance of drugs by the immune system. For example, polyethylene glycol (PEG) is widely used to coat nanodrugs, forming a protective barrier that reduces immune system recognition. This PEG modification can extend the circulation time of nanodrugs in the body, enhancing the drug bioavailability [139]. Additionally, nanomaterials improve the distribution of drugs in the body, achieve accurate control of drug release, and reduce toxic side effects [140]. Moreover, nanomaterials can passively target tumors by enhancing tumor permeability and retention and can enhance active targeting via surface modification with targeting molecules [141,142]. Drug delivery systems can effectively transport one or more kinds of drugs, immunomodulators, antibodies, or functional molecules to tumor sites. This achieves enrichment, regulates local immunity, and ameliorates the immunosuppressive nature of the microenvironment, ultimately enhancing the effectiveness of immunotherapy for tumors.

Nanodrugs are nanoscale drug particles that can deliver drugs via physical embedding and chemical bonding and promote drug accumulation in tumor tissues through the EPR effect. At present, nanomedicine can be divided into liposomes, polymer nanoparticles, micelles, dendritic macromolecules, quantum dots, carbon nanotubes and other types [143]. Nanodrugs have many advantages in the treatment of tumors. First, some chemotherapeutic medications have drawbacks, such as low solubility in water, strong toxicity and side effects, and a short metabolism time *in vivo*. Nanodrugs can slow the clearance of drugs *in vivo* and increase the circulation time of drugs through PEG modification. Nanodrug delivery can promote the passive targeting of drugs, reduce the toxicity of drugs to normal tissues, and lower the side effects of drugs. Second, the rich specific surface area of nanoparticles can be modified with various targeting groups to promote the active targeting and accumulation of antitumor drugs in tumor tissues [5]. In addition to strategies that involve a single treatment, drug combinations can overcome the limitations of single-drug therapies in clinical practice and inhibit the growth of tumors through multiple pathways to achieve better effects than single-therapy approaches [144,145]. However, when nanomaterials are used to deliver drug combinations through cotransport, problems such as limited therapeutic effects still occur due to the different solubilities and pharmacokinetic parameters of different drugs [145], for example, the insufficient accumulation of drugs in the tumor site due to the biological barrier limits the effectiveness of drug therapy. Therefore, a variety of innovative nanoparticle designs should be introduced. In addition, the complexity of the TME makes it more difficult to achieve ideal drug release and therapeutic effects. The possible problems include leakage of the packaged drug during systemic circulation, which leads to systemic toxicity and side effects; weak stimulation signal in tumor tissues, which results in insufficient drug release; and detoxification mechanisms in tumor tissues [146]. For these reasons, nanodrugs must be able to modify the TME after reaching the tumor site, adapt to the needs of different nanodrugs, and enhance tumor immunotherapy to achieve more efficient therapeutic effects.

In recent times, there have been great breakthroughs in the development of strategies to improve TME, but these strategies still suffer from problems such as limited efficacy and toxicity [147]. In addition, because of the intricate nature of the tumor immune microenvironment, a single agent is often insufficient to trigger a robust anticancer immune response. Therefore, multidrug combinations and targeting of multiple pathways are necessary to improve the TME and thus enhance immunotherapy. Recently, based on the goal of preferentially targeting the TME to regulate the immune response, increasing numbers of nanodrugs have been designed for the diagnosis and treatment of tumors. The regulatory effects of nanodrugs on the tumor immune microenvironment mainly include enhancing tumor immunogenicity (ICD), specifically activating antigen-presenting cells, activating T cells, regulating TAMs, inhibiting or even eliminating MDSCs, and activating NK cells. Notably, nanodrug delivery systems can deliver drugs and effectively target stimulatory effects to specific cells or tissues, thereby minimizing systemic diffusion and adverse side effects.

At present, nearly ten kinds of nanomedicine are authorized for clinical use to treat malignant tumors [148]. The list includes Doxil (doxorubicin liposomes), Abraxane (albumin-bound paclitaxel), Onivyde (irinotecan liposomes), Marqibo (vincristine liposomes), DaunoXome (daunorubicin liposomes), Vyxeos (daunorubicin/cytarabine liposomes), Myocet (nonpegylated liposomal doxorubicin), Lipusu (PEGylated liposomal doxorubicin), and Mepact (mifamurtide liposomes). Drug encapsulation by nanocarriers promotes the delivery of drugs, such as chemotherapeutic drugs, to tumor tissues, prevents rapid drug degradation and improves

drug bioavailability [149]. Nanomedicine carriers can also play a role in reprogramming the immunosuppressive microenvironment. Nanomedicine carriers capable of achieving this effect include the following: (1) Liposomes: liposomes are minute lipid vesicles that encapsulate drugs and can extend a drug's circulation time by surface modification, such as PEGylation. This alteration helps improve drug accumulation within tumors while reducing the impact of the immunosuppressive microenvironment [150]. For instance, Doxil (doxorubicin liposomes) serves as a liposomal carrier to deliver the anticancer drug doxorubicin. A recent study in Biomacromolecules by Liu et al. loaded matrix metalloproteinase (MMP) and PD-L1 inhibitors in liposomes and combined them with the low-dose chemotherapeutic drug adriamycin to construct liposome LPDp. The experimental data in mice showed that it had the highest tumor inhibitory efficiency (~78.7%), which suggested that it could enhance the anti-tumor efficacy [151]. (2) Polymeric nanoparticles: polymeric nanoparticles are drug carriers constructed from biocompatible polymers. They enable controlled drug release by adjusting the properties of the polymers. This enhances drug targeting and thus the efficacy of immunotherapy [152]. A study in Biomaterials by Dai et al. developed a shrinkable micellar polymer nanoparticle that was loaded with the IDO inhibitor NLG919 and curcumin, and the nanoparticle, through the combined effect of chemotherapy-enhanced immunogenicity and NLG919-induced IDO-blocking immunotherapy, had an *in vivo* highly efficient inhibition of tumor growth, metastasis, and recurrence of tumors *in vivo* [153]. (3) Metal nanoparticles: metal nanoparticles, including gold and silver, can enhance immunotherapy, for example, through photothermal therapy. These nanoparticles can locally heat tumor tissues, thereby amplifying the effectiveness of immunotherapy [154]. A study by Chen et al. developed a multifunctional nanoplatform (FA-CD@PP-CpG) consisting of metal particles, which can synergize with photothermal therapy to enhance immunotherapy and improve anti-tumor efficacy by promoting the infiltration of CTLs and suppressing immune-suppressing cells, among other things, which can reduce tumor load [155]. (4) Multifunctional nanoparticles: these carriers often combine multiple desirable characteristics, including targeting, drug release, and imaging capabilities. Through tailored design, they can reprogram the immunosuppressive microenvironment, thereby enhancing the effectiveness of immunotherapy, among other functions [156]. In addition, nanodelivery systems increase the concentration of drugs in tumor cells via a passive/active targeting strategy while greatly reducing the toxic effects on normal tissues or cells [157]. Compared with the nanoparticle-mediated delivery of chemotherapy and other drugs, nanodrug delivery systems have many advantages in the application of tumor immunotherapy [158]. Moreover, some nanocarriers can also be used to improve tumor immunotherapy due to their inherent characteristics (such as light and thermal effects and ICD induction) [8,9]. Therefore, the use of nanomedicine and a nanomedicine delivery system to remodel the TME is a very good strategy for improving immunotherapy.

4.2. *Nanomedicine strategies to improve immunotherapy by regulating the TME*

4.2.1. *Improving tumor hypoxia*

Hypoxia is an inherent characteristic of most solid tumors. Severe tumor hypoxia can significantly decrease the efficacy of nonsurgical tumor treatments and even lead to tumor metastasis and drug resistance. The hypoxic microenvironment can also affect the ability of photodynamic therapy (PDT), chemotherapy and radiotherapy to kill tumor cells, diminishing the effectiveness of antitumor treatment [159]. Among these, PDT is a treatment method that utilizes photosensitizers to generate oxygen radicals, thereby destroying cancer cells. However, in hypoxic environments, the production of oxygen radicals is limited, which diminishes the effectiveness of PDT. Therefore, increasing the oxygen content in tumor tissue and ameliorating the hypoxic environment of tumors are beneficial for improving immunotherapy. Based on the advantages of nanodelivery systems, various nanodelivery systems have been designed to improve nanomaterials that target tumor hypoxia (Fig. 4A) [160]. At present, nanodrug delivery carriers are designed to increase the oxygen content in tumor tissues in two main ways: on the one hand, blood substitutes (such as hemoglobin, perfluorocarbons, etc.) are used to deliver O_2 to the oxygen-carrying nanosystems in tumor tissues, and on the other hand, drug delivery systems that catalyze the decomposition of hydrogen peroxide (H_2O_2) in tumors to produce O_2, such as nanoparticles based on manganese dioxide (MnO_2) or catalase (CAT), CAT is an antioxidant enzyme capable of catalyzing the decomposition of endogenous H_2O_2 within tumors to generate O_2 [161]. Such catalytic nanoparticles can be injected intravenously or directly into tumors. In addition, we can also use hyperbaric oxygen (HBO) to ameliorate TME hypoxia.

(1) Oxygen-carrying nanosystems that deliver O2 to tumor tissues

Currently, many nanomaterial researchers have devoted substantial attention to designing various types of oxygen-carrying delivery systems, like hemoglobin (Hb), perfluorocarbons (PFCs), and metal-organic framework materials (MOFs). After the treatment and design of nanoparticles by changing their surface properties, adding oxygen-carrying molecules, or enhancing their oxygen-transport capacity through other modifications, these nanoparticles can deliver loaded O_2 to hypoxic tumor tissues, raising the content of O_2 in the tumor location, reversing the hypoxic conditions of the TME, and improving therapeutic efficacy in killing tumors [162].

Hb is a natural oxygen carrier primarily used in the context of artificial blood, but because it is easily oxidized and decomposed into dimers during circulation and due to the production of harmful substances such as high iron [163], with its substantial organ toxicity and high oxygen affinity, this results in the inhibition of oxygen release. Consequently, hemoglobin must undergo modification or encapsulation for use as an oxygen transporter. For instance, glutaraldehyde is used to cross-link hemoglobin to superoxide dismutase (SOD) by stimulating the red blood cell antioxidant system. The

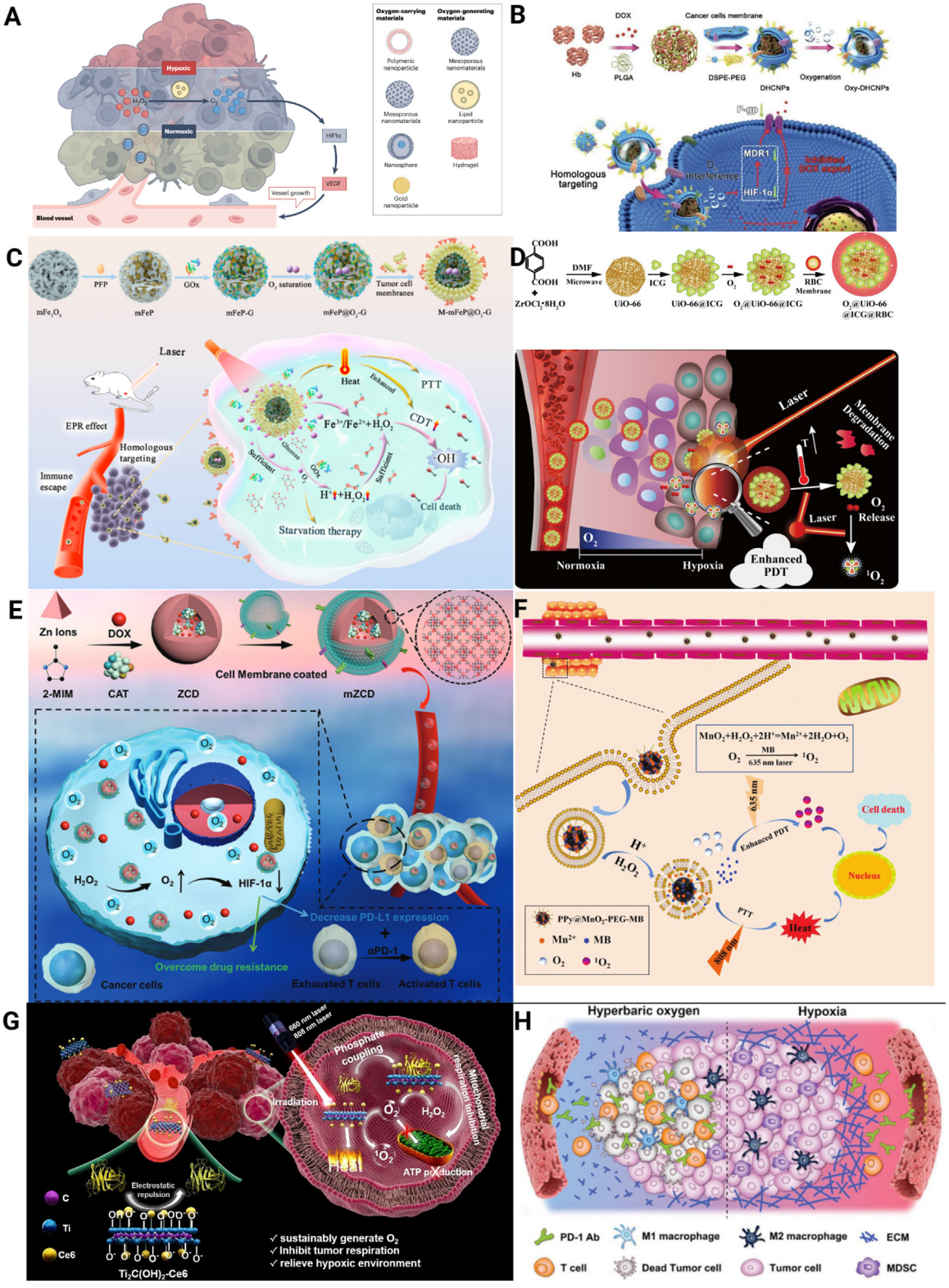

Fig. 4 – Strategies to ameliorate the hypoxic conditions of the TME to enhance immunotherapeutic effects. (A) Nanomaterials to ameliorate the hypoxic conditions of the TME. Reproduced from [160] with permission from Springer Nature. (B) Self-delivery vectors encapsulating Hb for targeted delivery of O_2 to enhance tumor therapy. Reproduced from [166] with permission from.

resulting polymers can serve as antioxidant blood substitutes for delivering oxygen to mouse breast cancer tumors (4T1) and mouse colon cancer tumors (CT26) [164]. Chen et al. synthesized several O_2 biomimetic nanocarriers. Hb was loaded into self-delivery carriers composed of PLGA, cancer cell membranes and human serum albumin, and they were used to provide O_2 to target tumors and enhance the tumor therapeutic effect [165]. One example is oxy-DHCNPs (Fig. 4B) [166]. Although some progress has been made in the research of nanosystems carrying Hb, due to the limited stability of Hb itself, its clinical application still needs to be further studied.

PFCs are often referred to as "artificial blood" due to their excellent gas solubility and oxygen-carrying capacity [167]. Because of the low polarization of fluorine, PFC has good histocompatibility and high biological safety [168]. However, the hydrophobic structure of PFCS limits its application in cancer therapy. Therefore, different types of nanodelivery systems that use PFC for oxygen delivery need to be designed to ameliorate hypoxia [161]. For example, wang et al. developed mesoporous iron-based nanoparticles that were disguised as cell membranes and loaded with the PFC as oxygen-carrying agent, and glucose oxidase (Fig. 4C). This system can synergistically enhance antitumor effects through a cascade of chemokinetic therapy, starvation therapy, and photothermal therapy [169]. Song et al. prepared a nanodelivery system to improve tumor oxygen supply and provide radiosensitization therapy. They utilized hollow PEG-Bi2SE3 mesoporous inorganic nanoparticles as carriers for anticancer medications or photosensitizers. The cavity of these nanoparticles was then filled with PFC droplets carrying oxygen. In response to near-infrared light (NIR) irradiation, PFC releases a large amount of oxygen to reverse the hypoxic conditions of TME and synergistically enhance the effects of radiotherapy, and this agent has good biological safety and tumor-killing ability [170].

MOFs are nanoporous materials with consistent pore dimensions and extensive specific surface areas, serving as natural carriers for oxygen transport. To enhance the effectiveness of PDT, Gao and colleagues developed an oxygen-carrying carrier, @UiO-66@RBC@ICG (Fig. 4D). This was achieved by incorporating a photosensitizer (ICG) onto the surface of UiO-66, filling its mesoporous structure with oxygen, and subsequently enveloping its surface with a red blood cell membrane [171].

(2) Oxygen self-sufficient nanosystem for *in situ* oxygen delivery to tumor tissues

Due to abnormal blood vessels in tumor tissues and the distant location of most tumor cells from these vessels, oxygen circulation is inadequate. As a result, methods for improving the hypoxic TME by delivering O_2 into tumor tissues have certain limitations. Thus, developing a novel form of nanodelivery system that can catalyze the breakdown of endogenous H_2O_2 to create O_2 has been the focus of study in recent years. This approach aims to increase the oxygen content in tumor tissues and ameliorate the hypoxic TME. It has been reported that nanoparticles based on CAT [172] or inorganic nanomaterials MnO_2 [173] can be used as catalysts to induce the decomposition of H_2O_2 in tumor tissues to generate O_2, thereby raising the oxygen concentration in tumor tissues and ameliorating the tumor hypoxia microenvironment.

Because of the abnormal metabolism of tumor cells, the concentration of H_2O_2 in tumor tissues is higher than that in healthy tissues [174,175]. H_2O_2 catalyzes decomposition in tumors, accompanied by the production of oxygen molecules, which can ameliorate tumor hypoxia. The short half-life of CAT in the circulatory system, like that of Hb, severely restricts its utilization in clinical application [176]. Therefore, it is necessary to construct a self-delivery vector that can be loaded with CAT to prevent proteases in the circulatory system from hydrolyzing CAT and to facilitate its enrichment in tumor lesions, aiming to ameliorate hypoxia and improve therapeutic effects on tumors. For instance, Cheng et al. encapsulated CAT into MOF-based nanodrug delivery vectors with anticancer drugs or photosensitizers. This delivery system enhances the efficacy of chemotherapy and PDT through *in situ* oxygen delivery by preventing the rapid breakdown of CAT and promoting its efficient enrichment at the tumor site [177]. Zou et al. embedded catalase and doxorubicin in a pH-sensitive zeolite imidazolate framework (mZCD) (Fig. 4E). This oxygen-producing biomimetic core-shell nanoplatform can accumulate in tumors and downregulate HIF-1α expression, thereby further strengthening chemotherapy's therapeutic effect, reducing PD-L1 expression, and improving the effect of chemotherapy [172]. Song et al. devised a self-contained nanoplatform for tumor oxygenation by sequentially delivering liposome@CAT and exogenous liposome@H_2O_2 into the tumor site. Using photoacoustic (PA) imaging, a common method for intratumoral hypoxia assessment, they measured oxygenated hemoglobin saturation across the entire tumor region. The results indicated that, in comparison to the effects achieved by the intravenous injection of liposome@CAT alone, the additional intravenous injection of exogenous liposome@H_2O_2 contributed to extending the relief time of tumor hypoxia. In addition to compensating for O_2 consumption during radiotherapy (RT), this exogenous H_2O_2 delivery strategy boosted the polarization of tumor-associated macrophages from the M2 phenotype to the M1 phenotype. Since M1 phenotype macrophages promote immune resistance, this nanoplatform effectively enhanced the antitumor immune response [178].

Certain inorganic materials, for instance, MnO_2, platinum (Pt), and Prussian blue (Pb), possess CAT-like properties and can effectively catalyze the decomposition of H_2O_2 to generate O_2 [179]. These special materials offer superior physicochemical stability compared to CAT and are therefore other potential candidates for the in-situ delivery of oxygen to ameliorate hypoxia in the TME. A mesoporous organic silicon dioxide nanoparticle delivery system was co-loaded with Pb and Ce6 to improve the effectiveness of PDT via the self-generation of O_2 [180]. In addition, it has been demonstrated that metal oxides with CAT-like activity, including MnO_2, are efficient at producing O_2 to improve hypoxia in the TME. For example, Li et al. anchored MnO_2 nanosheets to polypyrrole (PPy) nanoparticles through *in situ* redox reactions and then linked the polyethylene glycol (PEG) modifier and methylene blue (MB) photosensitizer by electrostatic interactions to generate PPy@MnO_2-PEG-MB

nanostructures (Fig. 4F). Polypyridine nanoparticles enhance the effects of photothermal therapy (PTT), and MnO_2 nanosheets ameliorate tumor hypoxia to enhance the effects of PDT; thus, this represents a multifunctional nanotherapeutic system for tumor PTT/PDT [173,182]. Yang and colleagues developed a hollow mesoporous manganese dioxide (H-MnO_2) nanoplatform coloaded with doxorubicin (DOX) and chlorin e6 (Ce6). Following treatment with this nanoplatform, the hypoxic conditions of the tumor were significantly improved. The results demonstrated that the therapeutic effects of PDT and chemotherapy were enhanced with the assistance of the abundant O_2 supply provided by this nanoplatform. PDT and chemotherapy, in turn, induced ICD, promoting dendritic cell (DC) maturation and T-cell activation. Concurrently, the tumor-associated M2 phenotype in TAMs shifted to an antitumor M1 phenotype, thereby reshaping the immunosuppressive TME [181].

(3) Other ways to ameliorate tumor tissue hypoxia

The use of inorganic nanomaterials with CAT-like activity has resulted in significant advancements in oxygen delivery. However, oxygen delivery to the TME is highly dependent on H_2O_2, making it challenging to sustain O_2 generation in extended tumor therapy [182]. The development of self-delivery nanosystems that do not rely on endogenous H_2O_2 can effectively overcome these limitations, and this is a new key breakthrough for alleviating tumor hypoxia. For example, Huang et al. developed $Ti_2C(OH)_2$-Ce6, which can ameliorate the hypoxic environment by inhibiting mitochondrial respiration and continuously delivering oxygen (Fig. 4G). $Ti_2C(OH)_2$-Ce6 can substantially alleviate tumor hypoxia by combining continuous O_2 generation with strong inhibition of mitochondrial respiration by binding phosphorylated proteins to the cancer cell surface. Sufficient $^1O_2$ is produced by PDT to kill cancer cells, and the absorbed light energy is effectively converted into heat to damage cancer cells by PTT, thereby significantly boosting the cancer treatment impact [183].

HBO has been used to improve hypoxia in TME. HBO is administered based on 100% oxygen above normal atmospheric pressure. HBO therapy increases the quantity of dissolved oxygen in the plasma, thus increasing the tissue delivery of oxygen independent of hemoglobin [184]. Liu et al. found that HBO could promote anti-PD-1 Ab delivery and T-cell infiltration into the tumor site by depleting the main components of the ECM, including collagen and fibronectin (Fig. 4H). HBO ameliorates hypoxia to reverse immunosuppressive conditions, and HBO enhances the antitumor effect of anti-PD-1 Ab, making the HBO-anti-PD-1 Ab combination a promising method for the treatment of solid tumors in the clinic [185].

The oxygen-poor microenvironment in TME has a large impact on tumor immunotherapy. Improving the oxygen-poor characteristics of the TME through the unique properties of some nanomaterials and a series of other strategies can facilitate anti-tumor treatments, such as chemotherapy or photothermal therapy, to reverse immunosuppression and improve immunotherapy effects.

John Wiley and Sons. (C) Loaded with PFCs and glucose oxidase, PFC release a large amount of oxygen, reverse the hypoxic conditions of the TME, and enhance antitumor effects through synergistic effects of chemodynamic therapy and photothermal therapy. Reproduced from [169] with permission from Elsevier. (D) Oxygen is delivered to tumor tissues via MOF materials. Reproduced from [171] with permission from Elsevier. (E) CAT-based nanodrug delivery system to deliver oxygen to tumor tissue *in situ*. Reproduced from [172] with permission from John wiley and sons. (F) Inorganic materials with CAT-like properties are used as delivery systems for *in situ* oxygen delivery to enhance therapeutic effects. Reproduced from [173,182] with permission from Royal Society of Chemistry. (G) The hypoxic environment is ameliorated by inhibiting mitochondrial respiration and continuously supplying oxygen to improve immunotherapeutic effects. Reproduced from [183] with permission from Royal Society of Chemistry. (H) Materials based on HBO that ameliorate hypoxia and improve the effect of immunotherapy. Reproduced from [185] with permission from Wiley-VCH.

4.2.2. *Normalizing blood vessels*

Abnormal blood vessel proliferation is an important characteristic of solid tumors. Hypoxia and other conditions in the TME can promote tumor blood vessel proliferation, form a new vascular system in the TME, and provide various nutrients for the unlimited proliferation of tumors. Generally, the causes of abnormal tumor blood vessel proliferation are the following [186]: (1) angiogenic factors like VEGF and angiopoietin (ANG2); (2) molecules that are involved in pericyte infiltration and vascular maturation, like platelet-derived growth factor B (PDGFB) and G protein signaling 5 (RGS5); (3) TAM-mediated proangiogenic mechanisms; and (4) Regulation of disorganization factors in tumor vasculature, such as prolyl hydroxylase domain-containing protein 2 (pHD2).

Moreover, abnormal blood vessels promote tumor growth by impairing perfusion, which further leads to hypoxia and acidic conditions within the tumor [59]. Furthermore, the leaky nature of tumor vessels leads to increased tissue fluid pressure in the TME [58,190]. The abnormal proliferation of tumor blood vessels significantly impacts both drug delivery and the infiltration of immune cells. For instance, the irregular structure of these aberrant blood vessels in tumors imposes limitations on drug delivery. Consequently, drugs tend to become entrapped in the stromal tissue surrounding the tumor rather than reaching malignant cells, ultimately decreasing the local drug concentration and, as a result, the treatment efficacy [58]. Furthermore, the atypical vascular structure hinders the entry of immune cells into tumor tissue through the blood vessels, resulting in a diminished presence of immune cells within the TME and the consequent suppression of the antitumor immune response [51]. Abnormal blood vessels and their consequences can limit the antitumor activity of cytotoxic drugs and immune cells by limiting their migration from circulation and entry into the tumor. Therefore, normalizing tumor blood vessels can efficiently block the supply of energy and material needed for tumor development and reverse immunosuppressive conditions to enhance the effects of tumor immunotherapy. The discovery and mechanism of the EPR effect, combined with the benefits of nanodrug delivery vehicles, provides

researchers with new strategies for reshaping the TME to reverse immunosuppressive conditions and improve the effects of immunotherapy by targeting tumor blood vessels, normalizing tumor blood vessels, or enhancing the tumor immune responses to achieve antitumor effects. This is also a popular direction of research.

(1) Targeting of vascular growth factors such as VEGF

In various preclinical studies, it has been found that increases in VEGF and other vascular growth factors, which are basic cytokines involved in tumor progression, can cause vascular abnormalities [187]. We found that doses of anti-VEGF drugs that normalize the vasculature can also reverse the immunosuppressive conditions of the TME and improve the efficacy of vaccine-based antitumor immunotherapy [72]; thus, a feasible strategy for tumor vascular normalization in the TME involves blocking VEGF and other vascular growth factors. For example, Osswald and colleagues developed an injectable nanosystem for antitumor angiogenesis therapy consisting of poly (N-isopropyl acrylamide)-based hydrogel, a VEGF inhibitor and PLGA microspheres. The findings of the research indicated that the lesion area in mice injected with the anti-VEGF-loaded DDS group (60%) was significantly smaller than in untreated animals throughout the study [188]. The clinical use of the epidermal growth factor receptor (EGFR) inhibitor erlotinib combined with nanoparticles can improve blood perfusion and oxygenation, increase drug penetration and reduce immunosuppression in a CT26 colon cancer mouse model [189]. Deng et al. designed and prepared two nanomedicines, FLG and MAR/MPA (Fig. 5A), which directly regulated the VEGF/VEGFR vascular repair-related pathway and blocked the CCL5/CCR5-mediated TME negative regulation pathway, respectively, to improve antitumor efficacy by establishing positive feedback regulatory loop between vascular repair and TME remodeling [190]. Li et al. developed a pH/redox-sensitive polymer-based siVEGF and etoposide (ETO) drug delivery vector (called PHCL-Lip/ETO-siVEGF), and it has the combined advantages of inhibiting angiogenesis and killing tumors (Fig. 5B). This vector can be applied for the treatment of metastatic non-small cell lung cancer [191]. It achieves sustained drug release under low pH conditions in the TME as well as in response to redox. The siVEGF and ETO that are released together inhibit tumor angiogenesis, enhance tumor killing, and improve tumor therapeutic effects.

(2) Other drug delivery systems, such as antiangiogenic peptides

The utilization of gold nanoparticles (AuNPs) as DDSs for targeting tumors in short-term treatments has led to transient tumor vascular normalization, decreased permeability and hypoxia, enhanced vascular integrity, and heightened blood perfusion [192]. The combination of combretastatin A4 nanoparticles and DC101 promotes tumor vascular destruction and normalization and enhances anti-PD-1 therapy in hepatocellular carcinoma [193]. Peptide amphipathic nanoparticles consisting of an antiangiogenic peptide (FSEC) and an immune checkpoint blocking peptide can normalize tumor blood vessels (Fig. 5C) and boost immune cell infiltration, enhancing checkpoint blocking peptides' antitumor therapeutic efficacy [194].

(3) Nitric oxide (NO) delivery

NO plays a crucial role in the regulation of angiogenesis and the maintenance of vascular homeostasis. However, there is a lack of NO delivery systems with extended half-life and sustained release mechanisms. Chen et al. reported the development of NanoNO, a nanosized carrier capable of continuously releasing NO for its efficient delivery to hepatocellular carcinoma. They found that low-dose NanoNO normalized tumor vasculature and improved the delivery and efficacy of chemotherapeutic agents and tumor-associated necrosis factors in primary and metastatic tumors. In addition, the reprogramming of the immunosuppressive TME into an immunostimulatory phenotype by low-dose NanoNO enhanced the effectiveness of tumor immunotherapy. They used liposomes and PLGA-based nanocarriers [195], to deliver NO donors along with therapeutic agents. The released NO normalized the tumor vasculature of H22 liver tumors in mice, leading to improved delivery and efficacy of chemotherapeutic agents. In addition, Tian et al. discovered that by mixing Zn^{2+} with sodium nitroprusside, a clinical anti-hypertensive drug, two-dimensional $ZnFe(CN)_5NO$ nanosheets (Fig. 5D) can be synthesized [196]. These nanosheets can release NO under certain conditions, reversing the immunosuppressive microenvironment and thus improving tumor immunotherapy.

(4) Regulation of TAMs

TAMs are mainly polarized toward the M2 phenotype in the TME, actively result in tumor angiogenesis, foster tumor immune evasion, and have a noteworthy impact on the emergence and progression of malignant tumors. It has been shown that M2 TAMs can lead to vascular abnormalities by secreting vascular growth factors such as PIGF, IL10, and CCL22 [186]. Therefore, blocking M2 polarization of TAMs can effectively improve tumor vascular abnormalities and improve the effects of immunotherapy. Rolny et al. showed that directing the polarization of TAMs toward the M1 phenotype could normalize the tumor vascular system and enhance anti-tumor immunity, thereby inhibiting tumor progression and metastasis [197]. For example, Theek and colleagues found that upregulation of histidine-rich glycoprotein (HRG) could further improve the efficiency of vascular normalization treatment (Fig. 5F), thereby improving immunotherapeutic effects [198]. Chen et al. promoted TAM M1 polarization via erlotinib to normalize blood vessels (Fig. 5E), thereby improving the effect of immunotherapy [189].

In summary, tumor vascular normalization can ameliorate the immunosuppressive conditions of TME by removing blood vessels that are necessary for tumor growth and metastasis, promoting antigen presentation and cytotoxic $CD8^+$ *T* cell activation, reprogramming the microenvironment of the tumor immunity and converting immunosuppressive conditions into immune stimulatory conditions. Among them, nanomaterials involved in improving the abnormal proliferation of tumor vasculature enhance the process of vascular normalization by improving drug targeting as well as bioavailability, thus further improving the effectiveness of tumor immunotherapy.

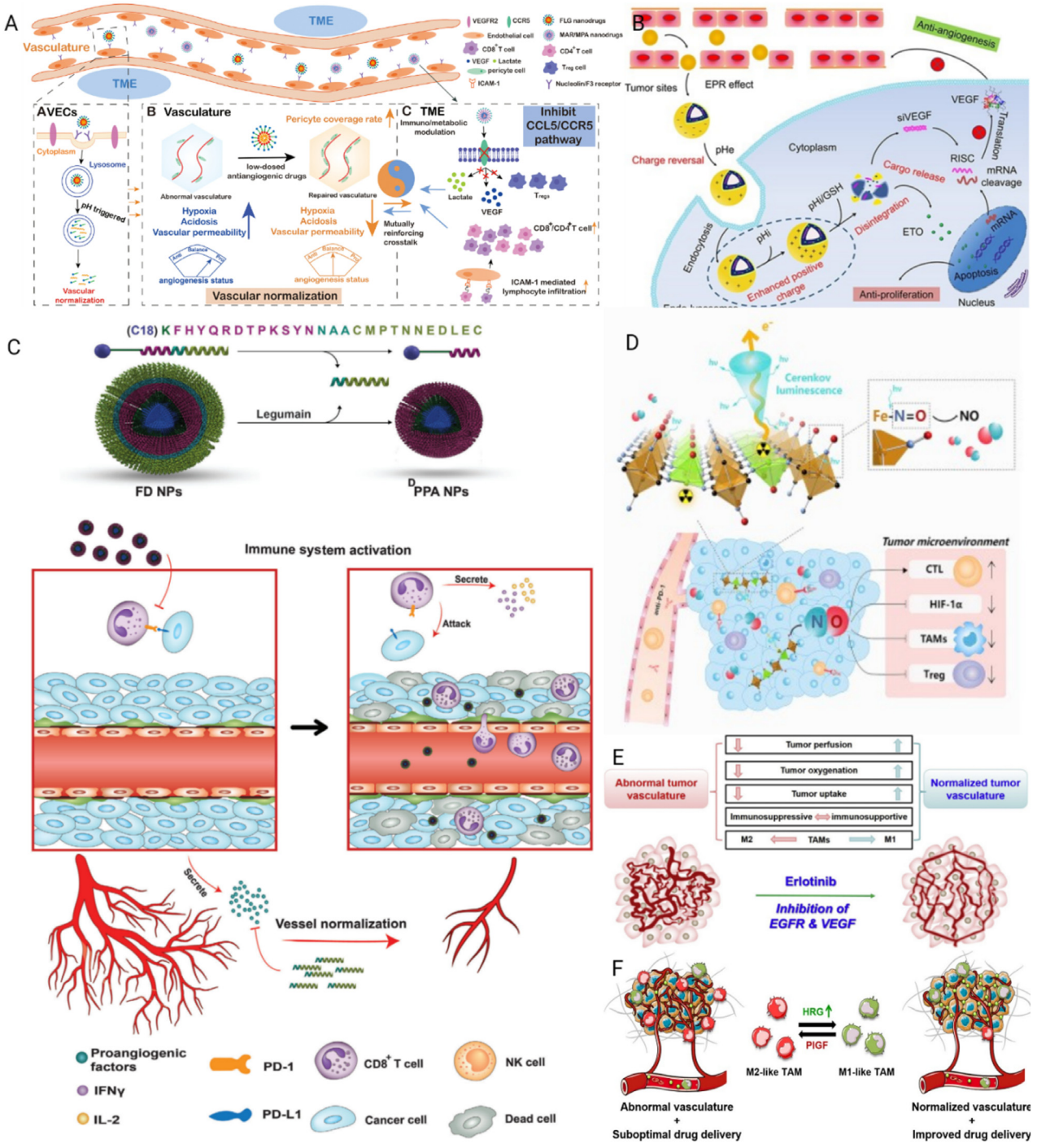

Fig. 5 – Strategies for ameliorating aberrant vascular proliferation in the TME via nanodelivery systems. (A) Regulation of the VEGF/VEGFR vascular repair-related pathway to ameliorate abnormal vascular proliferation and improve immunotherapy. Reproduced from [190] with permission from Elsevier. (B) A drug delivery vector based on the pH/redoxin-sensitive polymer siVEGF and etoposide (ETO) can inhibit tumor angiogenesis, enhance tumor-killing ability and improve tumor treatment effects. Reproduced from [191] with permission from Ivyspring International. (C) The antiangiogenic peptide (FSEC) can normalize tumor blood vessels and improve antitumor therapy. Reproduced from [194] with permission from John wiley and sons. (D) Two-dimensional ZnNO nanosheets ameliorate TME vascular abnormalities by providing NO. Reproduced from [196] with permission from Elsevier. (E) M1 polarization through erlotinib resulted in vascular normalization. Reproduced from [189] with permission from Elsevier. (F) Upregulation of histidine-rich glycoprotein (HRG) improves vascular abnormalities and enhances immunotherapy. Reproduced from [198] with permission from Elsevier.

4.2.3. *Modulating acidity*

Due to the unique aerobic glycolysis conditions of tumor cells, tumor cells preferentially use glucose to produce lactate, as well as ion exchange on their membrane, resulting in the production of a large number of acidic substances in the process of tumor progression. Weak acidity has emerged as another significant characteristic of the TME. An excessively acidic environment leads to the failure of normal cells to survive, and an acidic TME is often accompanied by hypoxia, which further promotes tumor growth. In addition, lactic acid can induce immunosuppression by impeding the immune response of effector T cells, and acidosis can also cause neovascularization [90]. Consequently, ameliorating the acidic microenvironment of tumors is conducive to improving immunotherapeutic effects. At present, there are two ways to ameliorate the hyperacidic microenvironment (Fig. 6A): direct and indirect mechanisms. The direct mechanism involves neutralizing the acid in the TME and interfering with pH-regulating enzymes. The indirect mechanisms involve inhibiting aerobic glycolysis and reducing lactate.

(1) Neutralizing the acidity in the TME

Sodium bicarbonate ($NaHCO_3$) is the typical alkaline reagent with the ability to reduce acidosis caused by tumors [90]. Although $NaHCO_3$ injection results in only temporary pH neutralization, it leads to increased T-cell infiltration, which in mice with B16 melanoma improved the effectiveness of anti-PD-1 and anti-CTLA4 therapies. Furthermore, in preclinical models, oral $NaHCO_3$ has been demonstrated to counteract the TME's acidity, which prevents tumor growth and spread [199]. For example, Banerjee et al. coated calcium phosphate with polycaprolactone to codeliver $NaHCO_3$ [200], thereby improving the bioavailability of $NaHCO_3$ and improving the effect of immunotherapy.

(2) Interfering with pH-regulating enzymes

Since the proton pump vesicular ATPase (V-ATPase) has the ability to transfer H^+ to the extracellular space, it results in an acidic TME. Thus, another direct method for correcting acidosis is the inhibition of pH-regulating enzymes [201]. Loading the glutamine hydrolysis inhibitor BPTES and the V-ATPase inhibitor KM91104 into a zeolite imidazolate framework (ZIF)-based nanodelivery system can improve the effects of cancer treatment by inhibiting proton efflux, inducing intracellular acid stress, and inhibiting glutamine metabolism to reduce energy supply [202].

Moreover, nanoparticle-based buffered nanosystems are another direct strategy to neutralize tumor acidity. Nanoscale calcium carbonate is characterized by large specific surface area, good water dispersibility, high pH sensitivity and easy modification [203]. In general, because of their strong ability to buffer acids, $CaCO_3$ nanoparticles are widely utilized to directly control local tumor acidosis. For example, Zhu et al. encapsulated azithromycin and NLG919 and took advantage of the characteristics of calcium carbonate to target these agents to reshape the TME (Fig. 6B) and achieve good immunotherapeutic efficacy [204].

(3) Inhibiting aerobic glycolysis

Aerobic glycolysis is an important cause of acidity in the TME, so inhibiting aerobic glycolysis in tumor cells is an effective method for improving the TME and enhancing the effects of tumor treatment. For example, Liu and colleagues prepared a dimer-based nanosystem to inhibit tumor glycolytic metabolism and alleviate the TME [205], which synergistically enhanced tumor therapeutic effects by combining the glycolysis inhibitor lonidamine (LND) and the immune checkpoint inhibitor NLG919 (Fig. 6C). Kolb et al. reported a nanodelivery system to target mitochondria that contained an inhibitor of the rate-limiting enzyme pyruvate dehydrogenase kinase 1 (PDK1) and a prodrug of dichloroacetate to normalize the TME [206]; this system preferentially inhibited glycolysis in cancer cells. This nanosystem, in combination with anti-PD-1 therapy, potentiated immune responses.

(4) Reducing lactic acid levels

Lactic acid is also an essential factor that leads to the acidification of the TME, so inhibiting lactate production and lactate excretion are efficient tactics for reversing the acidic conditions of the TME. For example, Li et al. demonstrated that coloading HCPT and siMCT-4 in a hollow mesoporous organosilicon dioxide delivery system can inhibit lactate efflux [207]. Chen et al. created Me&Flu@MSN@MnO2-FA, a tumor-targeting nanosystem that interfered with lactate metabolism to cure cancer [208]. Zhao et al. improved colorectal cancer immunotherapy by self-assembling Ce6, SB505124 (SB) and lonidamine (Lon) into ternary biological regulators (named TerBio) (Fig. 6D), which remodeled the TME with PDT to activate immune cascades [209]. The SB and Lon that are released can block the TGF-β pathway, inhibit lactate (LA) efflux, reverse the immunosuppressive conditions of the TME, and enhance tumor immunotherapeutic effects.

Currently, the state of hyperacidity in the TME can be effectively improved by direct or indirect means, and the effect of its strategy to reduce lactic acid with the help of nanocarriers is more direct and obvious, and the nanocarriers can be loaded with a variety of immunomodulators so that the effect of reversing immunosuppressive TME is more significant, thus enhancing immunotherapy.

4.2.4. *Reprogramming the ecm*

The ECM is a complex network that is composed of macromolecules that are secreted by cells, including proteins, enzymes, collagen and hyaluronic acid. The ECM is the main physical barrier that prevents drugs and cells from penetrating tumors [210]. Based on the stable physiological conditions of nanoparticles, the use of a nanodelivery system to improve the ECM components in the TME can increase the infiltration of CTLs and enhance immunotherapeutic effects. Improving the ECM in TME mainly involves directly reducing the levels of ECM components such as collagen and hyaluronic acid, regulating growth factors of the ECM, or indirectly improving the ECM in the TME.

(1) Reducing the levels of ECM components

To target components of the ECM, corresponding enzymes (such as matrix enzymes, hyaluronidase, and collagenase) can be encapsulated in nanoparticles and then released in the TME to degrade the ECM, increase the enrichment of drugs in the tumor lesions, and improve the efficiency of tumor treatment. Some studies have designed a CLG@NCP-PEG nanodelivery system for cancer treatment (Fig. 7A), and

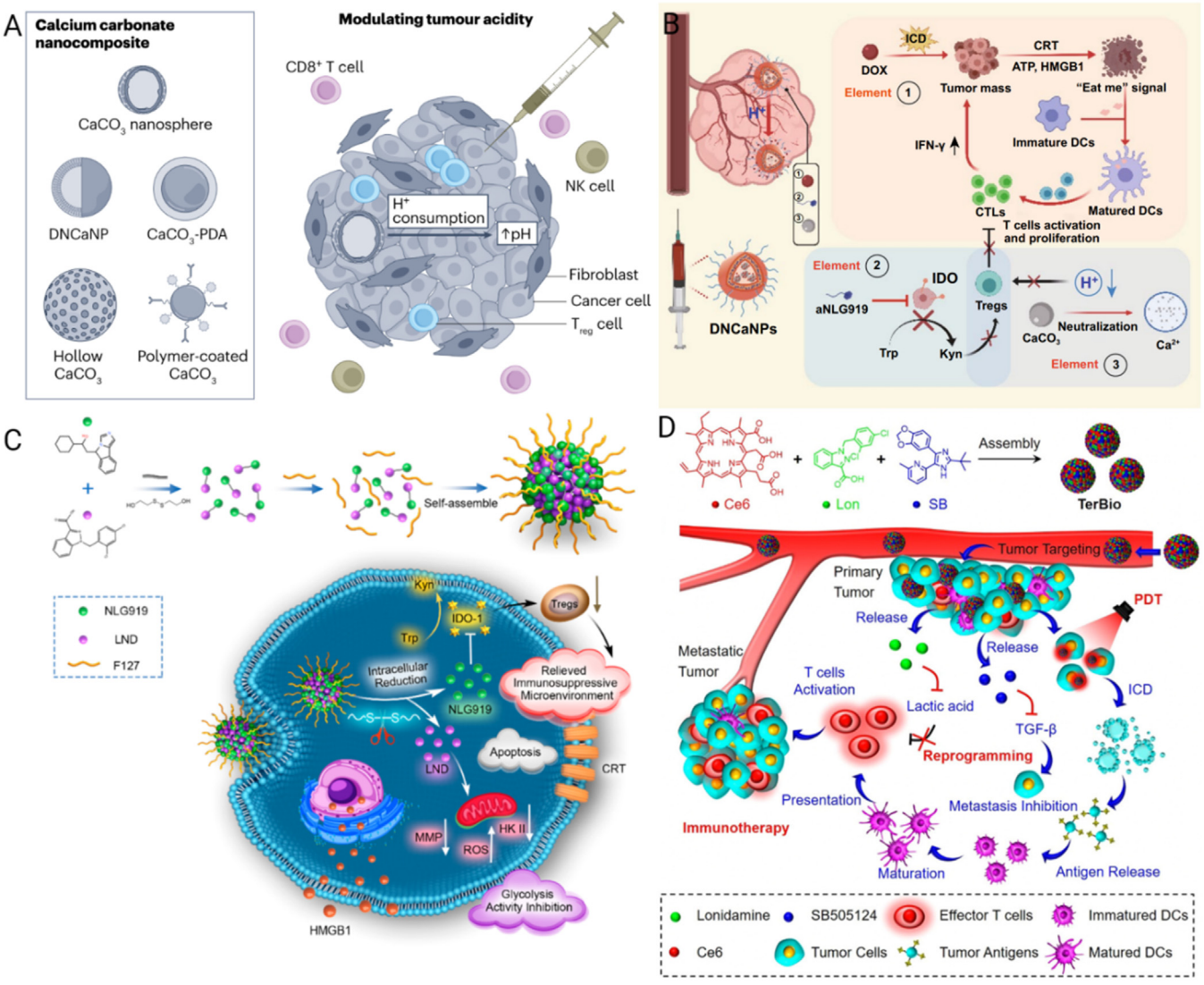

Fig. 6 – Strategies for modulating TME acidity via nanodelivery systems. (A) Review of nanomaterials that ameliorate the acidity of the TME. Reproduced from [160] with permission from Springer Nature. (B) Calcium carbonate is used to neutralize tumor acidity and ameliorate the acidic TME. Reproduced from [204] with permission from Springer Nature. (C) By inhibiting aerobic glycolysis to ameliorate the acidic TME, the LND and NLG919 can synergistically enhance the therapeutic effect on tumors. Reproduced from [205] with permission from American Chemical society. (D) Inhibition of lactate (LA) efflux, reversal of the immunosuppressive conditions of the TME, and enhancement of tumor immunotherapy. Reproduced from [209] with permission from American Chemical society.

this system includes a nanoscale coordination polymer (NCP) loaded with collagenase CLG and then modified with PEG. In the low pH conditions in the TME, this system can rapidly disaggregate and release collagenase, resulting in a sharp reduction (nearly 7-fold) in collagen levels in the TME, thereby improving drug delivery efficiency and tumor-killing effect [211]. A lactate-glycolic acid-polyethylene glycol nanoparticle delivery system (called rHuPH20), which was modified with a PEG layer and hyaluronidase, was also designed for tumor therapy. The delivery system enhances tumor permeability by degrading HA in the ECM. Research results confirmed that its ability to inhibit tumor growth was increased by 4 times [212]. In addition, dense ECM frequently coexists with high IFP, which presents another challenge for medication delivery and tumor treatment. He and colleagues have developed a nanosystem based on "nanolymphatic vessels", namely, MCdS-HA (Fig. 7C), to regulate IFP in the TME by targeting HA, thus enhancing the effects of tumor therapy [213].

(2) Inhibiting growth factors that regulate the ECM

We found that during ECM formation, tumor cells secrete many growth factors and stimulatory factors to influence ECM deposition. These factors include TGF-β, which can stimulate proteases to produce CAFs, which contribute to ECM regulation as well as ECM protein synthesis [97]. Using this idea, Chen and colleagues created self-assembling HES-Ce6 (Fig. 7B), which includes Ce6, hydroxyethyl starch, and LY2157299, an inhibitor of TGF-β to block the TGF-β-mediated regulation of the tumor ECM and enhance the effects of

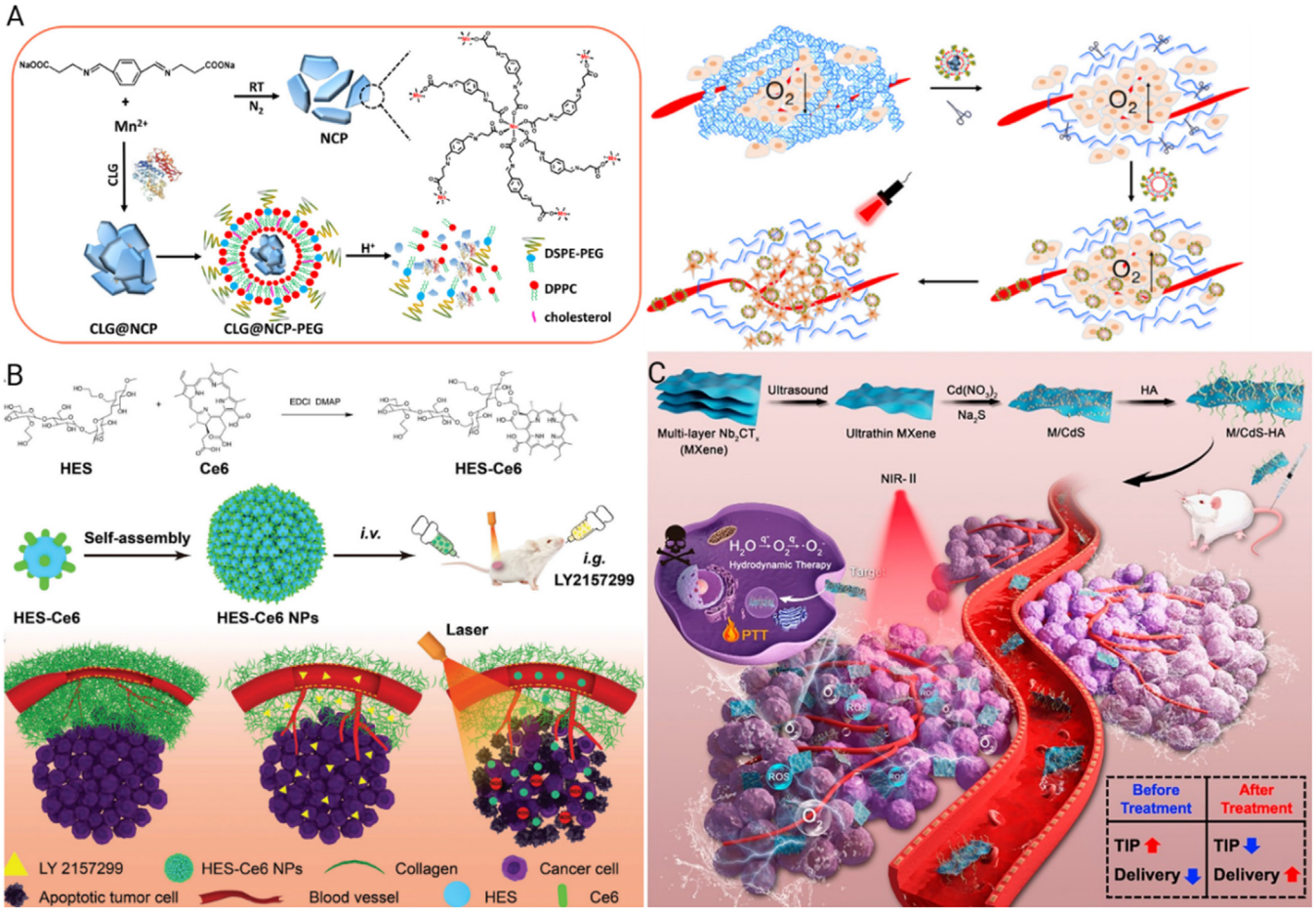

Fig. 7 – Strategies for remodeling the ECM in the TME via nanodelivery systems. (A) Loading of collagenase to reduce the levels of ECM components, thereby opening the physical barrier and improving drug efficacy. Reproduced from [211] with permission from American Chemical society. (B) Inhibition of TGF-β, a growth factor that regulates the ECM, improves the ECM of the TME. Reproduced from [214] with permission from RSC Pub. (C) Targeting HA in the ECM in the TME to improve the ECM. Reproduced from [213] with permission from American Chemical society.

photodynamic therapy (PDT) [214]. Chen and colleagues suggested a method to improve the TME by concurrently obstructing signals that are associated with the formation of ECM in tumor cells [215]. Overall, modulating the signaling molecules of the tumor ECM and reducing the expression of proteins like αSMA, TGF-β, collagen and F-actin can inhibit ECM formation, thereby remodeling the TME and enhancing the effects of tumor therapy.

Reducing the ECM in the TME by reducing the components of the ECM or inhibiting the growth factors that regulate the ECM can effectively improve the bioavailability of drugs, and researchers have been able to enhance anti-tumor immunotherapy by loading drugs that produce these effects into nanocarriers with unique delivery designs that allow for more effective remodeling of the TME.

4.2.5. *Reprogramming TAMs*

TAMs play a vital role in tumorigenesis, development, invasion, and metastasis, and in many solid tumors, TAMs are more abundant than other types of immune cells. TAMs can be generally classified into two categories, the M1-like phenotype (M1-TAMs) and the M2-like phenotype (M2-TAMs); between these types, M1-TAMs are linked to antitumor features, while M2-TAMs have tumor-promoting properties [102]. However, M2-TAMs make up the majority of TAMs in the TME. Therefore, M2-TAMs are an attractive target for antitumor treatment. Researchers have proposed several methods to effectively regulate TAMs [216]: first, direct consumption of M2-TAMs; second, blocking the recruitment of M2-TAMs; third, preventing the polarization of M2-like TAMs; and fourth, increasing M1-TAMs activity or reversing the transformation of M2-TAMs into M1-TAMs. This part will highlight how nanodelivery systems reprogram TAMs and improve tumor treatment effects.

(1) Direct consumption of M2-TAMs

The direct depletion of TAMs, which are important core players in tumor angiogenesis, metastasis and immune evasion, is thought to be the most straightforward method of controlling tumor regression. Depletion of TAMs has been reported to not only inhibit angiogenesis, tumor proliferation, and metastasis but also enhance local anticancer immune responses. TAM depletion can be initiated in two ways.

On the one hand, colony-stimulating factor 1 (CSF1) is the main regulator and chemotactic factor of most macrophage populations, and its receptor CSF1R (a tyrosine kinase) can promote the survival, proliferation and differentiation of monocytes and macrophages [217]. Therefore, CSF1R is a target for TAM depletion. On the other hand, bisphosphonates can affect TAM proliferation and induce their apoptosis, reduce new angiogenesis, and ultimately inhibit tumor growth and metastasis. Therefore, researchers have used bisphosphonate liposomal formulations or nanoparticles to target TAMs. For instance, Zang and colleagues designed lipid-coated calcium zoledronate nanoparticles (CaZol@pMNPs) that can specifically target TAMs and induce their apoptosis [218]. Zhang and colleagues [219] designed a multifunctional nanoscale proteolytic chimera (nano-PROTAC) named CREATE that can target both lung cancer cells and tumor-associated macrophages (Fig. 8A). An agent that can target lung cancer cells was developed by loading the biodegradable BRD4 super tail domain dBET6 on the pH/glutathione responsive polymer DS-PLGA. Then, plasmid transfection was used to selectively target tumor-associated macrophages.

(2) Inhibition of M2-TAM recruitment

Chemokines play a vital role in TAM recruitment, and research has indicated that TAM recruitment and poor prognosis are usually linked to the excessive production of CCL2 by tumor cells [220]. Monocytes and M-MDSCs are precursors of TAMs, and they are recruited to tumor sites by a variety of chemoattractants. Common inducers include chemokines (such as CCL2 and CCL5), cytokines (such as VEGF family members) [221] and CSF-1R. Therefore, the associated chemokines are potential targets for inhibiting TAM recruitment. For example, Qian et al. developed M2-like TAM dual-targeting nanoparticles (M2NPs) (Fig. 8B). These nanoparticles effectively suppressed TAMs recruitment, leading to prolonged survival in tumor-bearing mice. This was achieved by delivering anti-CSF-1R siRNA for tumor immunotherapy [222].

(3) Prevention of M2-like TAM polarization

TAM M2-like polarization is tightly linked to nuclear factor-clear factor kappa-B (NF-κB), activator of transcription protein-6 (STAT6), and activator of transcription protein-3 (STAT3) signaling [216]. Thus, blocking these signaling pathways may hinder macrophage polarization into the M2 phenotype, thereby impeding tumor advancement. For instance, Xiao et al. [223] created a nanodrug with both TME responsiveness and active targeting as its dual characteristics. They first wrapped the M2-targeting peptide with pH-sensitive polyethylene glycol. Subsequently, it was used to modify a nanomedicine loaded with siRNAs targeting the STAT6 inhibitor AS1517499 (AS) and the NF-κB kinase inhibitor (IKKβ), finally generating nanocomposites (Fig. 8D). Upon arrival at the tumor site, the nanocomplex sheds its protective PEG shell in the acidic TME conditions, revealing the M2-targeting peptide. This enables specific delivery of the drug to M2 macrophages, inducing their phenotypic transformation while minimizing adverse reactions, thus achieving safe and effective immunotherapy. Kulkarni et al. [224] used computational biology approaches to design a supramolecular agent capable of binding specifically to SIRPα and blocking CSF-1R, and this agent can self-assemble into nanoparticles containing specific compounds. Through supramolecularly targeting macrophages, blocking the interaction of SIRPα receptor with CD47 in macrophages and blocking the CSF-1R signaling pathway, TAMs can be polarized toward the M1 phenotype, thereby inducing an antitumor innate immune response. Studies have shown that resveratrol can reduce the M2-like polarization of TAMs by inhibiting STAT3 activity [225].

(4) TAM repolarization

Although TAMs mainly exhibit a protumor phenotype, macrophages act as important phagocytes with antigen presentation capabilities. TAMs can be converted from a protumor phenotype to an antitumor phenotype at different stages of tumor formation and during treatment, thereby activating the immune system to inhibit tumor growth [226]. TAM repolarization can be achieved in several ways. First, TAM repolarization can be achieved by blocking CD47/SIRPα signaling, enhancing the phagocytic properties of TAMs and restoring the mechanism of tumor cell clearance. Second, through toll-like receptors (TLRS), for example, different TLR agonists can polarize TAMs toward an antitumor phenotype by mimicking microbial signals. Activation of TLRs by viral nucleic acids (like RNA or DNA) or bacterial particles (like LPS) can result in immune system activation, triggering macrophage polarization toward a proinflammatory M1 phenotype. Third, tumorigenesis can be prevented by targeting and regulating key kinases in signaling pathways associated with macrophage phenotypic polarization, such as PI3Kγ. Fourth, TAM repolarization can be induced at the epigenetic level. For example, the histone deacetylase (HDAC) inhibitor TMP195 can change the epigenetic characteristics of TAMs, thus polarizing them toward the M1-like phenotype. Studies have shown that nanosystems can selectively target and regulate TAM polarization without impacting systemic immunity, exhibiting potent tumor-killing capabilities and ensuring favorable biosafety. For example, Li and colleagues created a porous hollow iron oxide that was altered with mannose (Fig. 8C) to deliver a 3-methyladenine P13Kγ inhibitor that can target TAM molecules against tumors [227]. Kim and colleagues developed a nanodelivery system based on nanoemulsions (NEs). This delivery system is employed to deliver TLR7/8a agonists for tumor immunotherapy [228]. It can induce effector T-cell proliferation, TAM polarization, as well as recruitment and proliferation, resulting in effective antitumor immune responses and reduced side effects. It has been shown that ROS are another key factor in TAM polarization, so Wang et al. [169] designed a smart multifunctional UCCG nanocatalyst that can achieve good cancer immunotherapeutic effects by reversing the immunosuppressive conditions of the TME. Cu^{2+} in UCCG is reduced by intracellular GSH to produce the Fenton reagent Cu^{+}, which in turn reacts with H_2O_2 to produce more ROS. The generation of ROS can convert M2 macrophages into M1 macrophages (Fig. 8E). A recent study in Science Translational Medicine by Song et al. designed an albumin nanoparticle containing a PI3Kγ inhibitor and paclitaxel and found that combining it with anti-programmed death 1 (α-PD1) can enhance anti-tumor immunotherapy, which led to the remission of breast cancer tumors in mice [229].

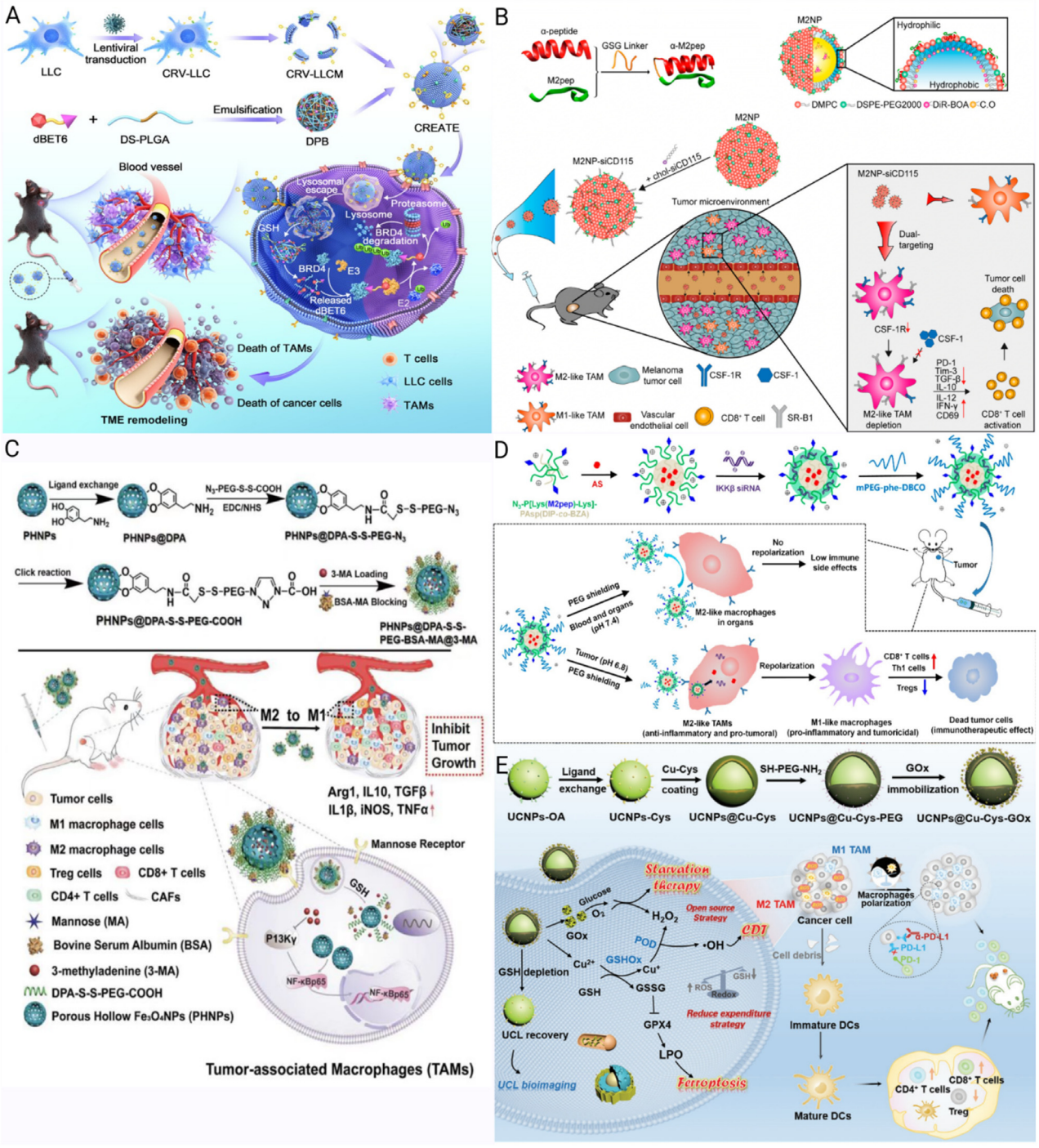

Fig. 8 – Strategies for regulating TAMs in the TME via nanodelivery systems. (A) Multifunctional nanoscale proteolytic chimeras (Nano-PROTACs) target lung cancer cells. Then, selective M2-TAMs were generated by plasmid transfection to reduce TAMs and improve immunotherapy. Reproduced from [219] with permission from Wiley-VCH. (B) M_2NPs nanoparticles successfully inhibited the recruitment of TAMs by delivering anti-CSF-1R siRNA for cancer immunotherapy, thereby enhancing the immunotherapeutic effects. Reproduced from [222] with permission from American Chemical society. (C) Mannose-modified, porous hollow iron oxide loaded with 3-methyladenine, a P13Kγ inhibitor, targets TAM molecules and prevents TAM repolarization, thereby improving the efficacy of immunotherapy. Reproduced from [227] with permission from RSC Pub. (D) This system masks the M2-targeting peptide with pH-sensitive PEG and prevents the polarization of M2-like TAMs, and it is a promising approach for improving the effects of immunotherapy. Reproduced from [223] with permission from American Chemical Society. (E) This system uses the generation of ROS to convert M2 macrophages into M1 macrophages. Reproduced from [230] with permission from John wiley and sons.

Compared with TAM depletion and inhibition of TAM recruitment strategies, the TAM repolarization strategy not only decreases the number of immunosuppressed TAMs but also augments the numbers of proinflammatory macrophages, which is more effective in reversing the immunosuppressive TME. Additionally, this strategy avoids the impact of drastic macrophage depletion on normal tissues and is associated with fewer adverse reactions. Therefore, the TAM repolarization strategy has attracted more attention in the field of tumor immunotherapy. Together with the addition of some multifunctional nano-delivery systems, the effect of reversing immunosuppressive TME and improving tumor immunotherapy can be achieved more efficiently by loading multiple immunomodulatory drugs or modifying the drugs with specific nano-designs.

4.2.6. *Reprogramming CAFs*

CAFs cannot just prevent the activation and function of immune cells but also prevent the penetration of drugs and immune cells into deep tumor tissues, thereby reducing the effect of tumor treatment. Tumor inhibition via the regulation of CAFs or overcoming their barrier function is a new method for cancer treatment. The design of nanocarriers that can target and regulate CAFs in order to inhibit tumor progression and that can promote the ability of drugs to cross the CAF barrier in order to improve drug accumulation at tumor sites is a hot topic in tumor treatment research. Based on this, this section describes research on targeting CAFs with nanocarriers for tumor treatment and provides new ideas for improving the effects of tumor immunotherapy. The therapeutic options for reprogramming CAFs include [231] (1) directly killing CAFs; (2) interfering with CAF function; and (3) interfering with CAF activation.

(1) Directly killing CAFs

It has been reported that CAF depletion can not only inhibit tumor proliferation but also significantly improve the delivery of chemotherapeutic drugs and nanomedicine to cancer sites [232]. For example, CAFs can secrete collagen and other ECM proteins, creating a physical barrier that restricts drug penetration into the tumor tissue. The depletion of CAFs can decrease the abundance of these matrix substances, thus increasing the chances of drugs entering the tumor tissue. Furthermore, the presence of CAFs can lead to elevated interstitial pressure within the tumor, hindering blood flow and drug diffusion. The depletion of CAFs contributes to reducing interstitial pressure, thereby improving drug delivery. Fourniols et al. [233] used liposomes as carriers to test the effects of various cytotoxic drugs on CAFs, and the results showed that acridine yellow and paclitaxel could effectively kill CAFs and inhibit the growth of 3D tumor spheres in fibroblast and cancer cell coculture systems. Nicolás et al. [234] took advantage of the off-target effects of nanomedicines in tumor tissues to deliver Fe_3O_4-Au hybrid nanoparticles to CAFs that are associated with liver cancer, irradiated them with a laser, and used photothermal effects to eliminate the CAFs and inhibit tumor progression. Zhao et al. fabricated M-CPA/PTX, a nanosystem loaded with paclitaxel and cyclopamine, for pancreatic tumor treatment (Fig. 9B). This study indicates that CAFs generate fibrotic deposits, leading to the widespread proliferation of connective tissue, which hinders the delivery of chemotherapy drugs within the tumor. This finding suggests that the nanosystem could not only remodel the TME by depleting CAFs but also enhance the antitumor effects of chemotherapy drugs by reducing the proliferation of the connective tissue matrix, thereby inhibiting tumor proliferation [235]. The above examples enhance immunotherapy by directly depleting CAFs to inhibit tumor growth.

(2) Interference with the function of CAFs

In the above discussion, we explained that CAFs can foster tumor progression and aggression through the secretion of multiple cytokines that promote malignant transformation of normal fibroblasts. Therefore, preventing the secretion of cytokines by CAFs can effectively inhibit CAF metastasis and tumor development. For example, Leaf Huang's research group used protamine liposomes as carriers to target CAFs in order to deliver plasmid DNA or siRNA-expressing "trap" molecules. The "trap" refers to a molecular or antibody strategy employed to modify the TME to enhance the antitumor immune response while simultaneously affecting CXCL12. This method blocked the exchange of signaling molecules such as CXCL12 [236] between CAFs and tumor cells and significantly inhibited the development and metastasis of bladder and pancreatic cancers in mice. Zhao et al. designed a red blood cell vesicle-based nanodelivery system that targets CAFs (RBC-FN–NP) for pancreatic ductal adenocarcinoma (PDAC) treatment [237]; this system inhibits CAF migration and reprograms the ECM by preventing CAFs from secreting matrix proteins. In this system, the exposed FnBPA5 peptide exhibited significant attraction for both CAFs and key components of the ECM, like collagen I and relaxed fibronectin. Additionally, retinoic acid (RA) disrupted the Golgi apparatus of CAFs, decreasing protein secretion from the source. The mechanism of this system involves the partial protection provided by RBC vesicles, which ensures that the FnBPA5 peptide can interact with CAFs and ECM components. When combined with the influence of RA on CAFs, this effect results in remodeling of the TME, enhanced drug penetration, and ultimately an increase in the efficacy of chemotherapy. Huang et al. [238] used lipid calcium phosphate modified with FHK peptides as a carrier (FHK-pLIGHT@CaMP) (Fig. 9A) to target CAFs in order to deliver the antifibrotic drug α-mangostin. CXCL12 is typically considered a chemoattractant that facilitates the immigration and invasion of certain tumor cells by drawing them into the TME. Therefore, a reduction in CXCL12 secretion may diminish the attractiveness of the TME to tumor cells, consequently reducing tumor cell migratory and invasive capabilities. CXCL12 within the TME is also linked to the infiltration of immune cells. It is generally viewed as an attractant for immune cells because it can recruit and position immune cells like T cells and macrophages within the TME. Hence, a decrease in CXCL12 secretion could impact the infiltration of immune cells into the TME, reducing both their quantity and their distribution. Consequently, the nanoparticles reduced the secretion of cytokines such as CXCL12 by pancreatic cancer-associated CAFs and blocked the communication between CAFs and tumor cells. This contributed to improving the effectiveness of immunotherapy.

Table 2 – Summary table of nanodrug delivery systems to modulating the TME.

Objective	Strategy	Delivery platform	Advantages and limitations	examples	The benefits of immunotherapy	Ref.
Ameliorating tumor hypoxia	Oxygen-carrying nanosystems that deliver O_2 to tumor tissues	Oxygen carriers containing Hb, PFC, or materials with mesoporous structures such as MOF	Has a high oxygen carrying capacity, but due to the abnormal blood vessels in the tumor tissue and the fact that most tumor cells are far away from these blood vessels, there is a lack of oxygen circulation, thus only achieving a short-term improvement in hypoxia	oxy-DHCNPs; PEG-Bi_2SE_3; @UiO-66@ICG@RBC	Enhancement of antitumor therapy through synergistic enhancement of cascade responses such as photothermal and chemodynamic therapies	[166,170,171]
	Oxygen self-sufficient nanosystem for *in situ* oxygen delivery to tumor tissues	Mesoporous nanomaterials loaded with CAT or with CAT-like properties	It has longer-lasting effects on improving hypoxia, but the oxygen production effect is affected by the H_2O_2 content of the tumor site	mZCD; PPy@MnO_2-PEG-MB	Promotes the polarization of TAMs from the M2 to M1 phenotype. Since M1 phenotype macrophages promote immune resistance, this nanoplatform can effectively enhance the anti-tumor immune response, in addition to enhancing the therapeutic effects of PDT as well as chemotherapy	[172,173,182]
	Other ways to ameliorate tumor tissue hypoxia	Inhibition of mitochondrial respiration and other measures that do not depend on endogenous oxygen production	Self-delivery nanosystems that do not rely on endogenous H_2O_2 for longer-lasting oxygen production capacity	$Ti_2C(OH)_2$-Ce6; HBO	HBO can reverse immunosuppression and enhance antitumor effects by depleting the major components of the ECM and promoting the delivery of anti-PD-1 Ab and the infiltration of T cells at the tumor site	[183,185]
Normalizing blood vessels	Targeting vascular growth factors such as VEGF	Nanomaterials containing VEGF, EGFR inhibitors	Nanomedicines can achieve a high degree of targeting of VEGF through surface modification or drug carrier design, reducing the impact on normal tissues and improving the precision of treatment	PHCL-Lip/ETO-siVEGF; PLGA	Targeting the vascular growth factor VEGF to improve tumor vascular abnormalities, thereby reversing the immunosuppression in TME and improving the efficacy of anti-tumor immunotherapy	[188,191]

(*continued on next page*)

Table 2 (*continued*)

Objective	Strategy	Delivery platform	Advantages and limitations	examples	The benefits of immunotherapy	Ref.
	Other drug delivery systems, such as antiangiogenic peptides	Nanomaterials containing gold nanoparticles or anti-angiogenic peptides, etc.	Has stronger tumor immunotherapy effects	AuNPs	Peptide amphiphilic nanoparticles were synergistic in improving TME as well as boosting the immune system for tumor suppression. Increased intratumoral infiltration of immune cells after normalization of blood vessels and simultaneous blockade of the immune checkpoint function of PD-L1 led to enhanced tumor immunotherapy	[192]
	NO delivery	Nanomaterials capable of being loaded to provide NO	A direct and continuous supply of NO is effective in improving abnormal tumor vascularity, but the amount of NO needs to be kept under control	ZnNO	Low-dose NanoNO reprograms immunosuppressive TME into an immunostimulatory phenotype and enhances the effectiveness of tumor immunotherapy	[196]
	Regulation of TAMs	Nanomedicines induced to promote TAM polarization to M1	The induced generation of type M1 releases inflammatory factors such as TNF-α and IL-1β, which help activate the immune system and prompt immune cells to recognize and attack tumor cells. However, M1 may be immune-tolerant in TME	Erlotinib and nanoparticles	Directing the polarization of TAMs towards the M1 phenotype can normalize tumor vasculature and enhance anti-tumor immunity, thereby inhibiting tumor progression and metastasis	[189]
Modulating acidity	Neutralizing the acidity in the TME	Nanomaterials loaded with $NaHCO_3$	$NaHCO_3$ is effective in rapidly reducing acidosis in tumors, but only has a short-term effect	$NaHCO_3$	can lead to increased T-cell infiltration, which enhances the efficacy of anti-PD-1 and anti-CTLA4 therapies	[200]
	Interfering with pH-regulating enzymes	Nanocarriers containing pH-regulated enzyme inhibitors	Nanocarriers loaded with enzymes inhibiting H^+ efflux, such as V-ATPase inhibitors	ZIF; DNCaNPs	Enhances therapeutic efficacy against cancer by inhibiting proton efflux and inducing intracellular acid stress, and has the ability to inhibit glutamine metabolism	[137,204]

(*continued on next page*)

Table 2 (*continued*)

Objective	Strategy	Delivery platform	Advantages and limitations	examples	The benefits of immunotherapy	Ref.
	Inhibiting aerobic glycolysis	Nanocarriers containing glycolysis inhibitors	Effective improvement of the tumor hyperacidic environment requires nanocarriers to enhance targeting	Inhibitors of glycolysis LND	Nanocarriers containing rate-limiting enzymes in glycolysis or inhibitors of glycolysis, etc., which can also be combined with anti-PD-1 therapy to enhance immunotherapy	[205]
	Reducing lactic acid levels	Nanocarriers loaded with drugs that inhibit lactate production or lactate efflux	Having a lasting effect on improving the acidic environment of the TME	Me&Flu@MSN@MnO_2-FA; TerBio	TerBio released SB and Lon to block the TGF-β pathway, inhibit lactate (LA) efflux, reverse immunosuppressive TME, and improve colorectal cancer immunotherapy	[208,209]
Reprogramming the ECM	Reducing the levels of ECM components	Nanocarriers loaded with enzymes that can hydrolyze the corresponding ECM components	Enhances drug delivery efficiency and tumor-killing efficacy	CLG@NCP-PEG rHuPH20 MCdS-HA	It can effectively reduce the components of the ECM and increase the enrichment of the drug at the lesion site, thus improving the therapeutic effect of the drug	[211–213]
	Inhibiting growth factors that regulate the ECM	Nanocarriers loaded with ECM growth factor inhibitors	More efficiently, regulating the dense ECM in the TME from the source	HES-Ce6	Signaling molecules that regulate the tumor ECM and reduce the expression of proteins such as αSMA, TGF-β, collagen, and F-actin can reduce the formation of the ECM, thereby remodeling the TME and enhancing tumor therapy	[214]
Reprogramming TAMs	Direct consumption of M2-TAMs	Nanocarriers loaded with nanocarriers that can affect the apoptosis of TAMs	The most direct strategy to modulate tumor TAMs and effectively improve the tumor microenvironment	CaZol@pMNPs; nano-PROTAC	Direct depletion of M2-type TAMs with pro-tumorigenic properties enhances anti-tumor immunotherapy	[218,219]
	Inhibition of M2-TAM recruitment	Nanocarriers loaded with chemokines resistant to induction of M2-type TAM recruitment	Reducing pro-tumorigenic TAM types at the source, thereby efficiently enhancing immunotherapy	Anti-CSF-1R called M2NPs	Weakening tumor growth by inhibiting chemokines or cytokines that can induce M2-type TAM recruitment	[222]
	Prevention of M2-like TAM polarization	Nanocarriers loaded with inhibitors of certain signaling pathways (*e.g.*, STAT3, STAT6, etc.), thereby preventing the polarization of TAMs toward the tumor-promoting M2 type	Enhanced M2 to M1 repolarization in the TME	Inhibit STAT6; inhibit CSF-1R; inhibit STAT4;	Promoting conversion of TAMs to M1 type and inducing intrinsic anti-tumor immune response	[223–225]

(*continued on next page*)

Table 2 (*continued*)

Objective	Strategy	Delivery platform	Advantages and limitations	examples	The benefits of immunotherapy	Ref.
	TAM repolarization	Nanocarriers loaded with drugs capable of repolarizing TAMs	Not only reduced TAMs with immunosuppressive effects but also increased the pro-inflammatory phenotype of macrophages. Fewer adverse effects	Blocking CD47/SIRPα signaling; TLRS; target key kinases; through epigenetic level; Increase ROS;	Modulators that repolarize M2-type TAMs to M1-type in the TME increase tumor immunotherapy when combined with immunotherapy	[227,228,169]
Reprogramming CAFs	Directly killing CAFs	Nanocarriers loaded with drugs capable of directly killing CAFs	Highly targeted, purposeful and effective	M-CPA/PTX	Not only can it remodel TME by depleting CAFs, but it can also increase the antitumor effect of chemotherapy, thereby inhibiting tumor proliferation	[235]
	Interfering with the function of CAFs	Nanocarriers loaded with drugs that interfere with cytokine secretion by CAFs	Reducing the impact of CAFs on TME production from the source, thus effectively inhibiting the communication between CAFs and tumor cells	Preventing secreting cytokines	Inhibits CAF migration and reprograms the ECM by preventing CAFs from secreting matrix proteins, reduces cytokines such as CXCL12 secreted by associated CAFs, and blocks communication between CAFs and tumor cells. This helped to improve the effectiveness of immunotherapy	[236–238]
	Interfering with the activation of CAFs	Nanocarriers loaded with drugs that inhibit the activation of CAFs	Effective and promising	inhibit stimulating factors such as TGF-β/PDGF	Blocking the activation of CAFs through a series of inhibitions of CAFs activation improves the immunosuppressive microenvironment at the tumor site	[239,240]
Inhibition of immunosuppressive cells and factors	Inhibition of immunosuppressive cells, including Tregs and MDSCs	Nanocarriers loaded with drugs that reduce immunosuppressive cells	Direct inhibition of immunosuppressive cells can more effectively reduce the immunosuppressive substances released by immunosuppressive cells, thus improving tumor immunotherapy	Gel/(REG+NG/LY); CLCeMOF	Induces T-cell infiltration, reduces MDSCs/Tregs in TME, and can synergize with siPD-L1 for effective immunotherapy	[241,242]
	Inhibition of immunosuppressive factors, including TGF-β and IDO1	Nanocarriers loaded with drugs that reduce immunosuppressive factors	Direct inhibition of immunosuppressive factors secreted by immunosuppressive cells can enhance tumor immunotherapy more effectively	OTX+IDOI@MPDAs; Gel/(REG+NG/LY)	Nanosystems significantly improve the effectiveness of tumor immunotherapy by affecting the immunosuppressive factors released by immunosuppressive cells	[243,244]

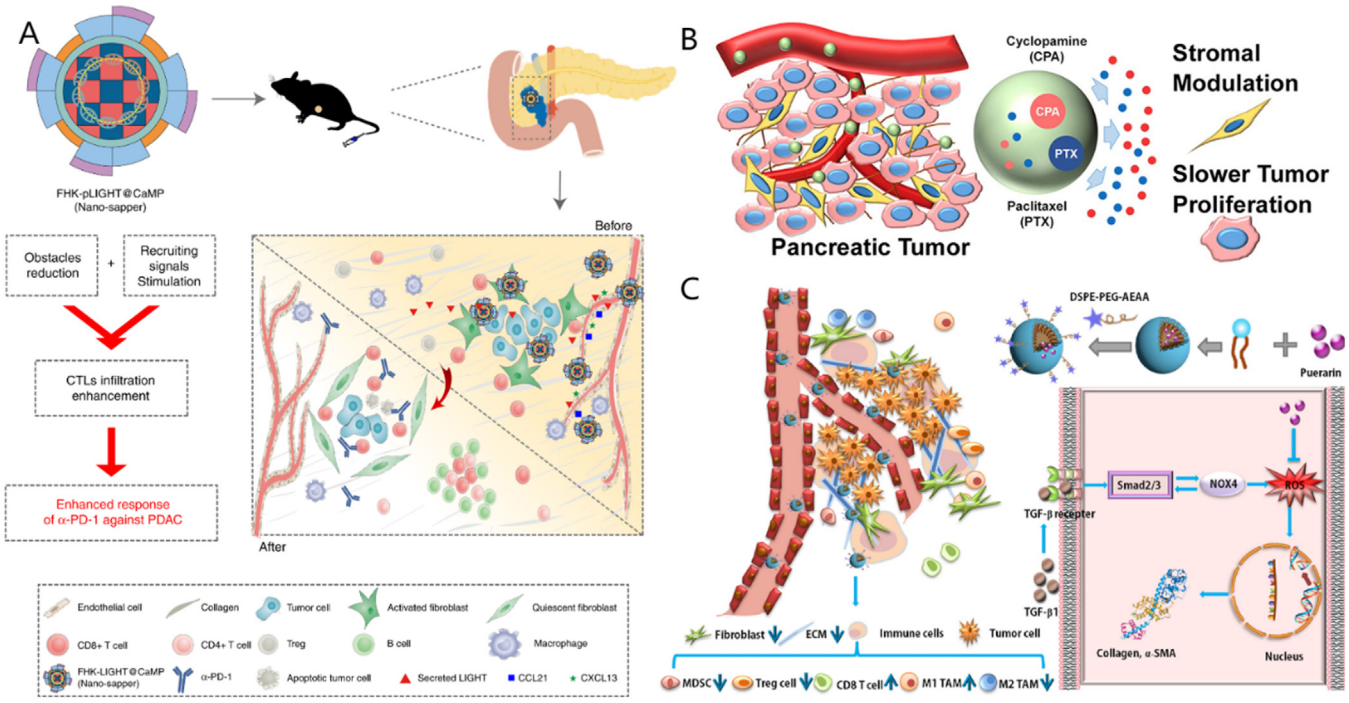

Fig. 9 – Strategies to regulate CAF in the TME. (A) FHK-pLIGHT@CaMP nanoparticles target CAFs, reduce the secretion of cytokines such as CXCL12 by pancreatic cancer-related CAFs, prevent CAFs from communicating with tumor cells, and improve immunotherapeutic effects. Reproduced from [238] with permission from Springer Nature. (B) M-CPA/PTX, a nanosystem constructed by loading paclitaxel and cyclopamine, can not only remodel the TME by depleting CAFs but also enhance the antitumor effect of chemotherapy, thus improving immunotherapeutic effects. Reproduced from [235] with permission from Elsevier. (C) These liposomes reduce the level of intracellular ROS, thereby inhibiting the activation of fibroblasts and ameliorating the immunosuppressive microenvironment at the tumor site. Reproduced from [240] with permission from Elsevier.

(3) Interfering with the activation of CAFs

CAF activation refers to the process by which static fibroblasts are transformed into an activated state in response to stimulatory factors, like TGF-β/PDGF, that are secreted by tumors. Stimulatory factors like TGF-β/PDGF are key to CAF activation; therefore, interfering with these factors is a promising approach for inactivating CAFs. For example, the activation of CAFs can be blocked by inhibiting the TGF-β/Smad/ROS pathway, increasing the expression of free fatty acids [239], and treatment with bromodomain protein 4 inhibitors. In the TGF-β/Smad/ROS pathway, excessive activation of TGF-β may lead to an increased production of ROS, thereby promoting the activation of CAFs. For example, Xu et al. designed puerarin-loaded liposomes targeted to CAFs and modified with aminoethyl anisamide (AEAA) (Fig. 9C) because puerargin can significantly reduce intracellular ROS levels and thus inhibit the activation of fibroblasts [240]. Furthermore, this system can ameliorate the immunosuppressive microenvironment at the tumor site.

Reprogramming CAFs is another effective strategy to improve the TME, based on which nanocarriers can be loaded with a variety of drugs to regulate the TME, which can not only dual-target the TME but also synergistically enhance chemotherapy and other immunotherapies so as to improve the effect of anti-tumor immunotherapy.

4.2.7. Inhibition of immunosuppressive cells and factors

The distinctive interplay between tumor cells and host immune cells establishes an immunosuppressive microenvironment shielding tumor cells from immune assault, resulting in immunosuppression and fostering tumor growth. Immunosuppressive cells can release immunosuppressive substances (such as TGF-β) on a continuous basis, inhibiting T-cell proliferation, promoting tumor growth, and playing a critical role in tumor immune evasion [51]. These cells include Tregs, MDSCs and other cells. Tregs can affect immunotherapy by regulating the activity of $CD4^+$ and $CD8^+$ cells and by secreting the immunosuppressive mediators IL-10 and TGF-β. MDSCs can reduce the activity of antitumor immune cells, such as T cells, by releasing cytokines that inhibit the immune system, including ROS and nitric oxide [131]. Immunosuppressive factors that are secreted by immunosuppressive cells, such as TGF-β, indoleamine 2,3-dioxygenase (IDO), COX-2 and IL10, are also important factors that allow tumor cell escape and promote tumor growth. Therefore, the inhibition of immunosuppressive cells and immunosuppressive factors is an effective strategy for remodeling the TME to reverse immunosuppression.

For example, Li et al. [241] designed an immunomodulatory nanoagent (FX/siPD-L1@HP) (Fig. 10A) that antagonizes CXCR4; this agent not only reduces the numbers of MDSCs

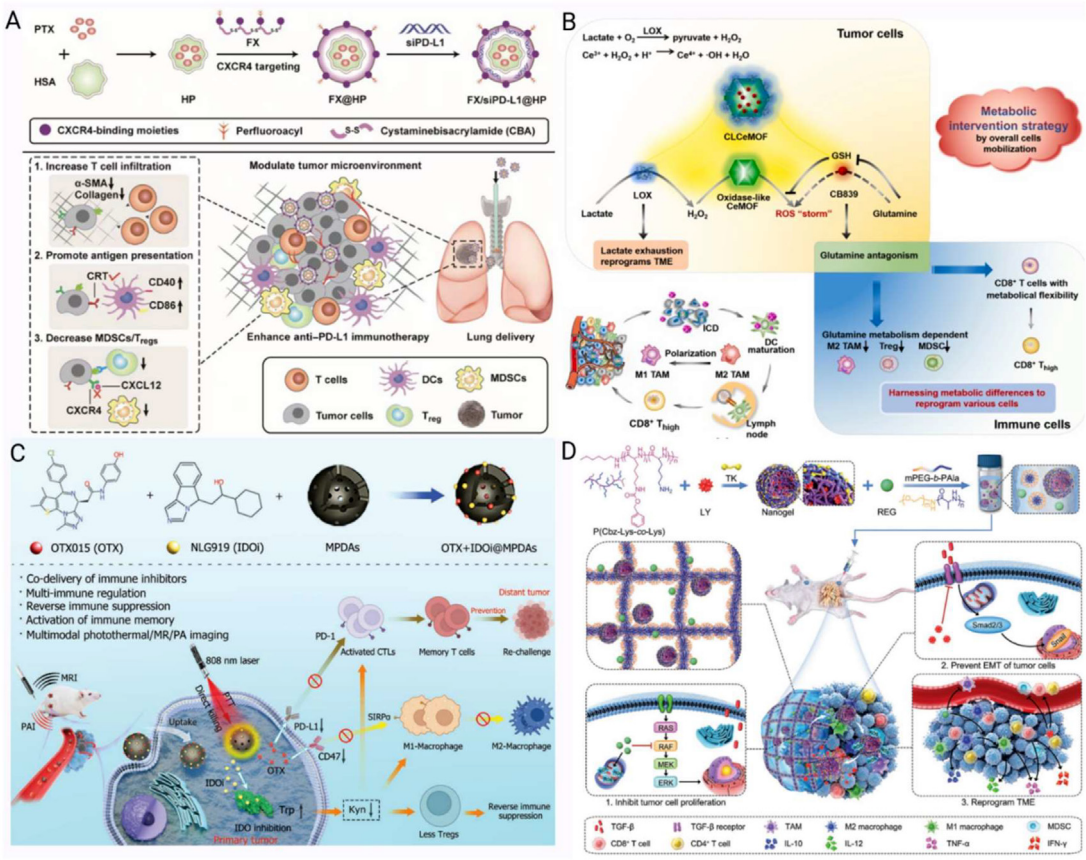

Fig. 10 – Strategies for improving immunotherapy by regulating immunosuppressive cells and immunosuppressive factors in the TME via nanodelivery systems. (A) Numbers of MDSCs and Tregs in the TME are reduced by antagonizing CXCR4 to improve the effects of immunotherapy. Reproduced from [241] with permission from American Association for the Advancement of Science. (B) The CLCeMOF nanosystem inhibits glutamine metabolism to reduce the number of immunosuppressive cells, thereby improving the efficacy of immunotherapy. Reproduced from [242] with permission from Acta Elsevier (C) A nanosystem loaded with the immunosuppressants OTX and IDOI reverses the immunosuppressive functions of PD-L1/CD47/Tregs and improves the effects of immunotherapy. Reproduced from [243] with permission from John wiley and sons. (D) Inhibiting the immunosuppressive factor TGF-β increases the tumor infiltration of CD8$^+$ cells and improves the effects of tumor immunotherapy. Reproduced from [244] with permission from John wiley and sons.

and Tregs in the TME but also reduces the secretion of TGF-β and IL-10. This system induces T-cell infiltration, increases the expression of tumor cell calreticulin, reduces MDSCs/Tregs in the TME, and synergizes with siPD-L1 to achieve effective immunotherapy. This study suggests that inhibiting CXCR4 with nanocomplexes can reduce tumor fibrosis, promote T-cell infiltration, alleviate immune suppression, and thereby modulate the immune process, ultimately enhancing the effectiveness of immunotherapy. This agent can also increase the exposure of calreticulin (CRT) on the surface of tumor cells and promote the maturation and antigen presentation of dendritic cells, thereby enhancing the positive regulation of the immune response. Feng et al. [242] constructed a nanoplatform (CLCeMOF) (Fig. 10B) based on a cerium metal-organic framework (CeMOF) that was reloaded with lactate oxidase (LOX) and glutaminase inhibitor (CB839). The nanosystem reduces the number of immunosuppressive cells (Treg, MDSCs, M2-TAM, etc.) by inhibiting glutamine metabolism and cooperates with lactate oxidase to reduce the amount of the metabolite lactate, thereby reversing the tumor immunosuppressive environment and improving the effects of immunotherapy. Tian et al. [243] designed an ideal nanomodulator based on a dual immunosuppressant that was loaded with mesoporous polydopamine nanoparticles. By loading the immunosuppressors OTX and IDOI onto MPDA, this nanosystem formed a novel nanomodulator (OTX+IDOI@MPDAs) (Fig. 10C). The nanosystem significantly inhibited the immunosuppressive functions of PD-L1/CD47/Tregs, promoted the activation of CTLs, and regulated the polarization of M2 macrophages, thus improving the effects of immunotherapy. Li et al. [244] developed a ROS-responsive nanogel (Gel/(REG+NG/LY)) (Fig. 10D) loaded with TGF-β inhibitors and regorafenib to enhance tumor immunotherapeutic effects. The nanogel was designed to inhibit tumor growth and migration by reducing the quantity of immune-suppressive cells and increasing the infiltration of killer cells, like CD8$^+$ T cells, into the tumor. This nanosystem can precisely release drugs in a sequential manner, beginning with regorafenib (REG), which inhibits the development of tumors and promotes ROS production.

Subsequently, it releases LY, a selective TGF-β inhibitor, which prevents the epithelial-mesenchymal transition and immune evasion of cancer cells caused by increased TGF-β. This sequential release mechanism contributes to increased infiltration of $CD8^+$ *T* cells within the tumor, reduces the recruitment of tumor-associated macrophages and MDSCs, and promotes the polarization of macrophages from the M2 to M1 type. Overall, this nanosystem significantly enhances the effectiveness of tumor immunotherapy by influencing immune-suppressive cells.

5. Conclusion and future prospects

As the key to tumor development, invasion and metastasis, TME is a major obstacle and potential target for the delivery of tumor-targeted drugs, and its immunosuppressive status also significantly affects the anti-tumor effects of drugs [245,246]. As mentioned above (Table 2), many researchers have demonstrated that strategies that aim to remodel the TME can achieve better antitumor effects. Not only has the remodeling of the TME shown useful antitumor effects in preclinical studies, but it has also shown great potential for improving the efficacy of drugs in clinical trials. Because the pathophysiological characteristics of a given tumor type in different populations or the pathophysiological characteristics of a given tumor in different physiological states and sites may be different, it is difficult to predict the results of TME remodeling. Therefore, a comprehensive assessment of the kind, stage, and physiological structure of individual tumors is required for the future clinical implementation of TME remodeling techniques. Moreover, unilateral TME regulation alone is not sufficient to achieve the desired efficiency of drug infiltration into tumors. Future research should emphasize the development of multifunctional strategies that simultaneously regulate multiple aspects of the TME. In addition, because of the TME regulation's effective time window, strategies that specifically combine TME-regulated drugs and other therapeutic drugs should be fully considered, including the administration sequence and administration ratio. The "effective time window for TME regulation" refers to a specific period during cancer treatment when it is possible to have the maximum impact on the TME to achieve better treatment outcomes. It is important to note that current clinical practice focuses on the combination of TME remodeling strategies with small-molecule drugs or approved nanomaterials [247]. The potential toxicity of the delivery of small molecule drugs may be another unfavorable consequence of the clinical application of such systems. The development of smart nanomaterials that combine TME remodeling with drug therapy is expected to overcome the existing limitations. For example, certain nanomaterials can be designed to release drugs under specific conditions within the TME. For instance, pH-sensitive nanoparticles can release drugs in the acidic microenvironment of tumor tissues while remaining stable in normal tissues. This technology has the potential to enhance the local concentration of drugs and reduce toxicity to healthy tissues. Alternatively, some nanomaterials can respond to external stimuli like light, magnetic fields, or ultrasound, triggering drug release. These stimulus-responsive nanomaterials can achieve precise drug delivery to meet the demands of the TME. Furthermore, specific nanomaterials can generate heat or optical effects under external stimuli, enabling hyperthermia or phototherapy on tumor tissues. These thermosensitive or photosensitive nanomaterials can be used for selectively killing tumor cells without harming surrounding normal tissues. All of these innovations represent promising prospects in the field of future cancer treatment, offering more effective and personalized therapeutic options for patients.

Although nanomedicine exhibits significant potential in cancer treatment, there are still some challenges in its clinical application, such as drug resistance and tumor heterogeneity. For example, currently clinically approved nanopreparations, such as DOXIL and the paclitaxel-albumin nanoparticle ABRAXANE, effectively reduce the toxicity and side effects of drugs but perform poorly in improving treatment efficacy [248,249]. Second, because of tumor heterogeneity, the tumor selectivity of microenvironment-responsive nanodrug delivery systems is not high [250]. Furthermore, biological barriers to the drug delivery process impede the accumulation of nanocarriers at the disease site, thus limiting the response to drug treatments. Despite extensive research efforts aimed at integrating various functionalities into the design of nanoparticles, many of these strategies have not adequately addressed these obstacles. Therefore, we can purposefully design nanoparticles to overcome the biological barriers encountered during drug delivery. By thoughtfully incorporating innovative design features, this approach may pave the way for a new generation of nanotherapeutics, enabling the successful transformation of drug delivery based on nanoparticles [251]. Therefore, based on the use of nanotechnology as a platform technology, the design and development of nanomaterials capable of modulating the TME in terms of improving tumor hypoxia, abnormal vascular proliferation, acidic environment, dense ECM, and immunosuppressive cells may further improve the selectivity of nanomaterials and alleviate the drug resistance that occurs in the course of treatment, thus improving the effectiveness of tumor therapy.

Declaration of competing interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

[1] Song W, Musetti SN, Huang L. Nanomaterials for cancer immunotherapy. Biomaterials 2017;148:16–30.
[2] Nam J, Son S, Park KS, Zou W, Shea LD, Moon JJ. Cancer nanomedicine for combination cancer immunotherapy. Nat Rev Mater 2019;4:398–414.
[3] Anderson NM, Simon MC. The tumor microenvironment. Current Biology 2020;30 R921–5.
[4] Roma Rodrigues C, Mendes R, Baptista P, Fernandes A. Targeting tumor microenvironment for cancer therapy. IJMS 2019;20:840.

[5] LY Chou T, Ming K, Chan WC W. Strategies for the intracellular delivery of nanoparticles. Chem Soc Rev 2011;40:233–45.
[6] Wang B, Tang M, Yuan Z, Li Z, Hu B, Bai X, et al. Targeted delivery of a STING agonist to brain tumors using bioengineered protein nanoparticles for enhanced immunotherapy. Bioact Mater 2022;16:232–48.
[7] Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. Adv Drug Deliv Rev 2014;66:2–25.
[8] Feng Y, Mu R, Wang Z, Xing P, Zhang J, Dong L, et al. A toll-like receptor agonist mimicking microbial signal to generate tumor-suppressive macrophages. Nat Commun 2019;10:1–14.
[9] Xu J, Lv J, Zhuang Q, Yang Z, Cao Z, Xu L, et al. A general strategy towards personalized nanovaccines based on fluoropolymers for post-surgical cancer immunotherapy. Nat Nanotechnol 2020;15:1043–52.
[10] Kruger S, Ilmer M, Kobold S, Cadilha BL, Endres S, Ormanns S, et al. Advances in cancer immunotherapy 2019 – latest trends. J Exp Clin Cancer Res 2019;38:1–11.
[11] Wang Y, Wang M, Wu HX, Xu RH. Advancing to the era of cancer immunotherapy. Cancer Commun 2021;41:803–29.
[12] Grupp SA, Maude SL, Rives S, Baruchel A, Boyer MW, Bittencourt H, et al. Updated analysis of the efficacy and safety of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory (r/r) acute lymphoblastic leukemia. Blood 2018;132:895.
[13] Topalian SL, Weiner GJ, Pardoll DM. Cancer immunotherapy comes of age. J Clin Oncol 2011;29:4828.
[14] Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. Nat Rev Cancer 2019;19:133–50.
[15] Pardi N, Hogan MJ, Naradikian MS, Parkhouse K, Cain DW, Jones L, et al. Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses. J Experimental Med 2018;215:1571–88.
[16] Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. Nat Med 2004;10:909–15.
[17] Dannull J, Su Z, Rizzieri D, Yang BK, Coleman D, Yancey D, et al. Enhancement of vaccine-mediated antitumor immunity in cancer patients after depletion of regulatory T cells. J Clin Invest 2005;115:3623–33.
[18] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases—elimination, equilibrium and escape. Curr Opin Immunol 2014;27:16–25.
[19] Hawkins RE, Gilham DE, Debets R, Eshhar Z, Taylor N, Abken H, et al. Development of adoptive cell therapy for cancer: a clinical perspective. Hum Gene Ther 2010;21:665–72.
[20] Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science (1979) 2015;348:62–8.
[21] Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR–T cells of defined $CD4^+$:$CD8^+$ composition in adult B cell all patients. J Clin Invest 2016;126:2123–38.
[22] Hillerdal V, Essand M. Chimeric antigen receptor-engineered T Cells for the treatment of metastatic prostate cancer. BioDrugs 2015;29:75–89.
[23] Dudley ME. Adoptive cell therapy for patients with melanoma. J Cancer 2011;2:360.
[24] Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and toxicity management of 19-28z CAR T Cell therapy in B Cell acute lymphoblastic leukemia. Sci Transl Med 2014;6 224ra25-224ra25.
[25] Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 2016;127:3321–30.
[26] Krishna S, Lowery FJ, Copeland AR, Bahadiroglu E, Mukherjee R, Jia L, et al. Stem-like CD8 T cells mediate response of adoptive cell immunotherapy against human cancer. Science (1979) 2020;370:1328–34.
[27] Marin Acevedo JA, Dholaria B, Soyano AE, Knutson KL, Chumsri S, Lou Y. Next generation of immune checkpoint therapy in cancer: new developments and challenges. J Hematol Oncol 2018;11:1–20.
[28] Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science (1979) 2018;359:1350–5.
[29] Wang Y, Du J, Gao Z, Sun H, Mei M, Wang Y, et al. Evolving landscape of PD-L2: bring new light to checkpoint immunotherapy. Br J Cancer 2022:1–12.
[30] Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. New England J Med 2015;372:2509–20.
[31] Monjazeb AM, Hsiao HH, Sckisel GD, Murphy WJ. The role of antigen-specific and non-specific immunotherapy in the treatment of cancer. J Immunotoxicol 2012;9:248–58.
[32] Srivastava PK. Neoepitopes of cancers: looking back, looking ahead. Cancer Immunol Res 2015;3:969–77.
[33] Blass E, Ott PA. Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol 2021;18:215–29.
[34] Hu Z, Leet DE, Allesøe RL, Oliveira G, Li S, Luoma AM, et al. Personal neoantigen vaccines induce persistent memory T cell responses and epitope spreading in patients with melanoma. Nat Med 2021;27:515–25.
[35] Kohler H. Superantibodies. Appl Biochem Biotechnol 2000;83:1–12.
[36] Kuhn C, Weiner HL. Therapeutic anti-CD3 monoclonal antibodies: from bench to bedside. Immunotherapy 2016;8:889–906.
[37] Weiner GJ. Building better monoclonal antibody-based therapeutics. Nat Rev Cancer 2015;15:361–70.
[38] Sathyanarayanan V, Neelapu SS. Cancer immunotherapy: strategies for personalization and combinatorial approaches. Mol Oncol 2015;9:2043–53.
[39] Kaplon H, Reichert JM. Antibodies to watch in 2019. MAbs 2019;11:219–38.
[40] Xia C, Yin S, To KKW, Fu L. CD39/CD73/A2AR pathway and cancer immunotherapy. Mol Cancer 2023;22:44.
[41] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. New Eng J Med 2010;363:711–23.
[42] Lin MJ, Svensson Arvelund J, Lubitz GS, Marabelle A, Melero I, Brown BD, et al. Cancer vaccines: the next immunotherapy frontier. Nat Cancer 2022;3:911–26.
[43] Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat Rev Cancer 2008;8:299–308.
[44] Vivekanandhan S, Bahr D, Kothari A, Ashary MA, Baksh M, Gabriel E. Immunotherapies in rare cancers. Mol Cancer 2023;22:23.
[45] Saxena M, van der Burg SH, Melief CJM, Bhardwaj N. Therapeutic cancer vaccines. Nat Rev Cancer 2021;21:360–78.
[46] Zinn S, Vazquez Lombardi R, Zimmermann C, Sapra P, Jermutus L, Christ D. Advances in antibody-based therapy in oncology. Nat Cancer 2023;4:165–80.
[47] Shalhout SZ, Miller DM, Emerick KS, Kaufman HL. Therapy with oncolytic viruses: progress and challenges. Nat Rev Clin Oncol 2023;20:160–77.

[48] Tabernero J, Shapiro GI, LoRusso PM, Cervantes A, Schwartz GK, Weiss GJ, et al. First-in-humans trial of an RNA interference therapeutic targeting VEGF and KSP in cancer patients with liver involvement. Cancer Discov 2013;3:406–17.
[49] Tamura R, Tanaka T, Akasaki Y, Murayama Y, Yoshida K, Sasaki H. The role of vascular endothelial growth factor in the hypoxic and immunosuppressive tumor microenvironment: perspectives for therapeutic implications. Med Oncol 2019;37:2.
[50] Vaupel P, Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. Cancer Metastasis Rev 2007;26:225–39.
[51] Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med 2018;24:541–50.
[52] Maggs L, Ferrone S. Improving the clinical significance of preclinical immunotherapy studies through incorporating tumor microenvironment–like conditions. Clinical Cancer Research 2020;26:4448–53.
[53] Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nat Rev Cancer 2009;9:239–52.
[54] Francis A, Venkatesh GH, Zaarour RF, Zeinelabdin NA, Nawafleh HH, Prasad P, et al. Tumor hypoxia: a key determinant of microenvironment hostility and a major checkpoint during the antitumor response. CRI 2018;38.
[55] Bamodu OA, Chang HL, Ong JR, Lee WH, Yeh CT, Tsai JT. Elevated PDK1 expression drives PI3K/AKT/MTOR signaling promotes radiation-resistant and dedifferentiated phenotype of hepatocellular carcinoma. Cells 2020;9:746.
[56] Wang B, Zhao Q, Zhang Y, Liu Z, Zheng Z, Liu S, et al. Targeting hypoxia in the tumor microenvironment: a potential strategy to improve cancer immunotherapy. J Exp Clin Cancer Res 2021;40:24.
[57] Sitkovsky MV, Kjaergaard J, Lukashev D, Ohta A. Hypoxia-adenosinergic immunosuppression: tumor protection by T regulatory cells and cancerous tissue hypoxia. Clin Cancer Res 2008;14:5947–52.
[58] Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. J Clin Oncol 2013;31:2205–18.
[59] Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. Cancer Cell 2014;26:605–22.
[60] Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol 2018;15:325–40.
[61] Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 2004;10:942–9.
[62] Huang Y, Snuderl M, Jain RK. Polarization of tumor-associated macrophages: a novel strategy for vascular normalization and antitumor immunity. Cancer Cell 2011;19:1–2.
[63] Voron T, Colussi O, Marcheteau E, Pernot S, Nizard M, Pointet A-L, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. J Exp Med 2015;212:139–48.
[64] Gabrilovich D, Ishida T, Oyama T, Ran S, Kravtsov V, Nadaf S, et al. Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages *in vivo*. Blood 1998;92:4150–66.
[65] Gabrilovich DI, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nat Med 1996;2:1096–103.
[66] Maenhout SK, Thielemans K, Aerts JL. Location, location, location: functional and phenotypic heterogeneity between tumor-infiltrating and non-infiltrating myeloid-derived suppressor cells. Oncoimmunology 2014;3:e956579.
[67] Chaudhary B, Khaled YS, Ammori BJ, Neuropilin Elkord E. 1: function and therapeutic potential in cancer. Cancer Immunol Immunother 2014;63:81–99.
[68] Jain RK, Koenig GC, Dellian M, Fukumura D, Munn LL, Melder RJ. Leukocyte-endothelial adhesion and angiogenesis in tumors. Cancer Metastasis Rev 1996;15:195–204.
[69] Melder RJ, Koenig GC, Witwer BP, Safabakhsh N, Munn LL, Jain RK. During angiogenesis, vascular endothelial growth factor and basic fibroblast growth factor regulate natural killer cell adhesion to tumor endothelium. Nat Med 1996;2:992–7.
[70] Hendry SA, Farnsworth RH, Solomon B, Achen MG, Stacker SA, Fox SB. The role of the tumor vasculature in the host immune response: implications for therapeutic strategies targeting the tumor microenvironment. Front Immunol 2016;7:621.
[71] Huang Y, Goel S, Duda DG, Fukumura D, Jain RK. Vascular normalization as an emerging strategy to enhance cancer immunotherapy. Cancer Res 2013;73:2943–8.
[72] Huang Y, Yuan J, Righi E, Kamoun WS, Ancukiewicz M, Nezivar J, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proc Natl Acad Sci USA 2012;109:17561–6.
[73] Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science (1979) 2005;307:58–62.
[74] Scholz A, Lang V, Henschler R, Czabanka M, Vajkoczy P, Chavakis E, et al. Angiopoietin-2 promotes myeloid cell infiltration in a β_2-integrin-dependent manner. Blood 2011;118:5050–9.
[75] Coffelt SB, Chen YY, Muthana M, Welford AF, Tal AO, Scholz A, et al. Angiopoietin 2 stimulates TIE2-expressing monocytes to suppress T cell activation and to promote regulatory T cell expansion. J Immunol 2011;186:4183–90.
[76] Holopainen T, Saharinen P, D'Amico G, Lampinen A, Eklund L, Sormunen R, et al. Effects of angiopoietin-2-blocking antibody on endothelial cell-cell junctions and lung metastasis. J Natl Cancer Inst 2012;104:461–75.
[77] Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-TIE pathway. Nat Rev Drug Discov 2017;16:635–61.
[78] Murdoch C, Tazzyman S, Webster S, Lewis CE. Expression of Tie-2 by human monocytes and their responses to angiopoietin-2. J Immunol 2007;178:7405–11.
[79] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the warburg effect: the metabolic requirements of cell proliferation. Science (1979) 2009;324:1029–33.
[80] Cairns RA, Harris IS, Mak TW. Regulation of cancer cell metabolism. Nat Rev Cancer 2011;11:85–95.
[81] Webb BA, Chimenti M, Jacobson MP, Barber DL. Dysregulated pH: a perfect storm for cancer progression. Nat Rev Cancer 2011;11:671–7.
[82] Lacroix R, Rozeman EA, Kreutz M, Renner K, Blank CU. Targeting tumor-associated acidity in cancer immunotherapy. Cancer Immunol Immunother 2018;67:1331–48.
[83] Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel) 2014;6:1670–90.

[84] Angelin A, Gil de Gómez L, Dahiya S, Jiao J, Guo L, Levine MH, et al. Foxp3 reprograms T Cell metabolism to function in low-glucose, high-lactate environments. Cell Metab 2017;25:1282–93 e7.
[85] Bohn T, Rapp S, Luther N, Klein M, Bruehl TJ, Kojima N, et al. Tumor immunoevasion via acidosis-dependent induction of regulatory tumor-associated macrophages. Nat Immunol 2018;19:1319–29.
[86] Baer C, Squadrito ML, Laoui D, Thompson D, Hansen SK, Kiialainen A, et al. Suppression of microRNA activity amplifies IFN-γ-induced macrophage activation and promotes anti-tumour immunity. Nat Cell Biol 2016;18:790–802.
[87] Sm P, L A, Aj S, Rl B, L S, Df Q, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. Nat Med 2013;19.
[88] Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y, et al. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. Cancer Cell 2022;40:201–18 e9.
[89] Ding M, Zhang S, Guo Y, Yao J, Shen Q, Huang M, et al. Tumor microenvironment acidity triggers lipid accumulation in liver cancer via SCD1 activation. Molecular Cancer Research 2022;20:810–22.
[90] Pillai SR, Damaghi M, Marunaka Y, Spugnini EP, Fais S, Gillies RJ. Causes, consequences, and therapy of tumors acidosis. Cancer Metastasis Rev 2019;38:205–22.
[91] Chao M, Wu H, Jin K, Li B, Wu J, Zhang G, et al. A nonrandomized cohort and a randomized study of local control of large hepatocarcinoma by targeting intratumoral lactic acidosis. Elife 2016;5:e15691.
[92] De la Cruz López KG, Castro-Muñoz LJ, Reyes Hernández DO, García-Carrancá A, Manzo-Merino J. Lactate in the regulation of tumor microenvironment and therapeutic approaches. Front Oncol 2019;9.
[93] Khawar IA, Kim JH, Kuh HJ. Improving drug delivery to solid tumors: priming the tumor microenvironment. J Controlled Release 2015;201:78–89.
[94] Lampi MC, Reinhart King CA. Targeting extracellular matrix stiffness to attenuate disease: from molecular mechanisms to clinical trials. Sci Transl Med 2018;10:eaao0475.
[95] Comito G, Giannoni E, Segura CP, Barcellos-de-Souza P, Raspollini MR, Baroni G, et al. Cancer-associated fibroblasts and M2-polarized macrophages synergize during prostate carcinoma progression. Oncogene 2014;33:2423–31.
[96] Wu B, Liu DA, Guan L, Myint PK, Chin L, Dang H, et al. Stiff matrix induces exosome secretion to promote tumour growth. Nat Cell Biol 2023.
[97] Bonnans C, Chou J, Werb Z. Remodelling the extracellular matrix in development and disease. Nat Rev Mol Cell Biol 2014;15:786–801.
[98] Goetz JG, Minguet S, Navarro Lérida I, Lazcano JJ, Samaniego R, Calvo E, et al. Biomechanical remodeling of the microenvironment by stromal caveolin-1 favors tumor invasion and metastasis. Cell 2011;146:148–63.
[99] Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 2017;14:399–416.
[100] Vari F, Arpon D, Keane C, Hertzberg MS, Talaulikar D, Jain S, et al. Immune evasion via PD-1/PD-L1 on NK cells and monocyte/macrophages is more prominent in hodgkin lymphoma than DLBCL. Blood 2018;131:1809–19.
[101] Perry CJ, Muñoz-Rojas AR, Meeth KM, Kellman LN, Amezquita RA, Thakral D, et al. Myeloid-targeted immunotherapies act in synergy to induce inflammation and antitumor immunity. J Experimental Med 2018;215:877–93.
[102] Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol 2010;11:889–96.
[103] Wu K, Lin K, Li X, Yuan X, Xu P, Ni P, et al. Redefining tumor-associated macrophage subpopulations and functions in the tumor microenvironment. Front Immunol 2020;11.
[104] Zhang W, Chen C, Zhou Z, Gao S, Tee TJ, Yang L, et al. Hypoxia-inducible factor-1 alpha correlates with tumor-associated macrophages infiltration, influences survival of gastric cancer patients. J Cancer 2017;8:1818.
[105] Van Overmeire E, Laoui D, Keirsse J, Van Ginderachter JA. Hypoxia and tumor-associated macrophages. Oncoimmunology 2014;3:e27561.
[106] Colegio OR, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature 2014;513:559–63.
[107] Allavena P, Sica A, Solinas G, Porta C, Mantovani A. The inflammatory micro-environment in tumor progression: the role of tumor-associated macrophages. Crit Rev Oncol Hematol 2008;66:1–9.
[108] Fullár A, Dudás J, Oláh L, Hollósi P, Papp Z, Sobel G, et al. Remodeling of extracellular matrix by normal and tumor-associated fibroblasts promotes cervical cancer progression. BMC Cancer 2015;15:256.
[109] Eble JA, Niland S. The extracellular matrix in tumor progression and metastasis. Clin Exp Metastasis 2019;36:171–98.
[110] Kim J, Park H, Kim H, Kim Y, Oh HJ, Chung S. Microfluidic one-directional interstitial flow generation from cancer to cancer associated fibroblast. Acta Biomater 2022;144:258–65.
[111] Ksiazkiewicz M, Gottfried E, Kreutz M, Mack M, Hofstaedter F, Kunz-Schughart LA. Importance of CCL2-CCR2A/2B signaling for monocyte migration into spheroids of breast cancer-derived fibroblasts. Immunobiology 2010;215:737–47.
[112] Cohen N, Shani O, Raz Y, Sharon Y, Hoffman D, Abramovitz L, et al. Fibroblasts drive an immunosuppressive and growth-promoting microenvironment in breast cancer via secretion of chitinase 3-like 1. Oncogene 2017;36:4457–68.
[113] Ruland J. Colon cancer: epithelial notch signaling recruits neutrophils to drive metastasis. Cancer Cell 2019;36:213–14.
[114] Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, et al. Inhibitory effect of tumor cell–derived lactic acid on human T cells. Blood 2007;109:3812–19.
[115] Afonso J, Santos LL, Longatto-Filho A, Baltazar F. Competitive glucose metabolism as a target to boost bladder cancer immunotherapy. Nat Rev Urol 2020;17:77–106.
[116] Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol 2002;3:349–63.
[117] Wang X, Ye N, Xu C, Xiao C, Zhang Z, Deng Q, et al. Hyperbaric oxygen regulates tumor mechanics and augments abraxane and gemcitabine antitumor effects against pancreatic ductal adenocarcinoma by inhibiting cancer-associated fibroblasts. Nano Today 2022;44:101458.
[118] Shimoda M, Mellody KT, Orimo A. Carcinoma-associated fibroblasts are a rate-limiting determinant for tumour progression. Semin Cell Dev Biol 2010;21:19–25.
[119] Kraman M, Bambrough PJ, Arnold JN, Roberts EW, Magiera L, Jones JO, et al. Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein–α. Science (1979) 2010;330:827–30.
[120] Olumi AF, Grossfeld GD, Hayward SW, Carroll PR, Cunha GR, Hein P, et al. Carcinoma-associated fibroblasts stimulate tumor progression of initiated human epithelium. Breast Cancer Res 2000;2 1–1.

[121] Lu L, Barbi J, Pan F. The regulation of immune tolerance by FOXP3. Nat Rev Immunol 2017;17:703–17.
[122] Togashi Y, Shitara K, Nishikawa H. Regulatory T cells in cancer immunosuppression — implications for anticancer therapy. Nat Rev Clin Oncol 2019;16:356–71.
[123] Sharma A, Rudra D. Emerging functions of regulatory T Cells in tissue homeostasis. Front Immunol 2018;9.
[124] Dong C. Cytokine regulation and function in T cells. Annu Rev Immunol 2021;39:51–76.
[125] Zabijak L, Attencourt C, Guignant C, Chatelain D, Marcelo P, Marolleau J-P, et al. Increased tumor infiltration by mucosal-associated invariant T cells correlates with poor survival in colorectal cancer patients. Cancer Immunol Immunother 2015;64:1601–8.
[126] Richardson JR, Schöllhorn A, Gouttefangeas C, Schuhmacher J. CD4+ T Cells: multitasking cells in the duty of cancer immunotherapy. Cancers (Basel) 2021;13:596.
[127] Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors in cancer therapy: a focus on T-regulatory cells. Immunology & Cell Biology 2018;96:21–33.
[128] Wang H, Zhang H, Wang Y, Brown ZJ, Xia Y, Huang Z, et al. Regulatory T-cell and neutrophil extracellular trap interaction contributes to carcinogenesis in non-alcoholic steatohepatitis. J Hepatol 2021;75:1271–83.
[129] Miller AM, Lundberg K, Ozenci V, Banham AH, Hellström M, Egevad L, et al. CD4+CD25high T cells are enriched in the tumor and peripheral blood of prostate cancer patients. J Immunol 2006;177:7398–405.
[130] Watson MJ, Vignali PDA, Mullett SJ, Overacre-Delgoffe AE, Peralta RM, Grebinoski S, et al. Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. Nature 2021;591:645–51.
[131] Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009;9:162–74.
[132] Bronte V, Brandau S, Chen S-H, Colombo MP, Frey AB, Greten TF, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun 2016;7:12150.
[133] Buoncervello Gabriele. Toschi. The janus face of tumor microenvironment targeted by immunotherapy. IJMS 2019;20:4320.
[134] Solito S, Bronte V, Mandruzzato S. Antigen specificity of immune suppression by myeloid-derived suppressor cells. J Leukoc Biol 2011;90:31–6.
[135] Wu Y, Yi M, Niu M, Mei Q, Wu K. Myeloid-derived suppressor cells: an emerging target for anticancer immunotherapy. Mol Cancer 2022;21:1–19.
[136] Xie Z, Ikegami T, Ago Y, Okada N, Tachibana M. Valproic acid attenuates CCR2-dependent tumor infiltration of monocytic myeloid-derived suppressor cells, limiting tumor progression. Oncoimmunology 2020;9:1734268.
[137] Weber R, Fleming V, Hu X, Nagibin V, Groth C, Altevogt P, et al. Myeloid-derived suppressor cells hinder the anti-cancer activity of immune checkpoint inhibitors. Front Immunol 2018;9.
[138] Chen H, Zhang W, Zhu G, Xie J, Chen X. Rethinking cancer nanotheranostics. Nat Rev Mater 2017;2:1–18.
[139] Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, et al. Analysis of nanoparticle delivery to tumours. Nat Rev Mater 2016;1:1–12.
[140] Martin JD, Cabral H, Stylianopoulos T, Jain RK. Improving cancer immunotherapy using nanomedicines: progress, opportunities and challenges. Nat Rev Clin Oncol 2020;17:251–66.
[141] Shi R, Zhang Z, Hu X. Nickamine and analogous nickel pincer catalysts for cross-coupling of alkyl halides and hydrosilylation of alkenes. Acc Chem Res 2019;52:1471–83.
[142] Mi P, Cabral H, Kataoka K. Ligand-Installed nanocarriers toward precision therapy. Advanced Materials 2020;32:1902604.
[143] Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol 2007;2:751–60.
[144] Shrestha B, Tang L, Romero G. Nanoparticles-mediated combination therapies for cancer treatment. Adv Ther (Weinh) 2019;2:1900076.
[145] Zhang RX, Wong HL, Xue HY, Eoh JY, Wu XY. Nanomedicine of synergistic drug combinations for cancer therapy – Strategies and perspectives. J Controll Release 2016;240:489–503.
[146] Chen J, Zhu Y, Wu C, Shi J. Nanoplatform-based cascade engineering for cancer therapy. Chem Soc Rev 2020;49:9057–94.
[147] Weiden J, Tel J, Figdor CG. Synthetic immune niches for cancer immunotherapy. Nat Rev Immunol 2018;18:212–19.
[148] Wicki A, Witzigmann D, Balasubramanian V, Huwyler J. Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications. J Controll Release 2015;200:138–57.
[149] Parveen S, Arjmand F, Tabassum S. Clinical developments of antitumor polymer therapeutics. RSC Adv 2019;9:24699–721.
[150] Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer 2017;17:20–37.
[151] Liu Y, Chen XG, Yang PP, Qiao Z-Y, Wang H. Tumor microenvironmental pH and enzyme dual responsive polymer-liposomes for synergistic treatment of cancer immuno-chemotherapy. Biomacromolecules 2019;20:882–92.
[152] Reddy ST, Rehor A, Schmoekel HG, Hubbell JA, Swartz MA. *In vivo* targeting of dendritic cells in lymph nodes with poly(propylene sulfide) nanoparticles. J Controll Release 2006;112:26–34.
[153] Dai L, Li X, Yao M, Niu P, Yuan X, Li K, et al. Programmable prodrug micelle with size-shrinkage and charge-reversal for chemotherapy-improved IDO immunotherapy. Biomaterials 2020;241:119901.
[154] Dreaden EC, Mwakwari SC, Sodji QH, Oyelere AK, El-Sayed MA. Tamoxifen−poly(ethylene glycol)−thiol gold nanoparticle conjugates: enhanced potency and selective delivery for breast cancer treatment. Bioconjugate Chem 2009;20:2247–53.
[155] Chen L, Zhou L, Wang C, Han Y, Lu Y, Liu J, et al. Tumor-targeted drug and cpG delivery system for phototherapy and docetaxel-enhanced immunotherapy with polarization toward M1-type macrophages on triple negative breast cancers. Adv Mater 2019;31:e1904997.
[156] Kroll AV, Fang RH, Zhang L. Biointerfacing and applications of cell membrane-coated nanoparticles. Bioconjugate Chem 2017;28:23–32.
[157] Acharya S, Dilnawaz F, Sahoo SK. Targeted epidermal growth factor receptor nanoparticle bioconjugates for breast cancer therapy. Biomaterials 2009;30:5737–50.
[158] Fan Y, Moon JJ. Nanoparticle drug delivery systems designed to improve cancer vaccines and immunotherapy. Vaccines (Basel) 2015;3:662–85.
[159] Liu Y, Jiang Y, Zhang M, Tang Z, He M, Bu W. Modulating hypoxia via nanomaterials chemistry for efficient treatment of solid tumors. Acc Chem Res 2018;51:2502–11.
[160] Chao Y, Liu Z. Biomaterials tools to modulate the tumour microenvironment in immunotherapy. Nat Rev Bioeng 2023;1:125–38.
[161] Sahu A, Kwon I, Tae G. Improving cancer therapy through the nanomaterials-assisted alleviation of hypoxia. Biomaterials 2020;228:119578.

[162] Wang S, Yuan F, Chen K, Chen G, Tu K, Wang H, et al. Synthesis of hemoglobin conjugated polymeric micelle: a ZnPc carrier with oxygen self-compensating ability for photodynamic therapy. Biomacromolecules 2015;16:2693–700.
[163] Rummer JL, McKenzie DJ, Innocenti A, Supuran CT, Brauner CJ. Root effect hemoglobin may have evolved to enhance general tissue oxygen delivery. Science (1979) 2013;340:1327–9.
[164] D'Agnillo F, Chang TMS. Polyhemoglobin-superoxide dismutase-catalase as a blood substitute with antioxidant properties. Nat Biotechnol 1998;16:667–71.
[165] Chen Z, Liu L, Liang R, Luo Z, He H, Wu Z, et al. Bioinspired hybrid protein oxygen nanocarrier amplified photodynamic therapy for eliciting anti-tumor immunity and abscopal effect. ACS Nano 2018;12:8633–45.
[166] Tian H, Luo Z, Liu L, Zheng M, Chen Z, Ma A, et al. Cancer cell membrane-biomimetic oxygen nanocarrier for breaking hypoxia-induced chemoresistance. Adv Funct Mater 2017;27:1703197.
[167] Riess JG. Understanding the fundamentals of perfluorocarbons and perfluorocarbon emulsions relevant to *in vivo* oxygen delivery. Artif Cells Blood Substit Immobil Biotechnol 2005;33:47–63.
[168] Castro CI, Briceno JC. Perfluorocarbon-based oxygen carriers: review of products and trials. Artif Organs 2010;34:622–34.
[169] Wang Y, Wang D, Zhang Y, Xu H, Shen L, Cheng J, et al. Tumor microenvironment-adaptive nanoplatform synergistically enhances cascaded chemodynamic therapy. Bioact Mater 2023;22:239–53.
[170] Song G, Liang C, Yi X, Zhao Q, Cheng L, Yang K, et al. Perfluorocarbon-loaded hollow Bi2Se3 nanoparticles for timely supply of oxygen under near-infrared light to enhance the radiotherapy of cancer. Advanced Materials 2016;28:2716–23.
[171] Gao S, Zheng P, Li Z, Feng X, Yan W, Chen S, et al. Biomimetic O2-evolving metal-organic framework nanoplatform for highly efficient photodynamic therapy against hypoxic tumor. Biomaterials 2018;178:83–94.
[172] Zou MZ, Liu WL, Li CX, Zheng DW, Zeng JY, Gao F, et al. A multifunctional biomimetic nanoplatform for relieving hypoxia to enhance chemotherapy and inhibit the PD-1/PD-L1 axis. Small 2018;14:e1801120.
[173] Li B, Wang X, Hong S, Wang Q, Li L, Eltayeb O, et al. MnO_2 nanosheets anchored with polypyrrole nanoparticles as a multifunctional platform for combined photothermal/photodynamic therapy of tumors. Food Funct 2021;12:6334–47.
[174] Chen Q, Liang C, Sun X, Chen J, Yang Z, Zhao H, et al. H_2O_2-responsive liposomal nanoprobe for photoacoustic inflammation imaging and tumor theranostics via *in vivo* chromogenic assay. Proc Nat Acad Sci 2017;114:5343–8.
[175] Laurent A, Nicco C, Chéreau C, Goulvestre C, Alexandre J, Alves A, et al. Controlling tumor growth by modulating endogenous production of reactive oxygen species. Cancer Res 2005;65:948–56.
[176] Gu Z, Biswas A, Zhao M, Tang Y. Tailoring nanocarriers for intracellular protein delivery. Chem Soc Rev 2011;40:3638–55.
[177] Cheng H, Zhu JY, Li SY, Zeng JY, Lei Q, Chen KW, et al. An O_2 self-sufficient biomimetic nanoplatform for highly specific and efficient photodynamic therapy. Adv Funct Mater 2016;26:7847–60.
[178] Song X, Xu J, Liang C, Chao Y, Jin Q, Wang C, et al. Self-supplied tumor oxygenation through separated liposomal delivery of H2O2 and catalase for enhanced radio-immunotherapy of cancer. Nano Lett 2018;18:6360–8.
[179] Yang ZL, Tian W, Wang Q, Zhao Y, Zhang YL, Tian Y, et al. Oxygen-evolving mesoporous organosilica coated prussian blue nanoplatform for highly efficient photodynamic therapy of tumors. Adv Sci (Weinh) 2018;5:1700847.
[180] Fan J, Yin JJ, Ning B, Wu X, Hu Y, Ferrari M, et al. Direct evidence for catalase and peroxidase activities of ferritin–platinum nanoparticles. Biomaterials 2011;32:1611–18.
[181] Yang G, Xu L, Chao Y, Xu J, Sun X, Wu Y, et al. Hollow MnO_2 as a tumor-microenvironment-responsive biodegradable nano-platform for combination therapy favoring antitumor immune responses. Nat Commun 2017;8:902.
[182] Zheng D, Li B, Xu L, Zhang QL, Fan JX, Li CX, et al. Normalizing tumor microenvironment based on photosynthetic abiotic/biotic nanoparticles. ACS Nano 2018;12:6218–27.
[183] Huang WQ, Wang F, Shen AZ, Zhang L, Nie X, Zhang Z, et al. Single nanosheet can sustainably generate oxygen and inhibit respiration simultaneously in cancer cells. Mater Horiz 2021;8:597–605.
[184] Gill AL, Bell CNA. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. QJM 2004;97:385–95.
[185] Liu X, Ye N, Liu S, Guan J, Deng Q, Zhang Z, et al. Hyperbaric oxygen boosts PD-1 antibody delivery and T Cell infiltration for augmented immune responses against solid tumors. Adv Sci 2021;8:2100233.
[186] Carmeliet P, Jain RK. Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. Nat Rev Drug Discov 2011;10:417–27.
[187] Chung AS, Lee J, Ferrara N. Targeting the tumour vasculature: insights from physiological angiogenesis. Nat Rev Cancer 2010;10:505–14.
[188] Osswald CR, Guthrie MJ, Avila A, Valio JA, Mieler WF, Kang Mieler JJ. *In vivo* efficacy of an injectable microsphere-hydrogel ocular drug delivery system. Curr Eye Res 2017;42:1293–301.
[189] Chen Q, Xu L, Chen J, Yang Z, Liang C, Yang Y, et al. Tumor vasculature normalization by orally fed erlotinib to modulate the tumor microenvironment for enhanced cancer nanomedicine and immunotherapy. Biomaterials 2017;148:69–80.
[190] Deng Y, Jiang Z, Jin Y, Qiao J, Yang S, Xiong H, et al. Reinforcing vascular normalization therapy with a bi-directional nano-system to achieve therapeutic-friendly tumor microenvironment. J Controll Release 2021;340:87–101.
[191] Li F, Wang Y, Chen W, Wang D, Zhou Y, You B, et al. Co-delivery of VEGF siRNA and etoposide for enhanced anti-angiogenesis and anti-proliferation effect *via* multi-functional nanoparticles for orthotopic non-small cell lung cancer treatment. Theranostics 2019;9:5886–98.
[192] Li W, Zhao X, Du B, Li X, Liu S, Yang XY, et al. Gold nanoparticle–mediated targeted delivery of recombinant human endostatin normalizes tumour vasculature and improves cancer therapy. Sci Rep 2016;6:1–11.
[193] Bao X, Shen N, Lou Y, Yu H, Wang Y, Liu L, et al. Enhanced anti-PD-1 therapy in hepatocellular carcinoma by tumor vascular disruption and normalization dependent on combretastatin A4 nanoparticles and DC101. Theranostics 2021;11:5955–69.
[194] Taleb M, Atabakhshi Kashi M, Wang Y, Rezvani Alanagh H, Farhadi Sabet Z, Li F, et al. Bifunctional therapeutic peptide assembled nanoparticles exerting improved activities of tumor vessel normalization and immune checkpoint inhibition. Adv Healthcare Mater 2021;10:2100051.

[195] Sung YC, Jin PR, Chu LA, Hsu FF, Wang MR, Chang CC, et al. Delivery of nitric oxide with a nanocarrier promotes tumour vessel normalization and potentiates anti-cancer therapies. Nat Nanotechnol 2019;14:1160–9.
[196] Tian L, Wang Y, Sun L, Xu J, Chao Y, Yang K, et al. Cerenkov luminescence-induced NO release from 32P-labeled $ZnFe(CN)_5NO$ nanosheets to enhance radioisotope-immunotherapy. Matter 2019;1:1061–76.
[197] Rolny C, Mazzone M, Tugues S, Laoui D, Johansson I, Coulon C, et al. HRG inhibits tumor growth and metastasis by inducing macrophage polarization and vessel normalization through downregulation of PIGF. Cancer Cell 2011;19:31–44.
[198] Theek B, Baues M, Gremse F, Pola R, Pechar M, Negwer I, et al. Histidine-rich glycoprotein-induced vascular normalization improves EPR-mediated drug targeting to and into tumors. J Controll Release 2018;282:25–34.
[199] Wang Y, Zhou X, Wang W, Wu Y, Qian Z, Peng Q. Sodium bicarbonate, an inorganic salt and a potential active agent for cancer therapy. Chinese Chemical Letters 2021;32:3687–95.
[200] Banerjee D, Bose S. Comparative effects of controlled release of sodium bicarbonate and doxorubicin on osteoblast and osteosarcoma cell viability. Mater Today Chem 2019;12:200–8.
[201] Li Z, Ning F, Wang C, Yu H, Ma Q, Sun Y. Normalization of the tumor microvasculature based on targeting and modulation of the tumor microenvironment. Nanoscale 2021;13:17254–71.
[202] Wang M, Lu F, Li N, Pan W, Tang B. A biomimetic ZIF nanoagent for synergistic regulation of glutamine metabolism and intracellular acidosis of cancer. Chem Commun 2022;58:1554–7.
[203] Dong Z, Feng L, Zhu W, Sun X, Gao M, Zhao H, et al. $CaCO_3$ nanoparticles as an ultra-sensitive tumor-pH-responsive nanoplatform enabling real-time drug release monitoring and cancer combination therapy. Biomaterials 2016;110:60–70.
[204] Zhu Y, Yang Z, Dong Z, Gong Y, Hao Y, Tian L, et al. $CaCO_3$-assisted preparation of pH-responsive immune-modulating nanoparticles for augmented chemo-immunotherapy. Nanomicro Lett 2020;13:29.
[205] Liu X, Li Y, Wang K, Chen Y, Shi M, Zhang X, et al. GSH-responsive nanoprodrug to inhibit glycolysis and alleviate immunosuppression for cancer therapy. Nano Lett 2021;21:7862–9.
[206] Kolb D, Kolishetti N, Surnar B, Sarkar S, Guin S, Shah AS, et al. Metabolic modulation of the tumor microenvironment leads to multiple checkpoint inhibition and immune cell infiltration. ACS Nano 2020;14:11055–66.
[207] Li K, Lin C, He Y, Lu L, Xu K, Tao B, et al. Engineering of cascade-responsive nanoplatform to inhibit lactate efflux for enhanced tumor chemo-immunotherapy. ACS Nano 2020;14:14164–80.
[208] Chen ZX, Liu MD, Guo DK, Zou MZ, Wang SB, Cheng H, et al. A MSN-based tumor-targeted nanoplatform to interfere with lactate metabolism to induce tumor cell acidosis for tumor suppression and anti-metastasis. Nanoscale 2020;12:2966–72.
[209] Zhao LP, Zheng RR, Kong RJ, Huang CY, Rao XN, Yang N, et al. Self-delivery ternary bioregulators for photodynamic amplified immunotherapy by tumor microenvironment reprogramming. ACS Nano 2022;16:1182–97.
[210] Pickup MW, Mouw JK, Weaver VM. The extracellular matrix modulates the hallmarks of cancer. EMBO Rep 2014;15:1243–53.
[211] Liu J, Tian L, Zhang R, Dong Z, Wang H, Liu Z. Collagenase-encapsulated pH-responsive nanoscale coordination polymers for tumor microenvironment modulation and enhanced photodynamic nanomedicine. ACS Appl Mater Interfaces 2018;10:43493–502.
[212] Zhou H, Fan Z, Deng J, Lemons PK, Arhontoulis DC, Bowne WB, et al. Hyaluronidase embedded in nanocarrier PEG shell for enhanced tumor penetration and highly efficient antitumor efficacy. Nano Lett 2016;16:3268–77.
[213] He Y, Li Z, Cong C, Ye F, Yang J, Zhang X, et al. Pyroelectric catalysis-based "nano-lymphatic" reduces tumor interstitial pressure for enhanced penetration and hydrodynamic therapy. ACS Nano 2021;15:10488–501.
[214] Chen J, Li S, Liu X, Liu S, Xiao C, Zhang Z, et al. Transforming growth factor-β blockade modulates tumor mechanical microenvironments for enhanced antitumor efficacy of photodynamic therapy. Nanoscale 2021;13:9989–10001.
[215] Chen W, Yuan Y, Li C, Mao H, Liu B, Jiang X. Modulating tumor extracellular matrix by simultaneous inhibition of two cancer cell receptors. Adv Mater 2022;34:e2109376.
[216] Genard G, Lucas S, Michiels C. Reprogramming of tumor-associated macrophages with anticancer therapies: radiotherapy *versus* chemo- and immunotherapies. Front Immunol 2017;8:828.
[217] O'Brien SA, Orf J, Skrzypczynska KM, Tan H, Kim J, DeVoss J, et al. Activity of tumor-associated macrophage depletion by CSF1R blockade is highly dependent on the tumor model and timing of treatment. Cancer Immunol Immunother 2021;70:2401–10.
[218] Zang X, Zhang X, Hu H, Qiao M, Zhao X, Deng Y, et al. Targeted delivery of zoledronate to tumor-associated macrophages for cancer immunotherapy. Mol Pharmaceutics 2019;16:2249–58.
[219] Zhang HT, Peng R, Chen S, Shen A, Zhao L, Tang W, et al. Versatile nano-protac-induced epigenetic reader degradation for efficient lung cancer therapy. Adv Sci 2022;9:2202039.
[220] Mantovani A, Allavena P, Sozzani S, Vecchi A, Locati M, Sica A. Chemokines in the recruitment and shaping of the leukocyte infiltrate of tumors. Semin Cancer Biol 2004;14:155–60.
[221] Argyle D, Kitamura T. Targeting macrophage-recruiting chemokines as a novel therapeutic strategy to prevent the progression of solid tumors. Front Immunol 2018;9.
[222] Qian Y, Qiao S, Dai Y, Xu G, Dai B, Lu L, et al. Molecular-targeted immunotherapeutic strategy for melanoma via dual-targeting nanoparticles delivering small interfering RNA to tumor-associated macrophages. ACS Nano 2017;11:9536–49.
[223] Xiao H, Guo Y, Li B, Li X, Wang Y, Han S, et al. M2-Like tumor-associated macrophage-targeted codelivery of STAT6 inhibitor and IKKβ siRNA induces M2-to-M1 repolarization for cancer immunotherapy with low immune side effects. ACS Cent Sci 2020;6:1208–22.
[224] Kulkarni A, Chandrasekar V, Natarajan SK, Ramesh A, Pandey P, Nirgud J, et al. A designer self-assembled supramolecule amplifies macrophage immune responses against aggressive cancer. Nat Biomed Eng 2018;2:589–99.
[225] Sun L, Chen B, Jiang R, Li J, Wang B. Resveratrol inhibits lung cancer growth by suppressing M2-like polarization of tumor associated macrophages. Cell Immunol 2017;311:86–93.
[226] Shapouri Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili S-A, Mardani F, et al. Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol 2018;233:6425–40.
[227] Li K, Lu L, Xue C, Liu J, He Y, Zhou J, et al. Polarization of tumor-associated macrophage phenotype via porous hollow iron nanoparticles for tumor immunotherapy *in vivo*. Nanoscale 2020;12:130–44.
[228] Kim SY, Kim S, Kim JE, Lee SN, Shin IW, Shin HS, et al. Lyophilizable and multifaceted toll-like receptor 7/8 agonist-loaded nanoemulsion for the reprogramming

of tumor microenvironments and enhanced cancer immunotherapy. ACS Nano 2019;13:12671–86.
[229] Song Y, Bugada L, Li R, Hu H, Zhang L, Li C, et al. Albumin nanoparticle containing a PI3Kγ inhibitor and paclitaxel in combination with α-PD1 induces tumor remission of breast cancer in mice. Sci Transl Med 2022;14:eabl3649.
[230] Wang M, Chang M, Li C, Chen Q, Hou Z, Xing B, et al. Tumor-microenvironment-activated reactive oxygen species amplifier for enzymatic cascade cancer starvation/chemodynamic /immunotherapy. Advanced Materials 2022;34:2106010.
[231] Chen X, Song E. Turning foes to friends: targeting cancer-associated fibroblasts. Nat Rev Drug Discov 2019;18:99–115.
[232] Mpekris F, Papageorgis P, Polydorou C, Voutouri C, Kalli M, Pirentis AP, et al. Sonic-hedgehog pathway inhibition normalizes desmoplastic tumor microenvironment to improve chemo- and nanotherapy. J Controll Release 2017;261:105–12.
[233] Fourniols T, Bastien E, Canevat A, Feron O, Préat V. Inhibition of colorectal cancer-associated fibroblasts by lipid nanocapsules loaded with acriflavine or paclitaxel. Int J Pharm 2020;584:119337.
[234] Nicolás Boluda A, Vaquero J, Laurent G, Renault G, Bazzi R, Donnadieu E, et al. Photothermal depletion of cancer-associated fibroblasts normalizes tumor stiffness in desmoplastic cholangiocarcinoma. ACS Nano 2020;14:5738–53.
[235] Zhao J, Wang H, Hsiao C-H, Chow DS L, Koay EJ, Kang Y, et al. Simultaneous inhibition of hedgehog signaling and tumor proliferation remodels stroma and enhances pancreatic cancer therapy. Biomaterials 2018;159:215–28.
[236] Shen L, Li J, Liu Q, Song W, Zhang X, Tiruthani K, et al. Local blockade of interleukin 10 and C-X-C motif chemokine ligand 12 with nano-delivery promotes antitumor response in murine cancers. ACS Nano 2018;12:9830–41.
[237] Zhao T, Zhang R, He Q, Zhou H, Song X, Gong T, et al. Partial ligand shielding nanoparticles improve pancreatic ductal adenocarcinoma treatment via a multifunctional paradigm for tumor stroma reprogramming. Acta Biomater 2022;145:122–34.
[238] Huang Y, Chen Y, Zhou S, Chen L, Wang J, Pei Y, et al. Dual-mechanism based CTLs infiltration enhancement initiated by Nano-sapper potentiates immunotherapy against immune-excluded tumors. Nat Commun 2020;11:622.
[239] MdN Hossen, Rao G, Dey A, Robertson JD, Bhattacharya R, Mukherjee P. Gold nanoparticle transforms activated cancer-associated fibroblasts to quiescence. ACS Appl Mater Interfaces 2019;11:26060–8.
[240] Xu H, Hu M, Liu M, An S, Guan K, Wang M, et al. Nano-puerarin regulates tumor microenvironment and facilitates chemo- and immunotherapy in murine triple negative breast cancer model. Biomaterials 2020;235:119769.
[241] Li Z, Wang Y, Shen Y, Qian C, Oupicky D, Sun M. Targeting pulmonary tumor microenvironment with CXCR4-inhibiting nanocomplex to enhance anti–PD-L1 immunotherapy. Sci Adv 2020;6:eaaz9240.
[242] Feng Q, Hao Y, Yang S, Yuan X, Chen J, Mei Y, et al. A metabolic intervention strategy to break evolutionary adaptability of tumor for reinforced immunotherapy. Acta Pharm Sin B 2023;13:775–86.
[243] Tian Y., Younis M.R., Zhao Y., Guo K., Wu J., Zhang L., et al. Precision delivery of dual immune inhibitors loaded nanomodulator to reverse immune suppression for combinational photothermal-immunotherapy. Small n.d.;n/a:2206441.
[244] Li Z, Xu W, Yang J, Wang J, Wang J, Zhu G, et al. A tumor microenvironments-adapted polypeptide hydrogel/nanogel composite boosts antitumor molecularly targeted inhibition and immunoactivation. Adv Mater 2022;34:2200449.
[245] Luo L, Iqbal MZ, Liu C, Xing J, Akakuru OU, Fang Q, et al. Engineered nano-immunopotentiators efficiently promote cancer immunotherapy for inhibiting and preventing lung metastasis of melanoma. Biomaterials 2019;223:119464.
[246] Min Y, Roche KC, Tian S, Eblan MJ, McKinnon KP, Caster JM, et al. Antigen-capturing nanoparticles improve the abscopal effect and cancer immunotherapy. Nat Nanotechnol 2017;12:877–82.
[247] Liu Y, Zhou J, Li Q, Li L, Jia Y, Geng F, et al. Tumor microenvironment remodeling-based penetration strategies to amplify nanodrug accessibility to tumor parenchyma. Adv Drug Deliv Rev 2021;172:80–103.
[248] Wang R, Billone PS, Mullett WM. Nanomedicine in action: an overview of cancer nanomedicine on the market and in clinical trials. J Nanomater 2013;2013:e629681.
[249] Min Y, Caster JM, Eblan MJ, Wang AZ. Clinical translation of nanomedicine. Chem Rev 2015;115:11147–90.
[250] Ye M, Han Y, Tang J, Piao Y, Liu X, Zhou Z, et al. A tumor-specific cascade amplification drug release nanoparticle for overcoming multidrug resistance in cancers. Adv Mater 2017;29:1702342.
[251] Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol 2015;33:941–51.