Journal of Nanobiotechnology

REVIEW

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Targeting the tumor microenvironment with biomaterials for enhanced immunotherapeutic efficacy

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Abstract

The tumor microenvironment (TME) is a complex system characterized by low oxygen, low pH, high pressure, and numerous growth factors and protein hydrolases that regulate a wide range of biological behaviors in the tumor and have a profound impact on cancer progression. Immunotherapy is an innovative approach to cancer treatment that activates the immune system, resulting in the spontaneous killing of tumor cells. However, the therapeutic efficacy of these clinically approved cancer immunotherapies (e.g., immune checkpoint blocker (ICB) therapies and chimeric antigen receptor (CAR) T-cell therapies) is far from satisfactory due to the presence of immunosuppressive TMEs created in part by tumor hypoxia, acidity, high levels of reactive oxygen species (ROS), and a dense extracellular matrix (ECM). With continuous advances in materials science and drug-delivery technologies, biomaterials hold considerable potential for targeting the TME. This article reviews the advances in biomaterial-based targeting of the TME to advance our current understanding on the role of biomaterials in enhancing tumor immunity. In addition, the strategies for remodeling the TME offer enticing advantages; however, the represent a double-edged sword. In the process of reshaping the TME, the risk of tumor growth, infiltration, and distant metastasis may increase.

Keywords Biomaterial, Nanoparticle, Tumor microenvironment, Tumor immunotherapy

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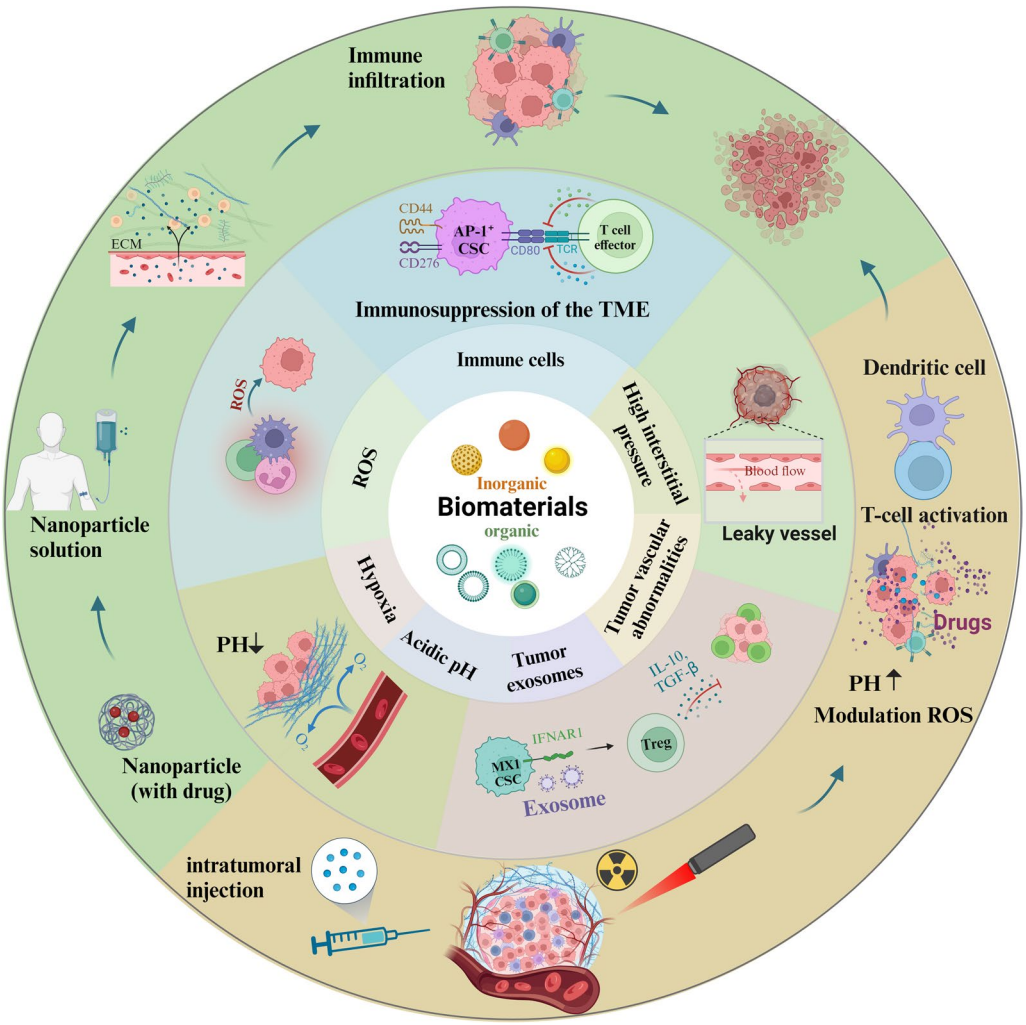
Graphical Abstract



Introduction

The tumor microenvironment (TME) represents an intricate milieu in which cancer cells subsist, comprising a multifaceted array of elements, including blood vessels, fibroblasts, immune cell populations, bone marrow-derived inflammatory cells, lymphocytes, signal transduction networks, and the extracellular matrix (ECM). Typically, cancer cells are enclosed within a dense ECM, characterized by collagen and proteoglycans, which serve as scaffolds for their microenvironment and participate in the secretion of an array of cytokines, chemokines, and other bioactive molecules [1]. The TME has emerged as a dynamic and intricate ecosystem replete with bidirectional interactions with tumor cells. Mounting evidence supports the pivotal roles played by innate immune cell subsets, such as macrophages, neutrophils, dendritic cells (DCs), innate lymphoid cells, myeloid suppressor cells, natural killer (NK) cells, and adaptive immune cells (T and B cells), in orchestrating tumor progression within the TME [2]. These immune components are equipped to either launch attacks against malignant cells to suppress tumor growth or instigate the suppression of immune cells that exert inhibitory effects on cancer cells. Regulatory T cells, among other specialized bone marrow-derived cells, are key players in the immunosuppressive niche. Myriad inflammatory cells, primarily nonspecific immune cells, also populate the TME. These cells can dampen the positive immune function within the TME, rendering normative immune cells ineffectual against malignant tumor cells and, in turn, fueling

tumor growth [3]. Collectively, the diverse constituents of the TME configure the localized homeostatic milieu of malignancies, endowing it with the requisite material for tumor initiation, progression, infiltration, and metastasis [3]. In light of the fundamental roles played by the TME in nurturing and propelling tumorigenesis, an emergent therapeutic paradigm revolves around deliberately modifying the TME. This approach is analogous to cultivating the "soil" with the aim of restraining the activity of tumor cells, conceptualized as the "seeds" within the TME, and presents a new avenue for therapeutic intervention.

Tumor immunotherapy is at the forefront of contemporary cancer treatments, representing an innovative approach that harnesses the immune system to unleash a potent assault on malignant cells. This modality has exhibited substantial promise, outperforming traditional anti-tumor strategies in extending progression-free and overall survival, as demonstrated by a compendium of experimental and clinical investigations [4]. Clinically, a cadre of immunotherapeutic modalities is in use, including adoptive T-cell therapy, chimeric antigen receptor T-cell therapy (CAR-T), immune checkpoint inhibition, and tumor vaccines [5–8]. Nonetheless, the clinical utility of immune checkpoint inhibitors is impeded by a notable limitation in their response rates, which typically range from 10 to 40%, and by the incidence of variable degrees of immune-related adverse events [9]. Furthermore, the efficacy of most cell therapy products remains suboptimal when applied to solid tumors [1]. Despite the remarkable progress in cancer immunotherapy over the past decade, key challenges remain, impeding its broad clinical applicability. These include low immunogenicity, limited specificity, reduced transfection efficiency, and adverse off-target side effects [2]. Evidence from diverse studies underscores the effectiveness of various strategies to rationally normalize the TME as a pivotal means of increasing cancer immunotherapy efficacy [10].

In this context, biomaterials have emerged as pivotal tools for constructing therapeutic platforms designed to modulate immune responses against malignancies [2, 11–14]. Biomaterials, categorized as inorganic or organic, play a profound role in interfacing biological systems. Inorganic biomaterials consist primarily of inorganic constituents. Utilizing inorganic nanocarriers has proven instrumental in enhancing drug and gene retention within tumors while reducing non-specific distribution in healthy tissues. This dual action facilitates the precise delivery of therapeutic agents to the tumor site. Organic materials similarly exhibit these beneficial properties. Specifically, organic biomaterials derived from carbohydrates, nucleic acids, lipids, proteins, and synthetic polymers have demonstrated advantages in orchestrating immune regulation and targeted tumor therapy [15]. Their exceptional biocompatibility, biodegradability, and biological recognition capabilities render them invaluable in therapeutic applications [16].

While various reviews have explored biomaterials targeting specific aspects of the TME, such as immunosuppressive cells, hypoxia, dense ECM, and acidic pH, a comprehensive discussion encompassing the entire field of biomaterials targeting the TME is notably lacking. Accordingly, this review meticulously delineates the physical and chemical composition of the TME, highlighting the challenges it presents to immunotherapy (Fig. 1). Moreover, we elucidate how biomaterials can strategically overcome these hurdles to augment cancer immunotherapy. Furthermore, strategies designed to remodel the TME offer compelling advantages but present a double-edged sword. Approaches such as disrupting the tumor ECM, elevating levels of ROS, and normalizing tumor vasculature, although intended to treat the tumor, may potentially heighten the risks of tumor growth, infiltration, and distant metastasis.

The tumor microenvironment

Aberrant blood vessels, hypoxia, weak acidity, high interstitial pressure, and dense ECM in the TME impede drug penetration and advance tumor progression [17] (Fig. 2). Furthermore, the immune cells in the TME can elicit immune surveillance via immune editing. Nanomedicine strives to overcome these barriers by focusing on two primary mechanisms: tumor interstitial diffusion and cellular delivery [18]. Targeting immune regulatory molecules within the immunosuppressive TME, either systemically or locally, reinstates anti-tumor immunity in cells that previously promoted tumorigenesis [19]. Although the multifaceted characteristics of the TME may challenge traditional therapeutic approaches, they underscore the fundamental and decisive role that the TME plays in modeling tumor morphology and physiology [20]. Hence, a comprehensive understanding of how the TME components influence tumor behavior remains crucial, underscoring the need for further research in this domain.

Immune cells

Within the TME, immune cells undergo dynamic interactions and evolution, perpetuating immunosuppression through immune editing. Key cellular targets for tumor immunotherapy include tumor cells and various TME components, such as tumor-associated macrophages (TAMs), DCs, T cells, and various immunosuppressive myeloid cells. By strategically reshaping the immune cell composition, elevating the proportion of anti-tumor immune cells, and

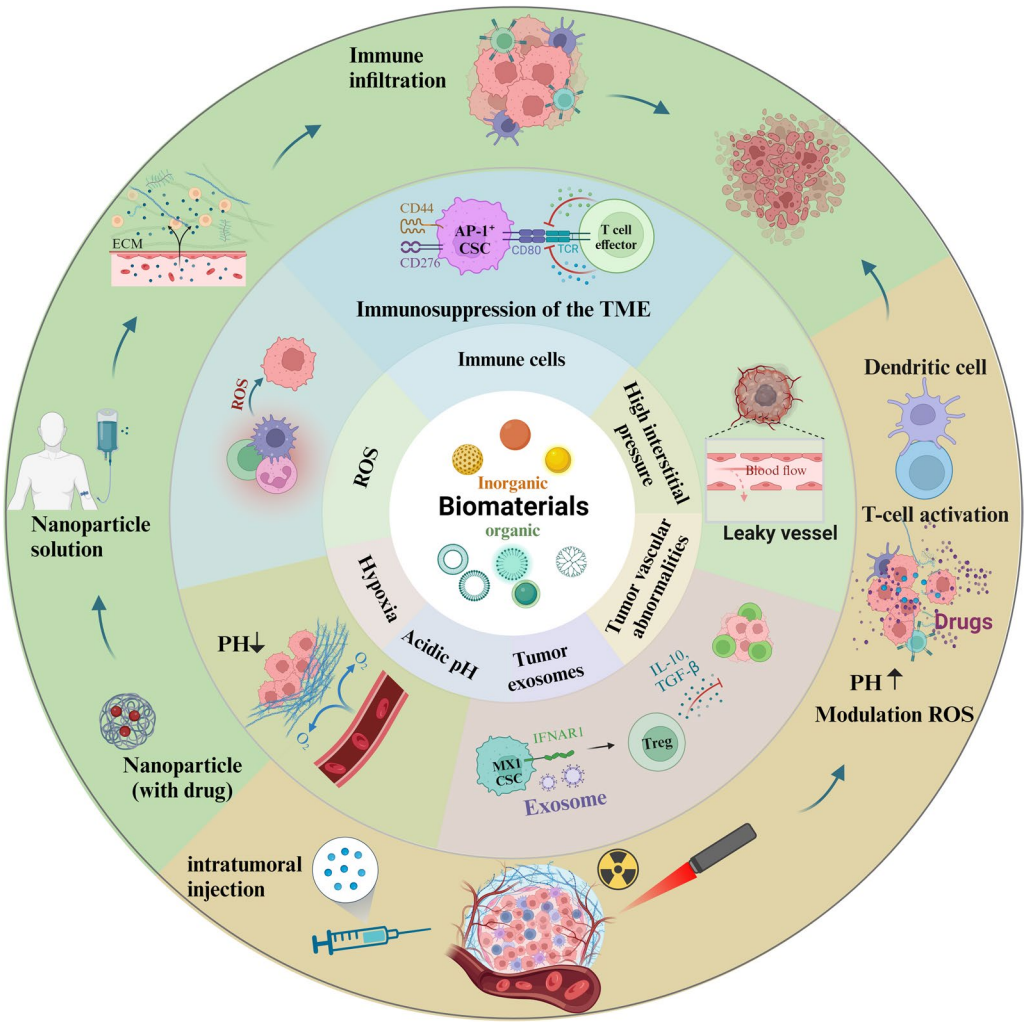


Fig. 1 Summative scheme of targeting the tumor microenvironment with biomaterials for enhanced immunotherapeutic efficacy. Created with BioRender.com

diminishing immunosuppressive cells, TME-mediated immune suppression can be reversed.

Macrophages are a diverse group of immune cells that play pivotal roles in innate and adaptive immunity. Within the intricate TME, macrophages can be recruited to tumor regions and polarized into M1, associated with anti-tumor activities, or M2 phenotypes, linked to tumor promotion. Notably, polarization is a continuous process, with M1 and M2 serving as the extreme states. M1-type macrophages are characterized by their response to pro-inflammatory cytokines, such as IFN-γ and inducible nitric oxide synthase, achieving an anti-tumor effect through pro-inflammatory mediator release. Conversely, M2-type polarization, driven by cytokines such as interleukin (IL)-4 and colony-stimulating factor 1 (CSF1), leads to the secretion of pro-tumor factors that support angiogenesis, invasion, metastasis, and immune suppression [21–23]. TAMs exhibit high plasticity during tumor progression and can transition toward an M2 state under factors such as cytokines, chemokines, and exosomes within the TME. Additionally, at primary and metastatic tumor sites, TAMs exert inhibitory effects on cytotoxic T cells and NK cells, which can potentially eradicate tumors [24].

DCs are proficient antigen-presenting cells (APCs), vital for initiating and sustaining T-cell–mediated cytotoxicity [25]. Activation of immature DCs in response to tumor-specific antigens or exogenous stimuli involves the upregulation of major histocompatibility complex (MHC) molecules and costimulatory molecules (CD80, CD86, and CD40) on the cell surface, playing a pivotal role in the initiation and expansion of T cells [26]. Conversely, tumor-associated DCs (TADCs) often fail to effectively present antigens, leading to the generation of

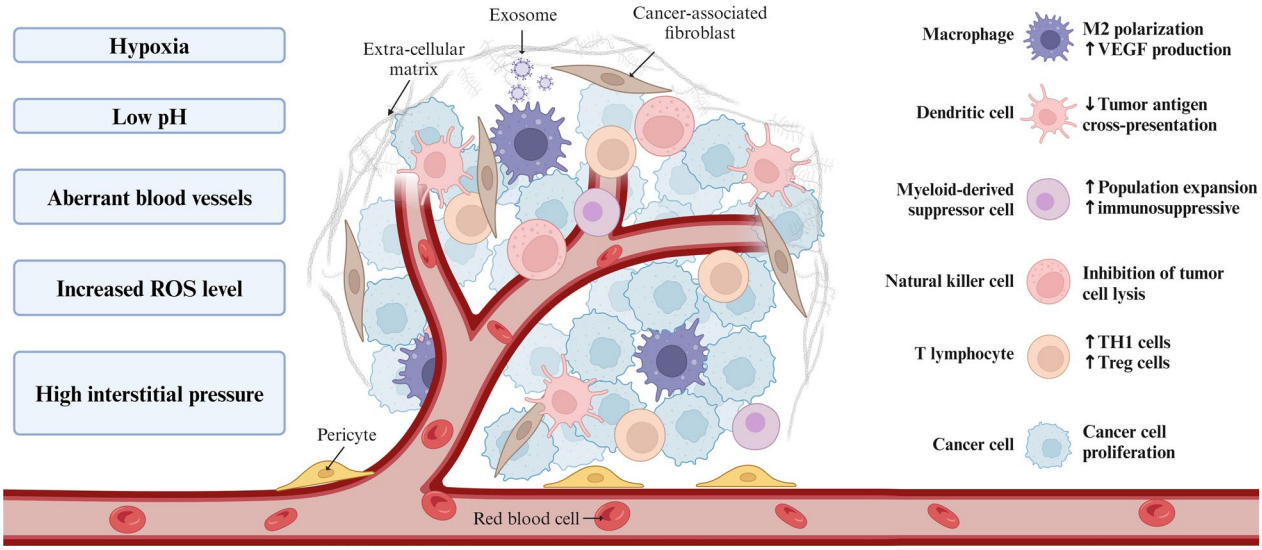


Fig. 2 The tumor microenvironment. The characteristics of the tumor microenvironment (including hypoxia, weak acidity, aberrant blood vessels, high interstitial pressure and increased ROS level) affect immune cells and promotes tumor infiltration. Created with BioRender.com

tolerogenic DCs (tolDCs). These tolDCs disrupt effector T-cell function and promote immunosuppression [27]. Thus, rectifying DC dysfunction in the TME has immense potential as a pioneering cancer treatment strategy.

NK cells serve as the first line of defense against tumors, executing non-specific tumor-cell killing via perforin-induced cell perforation, followed by granzyme B-mediated apoptosis induction. This process operates independently of antigen sensitization, antibodies, or MHC restrictions. Additionally, NK cells augment the anti-tumor activity of adaptive immune cells via cytokine secretion. However, metabolic interference in the form of lactic acid accumulation within the TME reduces intracellular pH in NK cells, inducing pH-dependent mitochondrial stress and metabolic disruption, ultimately promoting NK-cell apoptosis [28].

$CD4^+$ and $CD8^+$ T cells, expressing α/β T-cell receptors (TCRs), play pivotal roles in identifying tumor antigens and autoantigens in the immune response against cancer and autoimmune diseases. The hypoxia-induced intracellular metabolite 2-hydroxyglutarate inhibits $CD8^+$ T-cell activation, differentiation, cytokine secretion, and cytotoxic potential. Glucose deficiency in the TME hinders TCR-dependent Ca^{2+} and NFAT signaling, obstructing normal $CD8^+$ T-cell differentiation and leading to anti-tumor dysfunction. Targeting acetyl CoA acetyltransferase 1 enhances $CD8^+$ T-cell cholesterol esterification, TCR signaling, proliferation, and anti-tumor efficacy [29, 30]. Initially, $CD4^+$ T cells differentiate into various subtypes, including T-helper 1 (Th1), Th2, Th17, follicular-helper T cells (Tfh), regulatory T cells (Tregs), and long-term memory cells upon homologous antigen stimulation. Tregs, characterized by a high FOXP3, CD25, and CD4 expression, frequently accumulate in tumors [31]. They use lipid metabolism and oxidative phosphorylation pathways for energy generation and maintain an immunosuppressive TME that promotes tumor infiltration and metastasis. Additionally, lactic acid impedes Th-cell function and diminishes anti-tumor immune activity by disrupting the binding of C-X-C chemokine receptor 3 (CXCR3) to its ligand [32, 33].

Reactive oxygen species

Reactive oxygen species (ROS) are crucial oxidative stress response and signal transduction mediators. Various ROS, such as superoxide anion free radicals ($O_2^{\bullet-}$), singlet oxygen ($^1O_2$), hydrogen peroxide, and hydroxyl radicals, play pivotal roles in normal physiological cell signaling. However, under environmental stress or pathological conditions, these species can lead to oxidative damage to lipids, proteins, and DNA, promoting tumorigenesis [34, 35]. ROS accumulation is a hallmark of the oxidative stress-prone TME, triggering gene mutations, cell proliferation, angiogenesis, and metastasis [36]. ROS modulate tumor-cell proliferation, invasion, and migration in breast cancer by orchestrating TME interactions [37]. ROS modulation includes tumor-cell reprogramming, upregulates hypoxia-inducible factor-1α (HIF-1α), and activates a glycolytic gene-transcription cascade, fostering hypoxia and acidic pH. This, in turn, compromises anti-tumor immunity and promotes stromal-cell recruitment within the TME [35]. Furthermore, ROS act as secondary messengers,

hyperactivating nuclear factor kappa-light-chain-enhancer of activated B cells, provoking inflammation and forming a self-perpetuating cycle [38, 39]. In contrast to their tumor-promoting role, ROS-induced oxidative damage and ROS-mediated death signals also present opportunities to inhibit tumor progression and enhance the effectiveness of immunotherapy [40, 41]. Notably, in immunogenic cell death (ICD)-based immunotherapy, the role of ROS is significant. ROS-induced oxidative stress, alongside upregulated proteins like protein kinase R–like endoplasmic reticulum kinase and eukaryotic translation initiation factor 2-alpha, can effectively trigger ICD [42, 43]. ROS accumulation can also induce various forms of cell death, including ferroptosis, an emerging mode of cell death that relies on iron-dependent lipid peroxidation resulting from intracellular ROS [44].

However, the role of ROS and their therapeutic efficacy differ extensively depending on the tumor type, location, nature, and developmental stage. Understanding the intricacies of ROS regulation and interactions across diverse cell types is critical for developing and refining ROS-based and ROS pathway–targeted cancer therapies [45].

Hypoxia

Hypoxia is a prevalent feature in most solid tumors that arises due to rapid cell proliferation, disorganized vascular systems, and uneven blood perfusion, particularly in regions distant from blood vessels [46]. Cells within hypoxic microenvironments exhibit reduced sensitivity to various cancer treatment modalities, including chemotherapy, radiotherapy, immunotherapy, and photodynamic therapy (PDT) [47].

Hypoxia, driven by hypoxia-inducible factor-1α (HIF-1α), profoundly influences anti-tumor effector-cell function within the TME. HIF-1α production under hypoxia is linked to TAM activation and glycolysis enhancement in malignant cells [48]. In turn, TAMs produce factors that polarize M2 macrophages. In pancreatic ductal adenocarcinoma, hypoxic cancer-associated fibroblasts (CAFs) expressing high levels of HIF-2 promote TAM M2 polarization, whereas HIF-2 inhibition in CAFs reduces this polarization [49].

Hypoxia significantly upregulates the abundance of PD-L1, causing an increase in *PDL1* and *CTLA4* mRNA expression mediated by HIF-1α binding to the hypoxia response element (HRE) of PD-L1 [50]. The influence of hypoxia on immune checkpoints, including PD-L1, CD47, CD73, CD137, HLA-G, and CD70, all subject to HIF-1α regulation, has been discussed in a review article [51].

In addition to immune factors, hypoxia affects tumor cells by inducing resistance to conventional therapies through diverse pathways, including apoptosis, autophagy, DNA damage, mitochondrial activity, and drug efflux. Hypoxia also alters the cell cycle by arresting cells in the G1 phase, thereby diminishing sensitivity to chemotherapy and radiation therapy (RT).

Furthermore, hypoxia reduces the efficacy of PDT and RT. PDT relies on tissue oxygen to produce cytotoxic substances, such as ROS, whereas RT leverages oxygen to generate cytotoxic ROS under ionizing radiation. Oxygen also influences DNA self-repair after radiation damage and enhances radiation-induced cell death. Oxygen levels in tumor tissues are critical for the effectiveness of PDT and RT, and alleviating tumor hypoxia can significantly enhance their anti-tumor effects [52].

Acidic pH

While normally differentiated cells rely on oxygen for energy via mitochondrial oxidative phosphorylation, tumor cells often exhibit the Warburg effect, rapidly proliferating and producing significant lactate even in the presence of sufficient oxygen [53, 54]. Lactic acid production lowers the pH of the TME, hindering the anti-tumor activity of T and NK cells. Furthermore, tumor-derived lactic acid can be influenced by HIF-1α, enhancing the expression of M2-associated genes, including vascular endothelial growth factor (VEGF), promoting M2 polarization in TAMs [28, 54]. Moreover, the hypoxia-induced pH reduction creates an acidic TME, leading to drug resistance in tumor cells. Mechanisms behind this resistance encompass reduced drug concentration due to "ion capture," decreased likelihood of apoptosis, genetic changes such as P53 mutations, and increased activity of the multidrug transporter P-glycoprotein [46].

High interstitial pressure

The atypical structure and function of tumor blood vessels and inadequate lymphatic drainage contribute to elevated interstitial fluid pressure (IFP) [55]. Tumor cells recruit fibroblasts, endothelial cells, and stromal cells, forming a dense barrier that intensifies the IFP within tumors [56]. The IFP in tumor tissues ranges from 5 to 40 mmHg and can reach 75–130 mmHg, in contrast to the 0–3 mmHg found in normal tissue [57]. A highly elevated IFP can generate additional problems, including obstructed blood perfusion, limited oxygen, nutrients, and metabolite delivery, and a low-oxygen, low-pH TME. The disrupted TME and vascular system modify the normal hydrostatic and osmotic pressures, affecting the transport of small molecules and solutes into and out of the blood vessels. High tumor pressure impedes the distribution of active drugs, especially macromolecules, and antibodies, to distal tumor regions, hampering

effective drug delivery [58]. Various approaches have been proposed to mitigate high IFP levels, including reducing tumor collagen density to alleviate IFP and enhancing nanoparticle (NP) accumulation within tumors [59].

Tumor vascular abnormalities

Solid tumors acquire oxygen and nutrients through diffusion when their volume is < 2 mm^3. Developing new blood vessels becomes crucial for sustaining exponential growth [60]. The TME is pivotal in regulating pathological neovascularization throughout the tumor's progression and metastasis. ECM components and stromal cells within the microenvironment enhance proangiogenic factors while reducing angiogenesis inhibitors, fostering a pro-neovascularization environment. Unlike their normal counterparts, tumor blood vessels exhibit structural flaws, with the absence of pericytes and perivascular cells causing gaps between endothelial cells in capillaries to reach sizes of 10–1000 nm. This significantly boosts vascular permeability and conductance, leading to structural abnormalities in tumor blood vessels, ultimately resulting in interstitial hypertension, hypoxia, and acidosis within the TME [56, 61]. However, nanomedicines within specific size ranges can penetrate the blood vessels and access the tumor stroma. Anti-tumor angiogenic drugs can recalibrate the balance between pro-angiogenic and anti-angiogenic factors in the TME, temporarily normalizing the tumor blood vessels and their surroundings. Normalized blood vessels reduce in number, alleviating interstitial pressure, enhancing tumor oxygenation, and ameliorating the immunosuppressive TME [62, 63].

Tumor exosomes

EVs derived from cancer, immune, and non-immune host cells are integral to the TME [64]. Among these, exosomes play a critical role in facilitating the transfer of tumor-specific or enriched major histocompatibility complex (MHC) molecules and antigens, bolstering antigen presentation, and promoting immune recognition [65]. However, the sustained release of exosomes from tumors can result in profound immune suppression and inflammation, endowing tumor-derived exosomes (TEX) with prognostic value for tracking tumor progression. TEX serve as messengers that transmit immune stimulation and immunosuppressive signaling molecules, shaping targeted immune cells' development, maturation, and anti-tumor capacity. Host cells associated with tumors, including fibroblasts, adipocytes, and astrocytes, tend to support metastasis by releasing EVs. In contrast, EVs from immune cells, such as B cells, DCs, and macrophages, primarily promote anti-tumor immune responses [66, 67]. Understanding the intricate relationship between exosomes in tumor cells and the host microenvironment and harnessing exosomes for innovative treatment strategies holds substantial promise for advancing cancer therapeutics.

Impact of biomaterial properties on immunotherapy efficacy

Cancer treatment targets are typically located within the TME; however, most drugs accumulate elsewhere, leading to inevitable adverse events. Compared to conventional cancer therapies, the rational design of biomaterials offers the ability to endow materials with unique physicochemical properties that enable specific tumor targeting, prolonged circulation, and an improved immunosuppressive TME, ultimately enhancing cancer treatment (Fig. 3). The physicochemical properties of biomaterials primarily affect the tumor targeting efficiency and mechanisms passively. Passive targeting leverages factors such as biological material morphology, size, surface charge, and the enhanced permeation and retention (EPR) effect to enrich materials in tumor tissues during circulation within the bloodstream.

Biomaterial shape

Research has highlighted the substantial impact of the shape of biomaterials on their in vivo biological distribution [71]. Although the in vivo biological distribution and clearance of NPs of varying shapes and sizes have been investigated, no conclusive data have demonstrated the superiority of any specific shape in reducing clearance by the mononuclear phagocyte system [72, 73]. Nevertheless, non-spherical biomaterials leverage their high aspect ratios and augmented surface areas to bind receptors on tumor cell surfaces, enhancing the efficacy of targeted tumor treatment [68]. Sunshine et al. reported that prolate ellipsoidal artificial antigen-presenting cells (aAPC) bind to and activate antigen-specific T-cells more efficiently than spherical microparticles, ultimately eliciting superior anti-tumor immune responses in therapeutic models (Fig. 3A) [74]. Ben-Akiva et al. have engineered an enhanced nanoscale biodegradable aAPC that can be adjusted to achieve a nanoparticle geometry that effectively binds to and activates $CD8^+$ T cells [68]. Moreover, composite-shaped biomaterials, such as mesoporous silica (MSN), can improve NP blood residence and enhance the EPR effect. The TME-responsive MSN human H-chain ferritin anticancer drug delivery system utilizes inner and outer pores to carry excess drugs for enhanced tumor targeting [75]. Christian et al. found that worm-like micelles remain in the bloodstream longer than spherical micelles [76]. Spherical biomaterials, including NPs, liposomes, and ferritin, exploit their

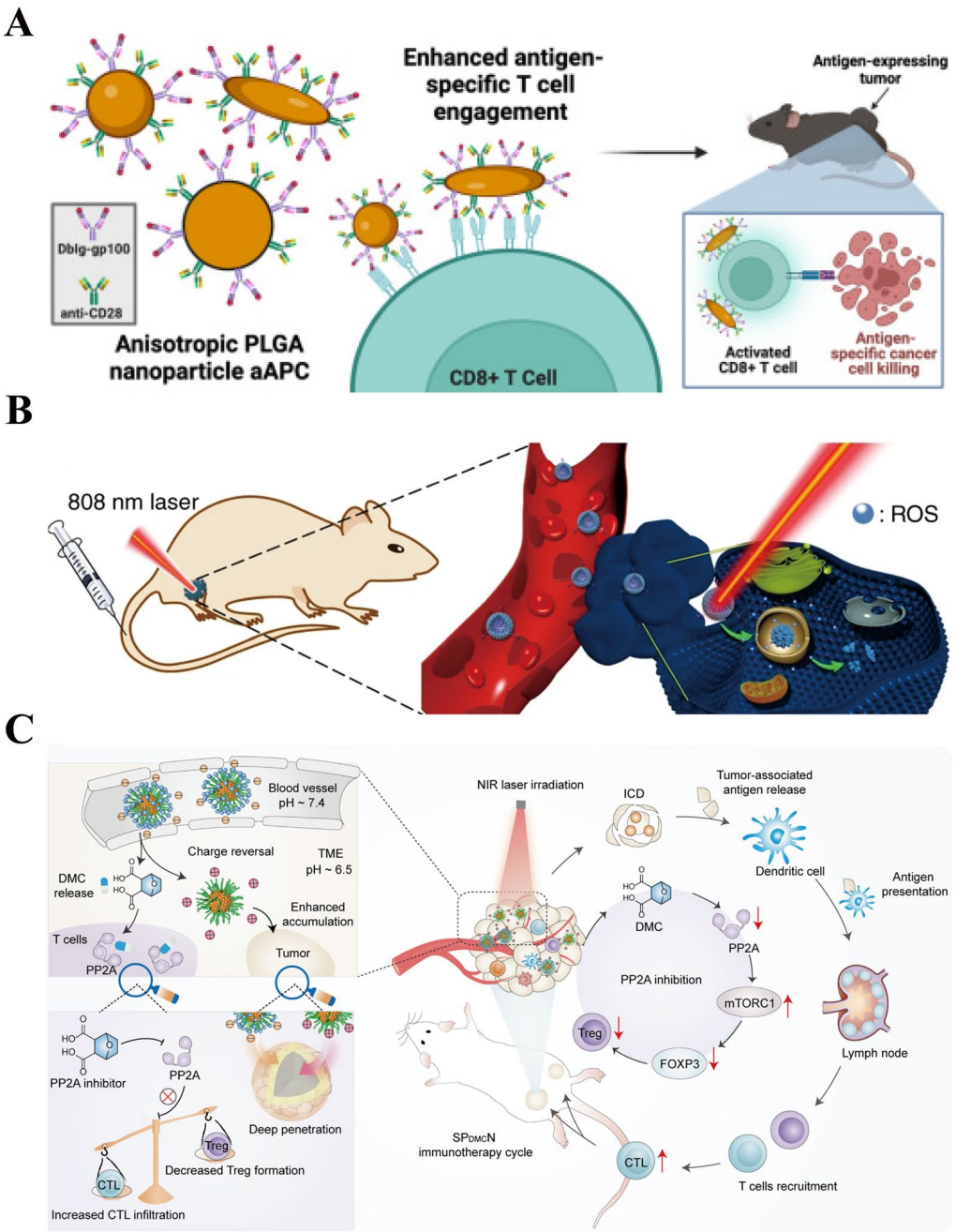


Fig. 3 Impact of biomaterial properties on immunotherapy efficacy. **A** Prolate ellipsoidal artificial antigen presenting cells bind to and activate antigen-specific CD8 + T cells more efficiently than spherical microparticles [68]. Copyright 2023, Elsevier. **B** Intelligently designed nanocapsules not only shrink and break down into small-sized nanodrugs upon drug release, but also modulate the TME to overproduce ROS, thereby enhancing synergistic treatment of tumors [69]. Copyright 2019, Springer Nature. **C** Illustration of $SP_{DMC}N$-mediated synergistic immunotherapy, including acidic tumor microenvironment induced DMC release, photoirradiation of $SP_{DMC}N$ for ICD induction, and immune cell modulation by DMC [70]. Copyright 2021, Wiley

small size and heightened fluidity to infiltrate tumor tissues through openings in tumor blood vessels and achieve passive targeting [77].

Particle size

Diverse NP sizes result in varied distribution, infiltration, clearance, and internalization, profoundly affecting their interactions with tumors and immune cells

[78]. NPs within the size range of 30–40 nm to several hundred nanometers can passively accumulate at tumor sites, facilitated by the EPR effects, which arise due to enhanced blood vessel permeability in tumors [79, 80]. Wang's group demonstrated that an adjuvant composed of MSN, apatite, and Ancer-derived PAMPs (MS-Ap-PAMP) exhibits particle size-dependent immunogenicity; 200 nm particles exhibit the lowest cytotoxicity and highest adjuvant activity. Mice treated with the MS-Ap-PAMP adjuvant exhibit a marked increase in cell-mediated immune-associated cytokines, such as granulocyte–macrophage colony-stimulating factor and IL-12, as well as significantly enhanced tumor immunotherapy efficacy compared with mice receiving the commercial alum adjuvant [81]. Cheng et al. systematically assessed the biological traits of three monodisperse drug-silica nanoconjugates (NCs) at 20, 50, and 200 nm [78]. Their study showed that smaller anti-cancer nanomedicine particles, particularly those of 50 nm, displayed enhanced tumor tissue permeability, reduced blood clearance rates, and increased cancer-cell internalization rates in vivo. Wang et al. report size-switchable nanocapsules (Fig. 3B). These nanocapsules are made of a PLGA-polymer matrix coated with Fe/FeO core–shell nanocrystals and co-loaded with chemotherapy drug and photothermal agent. Intelligently designed nanocapsules not only shrink and break down into small-sized nanodrugs upon drug release, but also modulate the TME to overproduce ROS, thereby enhancing synergistic treatment of tumors [69]. Then, when designing NPs for tumor immunotherapy, selecting an appropriate size (or size range) and considering factors such as drug or antigen properties, tumor types, and targeted ligands is essential to achieve optimal therapeutic outcomes.

Surface charge

The interaction of NPs with cells is profoundly influenced by their surface charge. Surface property modification is also widely used to improve the blood circulation and tumor accumulation of NPs [82]. Notably, highly cationic NPs are removed from circulation more rapidly than their highly anionic counterparts. For instance, Souris et al. reported that mesoporous silica NPs with a positive zeta potential began hepatobiliary clearance less than 30 min after administration, whereas Ye et al. described highly negatively charged gold nanotubes cleared after 72 h [83]. Conversely, neutral NPs and those with a slightly negative charge exhibit significantly prolonged circulating half-lives. Most nanomaterials employ neutral surface ligands based on a poly (ethylene glycol) (PEG) coating. This leads to less efficient clearance of PEG coating NPs by macrophages [79]. In contrast, research by McDonald and colleagues revealed that cationic liposomes exhibit enhanced binding and internalization by tumor-associated vascular endothelial cells compared to their interaction with normal vascular systems [79]. Therefore, for effective NP delivery to tumors, it is advantageous for the NP surface to be neutrally or slightly negatively charged upon intravenous administration and to switch to a positive charge upon arrival at the tumor site. Pu et al. introduced a charge-reversal polymer nano-modulator ($SP_{DMC}N$) designed to release demethylcantharidin within the acidic TME, triggering a surface charge shift to a positive state (+12 mV) that enhances permeability and retention. Upon near-infrared laser irradiation, $SP_{DMC}N$ generates $^1O_2$, effectively ablating primary tumors while inducing ICD and promoting DC maturation (Fig. 3C) [70]. Additionally, Zhou et al. designed a γ-glutamylamide-based zwitterionic polymer–camptothecin (CPT) drug conjugate. As the drug conjugate reaches the tumor site, the gamma-glutamyl amide on the cell surface hydrolyzes, releasing amino groups and positively charging the polymer. This expedites the rapid endocytosis of cationic conjugates by vascular endothelial or tumor cells, triggering endocytosis and cross-cell delivery within tumor tissues [84].

Deformability and degradability

When assessing the fate of therapeutic drugs in vivo, it is essential to consider their deformability and biodegradability. Jiang et al. introduced nanogels with varying hardness levels, revealing that softer NPs could extend the circulation time through a deformation [85]. Similarly, Li focused on tailoring the stiffness of poly (N-isopropylmethacrylamide-disulfide bond-methacrylic acid) nanogels by adjusting the degree of crosslinking. They found that soft nanogels led to substantial tumor accumulation and potent tumor suppression because of their superior deformability [86]. The deformability of biomaterials plays a crucial role in the targeted delivery of tumor immunotherapeutics. These materials can dynamically alter their morphology as needed, thereby enabling controlled release, improved tissue penetration, and modulation of immune cells at tumor sites. Equally important is the requirement for biomaterials to resist extracellular degradation before delivering their immunomodulatory payload to the target cellular population. Yang and colleagues developed mixed-micelle formulations using aliphatic polycarbonates comprising urea-containing block copolymers blended with acid-functionalized block copolymers. Their study demonstrated that particulate formulations with higher kinetic stability exhibit enhanced and faster tumor accumulation than formulations with lower kinetic stability [87].

Biomaterial tools targeting the TME

Biomaterials play a pivotal role in targeting the TME to enhance cancer therapy. Inorganic NPs, such as metal oxide NPs and mesoporous silica NPs, enable precise drug delivery and immunomodulation in the TME. Organic biomaterials, such as synthetic and natural biopolymers, offer versatile platforms for immune cell targeting. These strategies include TAM, DC, NK, and Treg cell modulation. Additionally, biomaterials tackle TME challenges, such as hypoxia, acidity, and ROS regulation (Table 1). They normalize tumor vasculature and disrupt the ECM, improving drug delivery and immune responses. These innovations hold promise for effective and precise cancer treatments.

Types of biomaterials

Inorganic nanomaterials

Nanomaterials have extensive utility across diverse sectors, including the biomedicine, electronics, construction, and food industries, as well as anti-cancer applications. Their diminutive size (typically below 100 nm) and expansive surface area make them ideal platforms for attaching various functional molecules, including therapeutically active agents [88, 89]. These versatile nanomaterials are broadly classified into metallic and non-metallic categories based on their origin. Inorganic nanomaterials, unlike their organic or polymeric counterparts, offer distinct advantages. They feature precisely defined chemical properties, enabling controlled manipulation of shape and size, easy customization, and unique optical, electrical, and magnetic properties. This combination not only confers heightened mechanical stability but also upholds a high level of bioactivity. Furthermore, inorganic nanomaterials can be seamlessly integrated with various carriers, including polymeric carriers and biocarriers. This adaptability enables the creation of tailored platforms that exhibit specific anti-tumor efficacies [90].

Metal-peroxide nanomaterials: Metal-based drug platforms have long been a cornerstone of the arsenal against cancer, proving effective for detection and early-stage treatment. Platinum-containing drugs have emerged as some of the most extensively investigated antitumor chemotherapeutic agents [11, 91]. However, they have certain drawbacks, including limited bioavailability, high systemic toxicity, drug resistance, and limited cancer cell selectivity [92]. Metal ions, which are pivotal in various cellular metabolic pathways, can cause irreparable cellular damage or activate apoptosis-triggering metabolic reactions when improperly distributed or absorbed by cells [93]. This has led to significant research interest in metal peroxides within the biological and medical domains, owing to their distinctive chemistry, reaction products, and the biochemical effects of the released metal ions.

Metal peroxides primarily consist of metal ions and peroxy groups, which yield hydrogen peroxide when combined with water while liberating metal ions [94]. In the TME, metal peroxides produce hydrogen peroxide, serving as a substrate for Fenton-like enzymatic reactions. This cascade generates myriad highly cytotoxic hydroxyl radicals, thus facilitating tumor cell apoptosis [95]. Additionally, the self-decomposition of hydrogen peroxide into oxygen can ameliorate the hypoxic TME, augmenting the efficacy of therapeutic modalities, such as PDT and RT. Metal peroxide-based NPs represent an emerging nanosystem with intrinsic physicochemical properties, reactivity, and bioactivity that align with diverse biological applications. Recent multifunctional metal peroxide nanoparticles have been developed for therapeutic purposes, including CuO_2, CaO_2, MgO_2, ZnO_2, BaO_2, and TiO_x [96, 97]. For instance, Lin et al. [98] successfully synthesized copper perovskite NPs, enabling self-sustained chemokinetic treatment through the controlled release of hydrogen peroxide and copper ions with Fenton-like catalytic activity under mildly acidic conditions. The Fenton-like reaction effectively generated hydroxyl radicals and demonstrated remarkable efficacy in cellular and in vivo animal experiments. When a chemically inert calcium component does not induce a chemical reaction, CaO_2 NPs are used in combination with Fenton compounds to achieve therapeutic effectiveness. Hyaluronic acid (HA)-assisted integration of CaO_2 NPs with Fe_3O_4 Fenton NPs resulted in CaO_2-Fe_3O_4/HA hybrid nanostructures, providing a self-sustaining source of hydrogen peroxide and facilitating a Fenton-based tumor eradication process [99, 100].

Metal oxide nanoparticles (MONPs): Metal-oxide nanoparticles (MONPs) have emerged as invaluable materials in the pharmaceutical and health-related sectors owing to their numerous advantages, including high stability, simple synthesis methods, and precise control over size, shape, porosity, and cell permeability. Indeed, various MONPs have practical applications in the clinical realm, having been featured in antimicrobial wound dressings, biosensors, anticancer agents, and image contrast agents [101]. The most promising candidates among MONPs for biomedical applications include zinc, cerium, manganese, iron, silver, magnesium, titanium, nickel, zirconium, and cadmium oxides. A substantial body of literature has recently elucidated their compelling ex vivo and in vivo biological activities, highlighting their potential in diverse medical contexts.

1) Zinc-oxide nanoparticles (ZnO NPs), distinguished by their non-toxic, biocompatible nature, offer versatile functionality contingent on size, shape, and aspect ratio

Table 1 Biomaterials tools modulating the tumor microenvironment

Strategy	Mechanism	Delivery platform	Advantages and limitations	Refs.
Immune cell-based regulation	The innate M2-type TAM-targeting and re-oxygenation abilities of V(Hb) re-educate the TAM phenotype	Hemoglobin–poly(ε-caprolactone) biomimetic nano red blood cell system	Long-term effects and prevent tumor recurrence, with poor stability	[145]
	Enhance the efficacy of DC activation in a lipid-rich environment and induce innate and adaptive immune responses	Self-assembled micellar NPs of the PCL-PEI copolymer with the ACC inhibitor TOFA, the XBP1 mRNA splicing inhibitor STF, and the MSR1 antagonist fucoidan	Visible curative effects, but its applicability to tumor types with lower lipid content remains to be explored	[147]
	Enhance the anti-tumor activity of NK and $CD8^+$ T cells	Self-assembled micellar NPs of the PBT polymer and PEG-b-PLGA	Potential for long-lasting antitumor immunity, but potential tumor type specificity, CD1d dependency	[149]
	Limit the proportion of regulatory T cells and induce TH17 cell-mediated anti-tumor responses	Pathogen-mimicking hollow nanoparticles of mannan polymers	Long-term effects, but potential immunological side effects require further investigation	[16]
	The inhibition of IDO reinstates CTL activity and facilitates its accumulation within tumors	Nanocarriers containing IDO	Precisely activate chemoimmunotherapy in situ to avoid side effects, but limited effect treatment with IDO inhibitors alone	[156]
Tumor hypoxia modulation	Oxygen delivery via specialized carriers and promote the formation of immunostimulatory M1-type macrophages	Nanocarriers containing PFC or hemoglobin	High oxygen-carrying capacities and the potential for application to various solid tumors, but only short-term effects	[160, 161]
	Generate oxygen inside tumors	Catalase-containing nanoparticles or hydrogels	Long-term effects, but oxygen-producing capability is limited by the H_2O_2 content in the tumor	[163–169]
Neutralizing tumor acidity	Reduce lactate levels, inhibit M2 macrophage polarization, and enhance M1 macrophage polarization	Nanomaterials based on $NaHCO_3$, CaP or $CaCO_3$	Biocompatible, but short-term neutralization effect	[172–174, 176]
ROS modulation	Reduce ROS levels within the TME to induce a significant decrease in M2-type TAMs and Tregs while augmenting TILs and CTLs	ROS-responsive hydrogels	Long-term effects, but potentially toxic degradation products	[179, 180]
	Generate large amounts of ROS and induce an ICD immune response	Photosensitizers	Visible curative effects, but poor stability	[185, 186]
Blood-vessel normalization	Enhance immune cell infiltration, promote drug penetration into tumor tissues and alleviate hypoxia	Nanocarriers delivering VEGF inhibitors	High bioavailability	[187]
Disrupting the tumor ECM	The heat-induced release of NO converts the oxidant peroxynitrite (ONOO-) into active matrix metalloproteinases, which degrade the dense tumor ECM and increase the depth of ablation and infiltration of immune cells	DCN and NO donors were mixed in amphiphilic polymers to form adamantane (ADA)-modified nanoparticles (DCN/S NPs) with a light–heat–gas chain reaction	Multiple functionalities and prevents tumor recurrence,	[197]

VEGF vascular endothelial growth factor, *PCL-PEI* poly(ε-caprolactone)-block-polyethyleneimine, *ACC* acetyl-CoA carboxylase, *TOFA* 5-(tetradecycloxy)-2-furoic acid, *CTL* cytotoxic T lymphocytes, *TILs* tumor-infiltrating lymphocytes, *PEG-b-PLGA* poly(ethylene glycol)-b-poly(lactic-co-glycolic acid)

[102]. Notably, ZnO NPs have been approved by the U.S. Food and Drug Administration (FDA) as potent anticancer agents due to their inherent antitumor activity [103]. Their solubility in low pH environments indicates that ZnO NPs are excellent pH-sensitive nanocarriers for precise tumor-targeted drug delivery and intracellular release [104]. Wu and Zhang revealed that chitosan-coated, positively charged ZnO NPs exhibit enhanced cytotoxicity at higher concentrations, potentially inducing apoptosis through increased cell internalization and ROS production [105]. ZnO NPs also selectively induce cytotoxicity in cancer cells by perturbing Zn-dependent protein activity [106, 107]. Furthermore, these NPs inhibit the proliferation, lipid accumulation, and oxidation of RCC cells by modulating ACSL4 function through miR-454-3p upregulation [108]. ZnO NPs can also target the TME, polarize macrophages toward the M1-like phenotype, and enhance the immunogenicity and anticancer potential of DOX [15]. Although ZnO NPs have promising prospects for cancer immunotherapy, their toxic effects on various cells and organisms must be determined. Therefore, comprehensive studies must be performed to identify the therapeutic benefits of these drugs relative to their potential toxicological risks [103].

2) Iron oxide nanoparticles (IONPs) play a pivotal role in cancer diagnosis and treatment by leveraging their high efficiency and specificity to accumulate in the TME [109]. These NPs are employed in iron replacement therapy and drug delivery systems [110, 111]. Moreover, IONPs exhibit enzyme-like activity, particularly when chemically doped with cobalt, as demonstrated by Liu et al. The Co-doped Co@Fe_3O_4 NPs exhibited significantly enhanced peroxidase activity, catalyzing ultra-low-dose H_2O_2 decomposition. This led to ROS generation, $^{-}$OH induction, and effective eradication of renal tumor cells in vitro and in vivo [112]. The immunomodulatory potential of IONPs has attracted increased interest. Their interaction with immune cells triggers robust antitumor immune responses. IONPs exhibit pharmacological properties by modifying macrophage polarization. For instance, carboxylic acid-containing IONPs combined with lactate oxidase increase the M1 macrophage population in the TME. Artificial reprogramming of macrophages using HA-modified superparamagnetic iron-oxide NPs substantially enhances intrinsic cellular immunity [113, 114]. In addition to macrophage phenotypic polarization, IONPs influence autophagy, augment killer T-cell infiltration, and boost DC-mediated immune responses. This opens new avenues for expanding the clinical application of IONPs [115].

3) Manganese oxide nanoparticles (MONs) serve as promising TME-responsive biomaterials that trigger potent anti-tumor immune responses, offering extensive potential in immunotherapy [116]. These Mn-based nanomaterials function as adjuvants to modulate the tumor immune microenvironment, promote immune responses, and activate the cGAS-STING pathway to initiate tumor immunotherapy [117]. Due to the multiple valence states of Mn, these nanomaterials can efficiently regulate the TME via redox reactions [118]. For example, MnO_2 NPs react with intracellular overexpressed glutathione, producing Mn^{2+} and glutathione disulfide through redox reactions. This significantly reduces the antioxidant GSH within tumor cells and increases their sensitivity to ROS [119]. Moreover, in an acidic TME, MnO_2 NPs alleviate tumor hypoxia by converting endogenous overexpressed hydrogen peroxide into Mn^{2+} within solid tumors, generating copious amounts of oxygen. These Mn-based nanomaterials play a pivotal role in treating ROS/oxygen-dependent tumors by modulating the TME. Their unique ability to ameliorate immunosuppressed TME makes them valuable assets for tumor immunotherapy [118, 120].

Mesoporous silica nanoparticles: Silica nanomaterial-based therapeutic systems offer multifunctionality; however, intricate post-processing and surface modifications hinder their broad biomedical applications. Among these inorganic nanomaterials, mesoporous silica NPs (MSNs) have emerged as significant innovations in materials science due to their superior biocompatibility, lower toxicity, larger specific surface area, smaller particle size, and uniform high-volume pores. Consequently, MSNs have become compelling nanoplatforms, particularly for cancer imaging and therapy [121, 122]. An ideal stimulus-responsive nano-delivery system should be capable of precisely selecting and targeting specific TMEs with high sensitivity and specificity. Furthermore, it should ensure the controlled release of active drugs in response to internal and external stimuli. MSN-based responsive drug delivery systems have been designed using various triggers, such as pH, redox state, temperature, enzymes, light, magnetic fields, or combinations thereof [123]. For instance, malignant and inflammatory tissues exhibit a weakly acidic extracellular pH (approximately 6.0–7.0), whereas healthy tissues maintain a pH of 7.4. This difference in pH serves as a cue for the MSNs to initiate drug release at therapeutic concentrations once they reach the target site [124]. Additionally, the overexpression of reduced GSH in tumor tissues relative to normal tissues triggers the cleavage of disulfide bonds in GSH-sensitive MSNs, thereby facilitating drug or gene delivery at the tumor site [125].

Organic biomaterials

Organic biomaterials capable of targeting the TME can be categorized into synthetic polymers, natural biomolecules, and cell-derived bioactive materials.

Synthetic polymer materials: Synthetic polymers are extensively used in medical applications, particularly as NP-based adjuvants and delivery systems for immunostimulatory agents that target tumor inhibition. Their remarkable attributes, such as biocompatibility, water solubility, and the capacity to efficiently load immune-related components, make them highly valued in cancer immunotherapy.

Poly(lactic-co-glycolic acid) (PLGA) is a biodegradable polymer known for its mechanical strength and biocompatibility. PLGA NPs excel in passive tumor targeting due to their stability and prolonged circulation in the bloodstream. These biocompatible and biodegradable copolymers are FDA-approved for use in drug delivery systems and naturally exhibit an affinity for DCs and other APCs. This quality has made them the preferred choice for encapsulating tumor antigens and immune adjuvants [126]. However, the degradation byproducts of PLGA, lactic acid, and glycolic acid can create a pro-inflammatory microenvironment by reducing the local tissue pH. Notably, lactic acid generated during PLGA degradation demonstrates potent immunosuppressive effects. For instance, treatment of DCs with low-molecular-weight PLGA NPs may lead to the development of an immunosuppressive phenotype, potentially due to the release of immunosuppressive lactate [127]. Recent insights have emphasized the pivotal role of lactate in the metabolic activity of immunosuppressive regulatory T cells within the TME. Lactate acts as an immunosuppressive agent, influencing the recruitment of cells associated with immunosuppression and ultimately promoting tumor progression [128]. Given the fundamental role of PLGA in numerous synthetic drug-release platforms currently in clinical trials, further investigation is essential to comprehend its utilization and impact on anti-tumor strategies.

PEG serves as an outer layer in most lipid- and polymer-based nanocarriers, significantly enhancing active targeting and consequently improving the anti-tumor effects. Its key function is to extend the circulation time of drugs within the body. For example, Pan et al. [129] synthesized PLA-mPEG2000 and TPGS3350-PHis-Folate polymers through nanoprecipitation to create NPs for loading DTX. In this formulation, PEG plays a crucial role; under normal physiological conditions, the PEG chain conceals the targeted folate molecules within the PEG2000 chain, effectively deactivating the active targeting of NPs. However, in a weakly acidic TME, specific molecular changes enable active targeting, facilitating receptor-induced endocytosis and release of DTX. Moreover, considering the distinct characteristics of the TME, including pH, redox potential, and enzyme activity, it is possible to load immunotherapeutic drugs and immunomodulators using carriers such as micelles and hydrogels [130]. This approach enables responsive drug release and modulation of the TME, enhancing drug targeting and bioavailability while minimizing side effects. Hydrogels offer an additional dimension that facilitates the creation of patient-derived tumor organoids (PDTOs) that replicate the attributes of the TME. These PDTOs maintain the stability of molecular markers and heterogeneity of the original tumor, representing valuable tools for constructing personalized drug screening models. This advancement promises to enhance the precision, cost efficiency, and overall efficacy of clinical treatments, further advancing the principles of precision medicine [131].

Biomolecule materials: Natural polymer materials possess an advantageous combination of biocompatibility and biodegradability, making them highly desirable for nano-drug carrier applications. Using natural biopolymers enhances drug utilization, minimizes toxicity, reduces side effects, achieves precise drug delivery, and alleviates patient suffering.

A wide array of polysaccharides have been used for targeted drug delivery and cancer treatment. Notably, HA is characterized by its water solubility, biocompatibility, biodegradability, and CD44-targeting properties [132]. Kim et al. [133] engineered a polymeric nanoconjugate comprising siPD-L1–based polysaccharides, PEGylated HA for CD44 targeting, and OVA, a model foreign antigen. This conjugate not only promotes the rejection of tumor cells by OVA-specific T-cells but also reshapes the TME, driving a robust T-cell response against endogenous tumor antigens, culminating in lasting protective immunity. Moreover, as drug carriers, silk fibroin (SF)-based NPs exhibit inherent passive targeting capabilities through EPR effects. Tan et al. [134] developed SF protein-based Adriamycin preloaded with calcium carbonate (CCs SF/DOX). CCs SF/DOX propels M1-like macrophage polarization and counteracts the immunosuppressive TME. Huo et al. [135] harnessed 4T1 cell–DC fusion cell membrane proteins immobilized within a biomineralized SF hydrogel to fabricate a $CaCO_3$-biomineralized hydrogel DC vaccine. This SF-hydrogel vaccine significantly enhanced immune activation, augmented immunogenicity, and reversed immunosuppressive activity within the TME. These findings represent a promising avenue for cancer immunotherapy.

Bioactive materials of cellular/bacterial origin: Bioactive materials are pivotal in the precisely regulating the

tumor immune microenvironment through biological interventions. Cellular and bacterial materials, known for their natural tropism and biocompatibility, offer effective tumor targeting and TME modulation [136].

Cellular and bacterial membranes contain an array of bioactive components, including proteins, phospholipids, and lipopolysaccharides. These naturally derived structures provide the flexibility and compatibility for seamless integration with synthetic materials. Surface modification of NPs using a range of cell membranes (such as blood cells, cancer cells, immune cells, and bacteria) has emerged as a promising strategy [137]. This imparts outstanding biocompatibility, prolongs circulation time, and enhances the target specificity of NPs. These advantages indirectly bolster immunotherapy by promoting anti-tumor immune activity (e.g., immunorecognition, immunogenicity, effector cell activation, and TME modulation) or directly delivering immunological agents. For instance, inspired by the oxygen transport capacity of red blood cells, perfluorocarbons (PFCs), hemoglobin (Hb), and MnO_2 have been designed to combat tumor hypoxia and enhance therapeutic efficacy [138]. Gao et al. [139] devised an artificial nanoscale system by embedding PFCs within the membranes of red blood cells to amplify tumor radiotherapy. Furthermore, harnessing the intrinsic biological functions of living cells has gained traction in antitumor immune regulation. Utilizing biological and chemical techniques to load drugs or nanomedicines into patients or donor-source living cells is an emerging therapeutic approach. Leveraging cellular drugs to modulate the TME and convert the immunosuppressive microenvironment into an immune-activating milieu holds immense promise for overcoming the limitations of current immunotherapies.

Exosomes have superior circulatory stability and inherent drug-delivery capabilities compared to alternative nanocarriers. They exhibit reduced toxicity and immunogenicity, partially attributable to the widespread presence of CD47, an integrin-associated transmembrane protein, on their surfaces. CD47 efficiently shields exosomes from phagocytosis by circulating monocytes, facilitating successful drug delivery [140]. Furthermore, exosomes are rich in plasma membrane-like phospholipids and membrane-anchored proteins, working synergistically to resist clearance from the circulation. Extensive research has demonstrated the capacity of DC-derived exosomes carrying tumor antigens to activate $CD8^+$ T cells specific to these antigens, provoking a cytotoxic response [67, 141, 142]. As shown in animal models and clinical trials, this effect significantly bolsters anti-tumor reactions. Moreover, exosomes enhance the activity of the Trp2 vaccine encapsulated by lipid calcium phosphate NPs, intensifying antigen-specific $CD8^+$ T cell responses. Thus, exosomes are promising candidates as vaccine adjuvants [143]. The ability of exosomes to traverse the blood–brain barrier is a promising strategy for brain tumor treatment. The potential of exosomes as clinical carriers is particularly exciting, with carefully engineered modifications to accommodate specific payloads, including anti-tumor drugs and tumor-targeting RNAs. These advances provide strong support for the prospects of exosomes in the medical field.

Application of biomaterials to improve the tumor microenvironment

The TME presents unique pathophysiological challenges that necessitate the effective penetration of multilayered barriers, including the tumor vasculature, tumor-associated fibroblasts (TAFs), stromal cells, and the ECM, to access the interior of tumor cells. Compared with immunotherapeutic drugs alone, biomaterial-based cancer immunotherapy offers a more precise and improved approach to anti-tumor immunity. This approach circumvents delivery limitations and allows for cell-specific targeting, enhanced internalization, and synergistic effects of various therapeutic drugs. Furthermore, it is essential to consider the intrinsic immunomodulatory potential of biomaterials, which, in addition to serving as drug delivery platforms, contribute to the success of cancer immunotherapy.

Biomaterial applications for immunosuppression modulation

In the context of TME immunosuppression, this section focuses on biomaterials that precisely convey immune signals within the TME, bypassing systemic and local immunosuppressive mechanisms. This strategic approach aims to reverse the immunosuppressive TME and reestablish anti-tumor immunity.

Immune-cell-based regulation

Targeting TAMs: TAMs exhibit M2-type functions, fostering an immunosuppressive and protumoral microenvironment. Targeting TAMs is a promising anticancer therapeutic strategy. BLZ-945, a selective CSF1R inhibitor, is a hydrophobic, small-molecule drug. Shen et al. designed a pH-responsive immunostimulatory nanocarrier loaded with BLZ-945 and Pt (BLZ-945SCNS/PT) [144]. This nanocarrier effectively targeted TAMs and tumor cells, achieving a synergistic anti-tumor effect (Fig. 4C). Upon passive delivery to the perivascular TME region, BLZ-945SCNS/PT responds to an acidic pH, leading to its structural collapse and simultaneous release of platinum prodrugs and BLZ-945 within the TME. TAMs take up BLZ-945, depleting TAMs, whereas

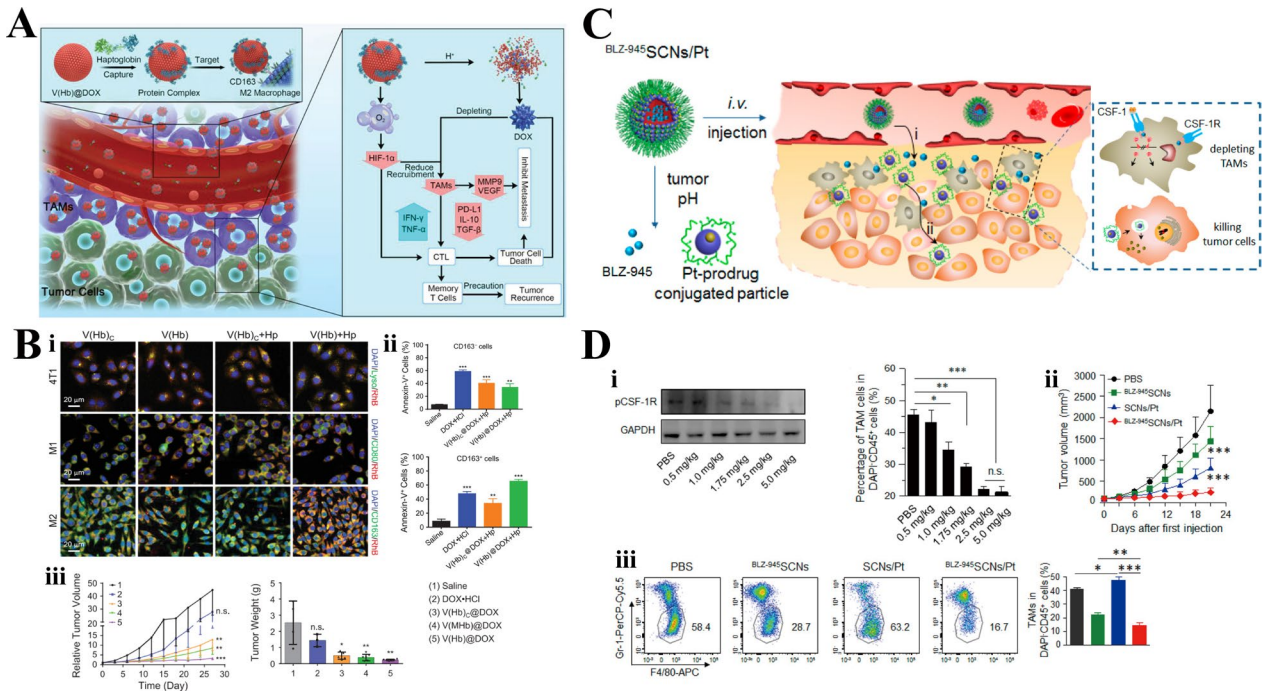


Fig. 4 Biomaterial tools targeting TAMs in TME. **A** Schematic illustration of engineered endogenous TAM-targeted biomimetic nano-RBC to reprogram the TME for enhanced cancer chemo-immunotherapy. **B** Evaluation of endogenous M2-type TAM-targeting ability of V(Hb) and V(Hb)@DOX. (i) M2-type macrophages incubated with V(Hb) + Hp exhibited stronger fluorescence intensity compared to cells exposed to V(Hb)C + Hp, V(Hb), or V(Hb)C alone; (ii)V(Hb)@DOX + Hp induced a high apoptosis rate of $CD163^+$ M2-type macrophages, which was also higher than that of $CD163^-$ cells (M1-type macrophages and 4T1 cells); (iii) V(Hb)C@DOX and V(MHb)@DOX significantly inhibited tumor growth and V(Hb)@DOX resulted in maximum tumor inhibition [145]. Copyright 2021, Wiley. **C** Schematic illustration showing the mechanism of spatial delivery of BLZ-945 and Pt-prodrug to TAMs and tumor cells. **D** (i) Dose effect of BLZ-945SCNs on CSF-1R phosphorylation and TAMs abundance in tumor tissues. (ii) Inhibition of tumor growth by various formulations in 4T1 tumor-bearing BALB/c mice. (iii) Relative abundance of TAMs in 4T1 tumor tissues at the end of treatment by flow cytometry [144]. Copyright 2017, American Chemical Society

platinum-bound NPs penetrate deep into the tumor, causing intracellular platinum release for tumor cell destruction (Fig. 4D). In vivo experiments demonstrated TAM reduction, increased $CD8^+$ T cells, and tumor growth inhibition in mice loaded with 4T1 tumors. Wang developed a hemoglobin-poly(ε-caprolactone) (Hb-PCL) self-assembled nano-erythrocyte system (V(HB)) for delivering the chemotherapeutic drug Adriamycin (i.e., DOX) and oxygen (Fig. 4A) [145]. The Hb portion of V(HB)@DOX binds to plasma-bound haptoglobin (Hp) proteins and targets M2-type TAMs via the CD163 surface receptor. Additionally, the released oxygen mitigates tumor hypoxia and enhances the antitumor immune response (Fig. 4B). TAM-targeted depletion, coupled with hypoxia alleviation, synergistically reprograms the TME, down-regulating PD-L1 expression in tumor cells, reducing immunosuppressive cytokines (e.g., IL-10 and TGF-β), and elevating immune-stimulating interferon-γ, thus enhancing cytotoxic T-lymphocyte responses and memory response.

Targeting DCs: DCs are pivotal in initiating and amplifying T-cell responses. Xiao et al. [146] developed biomimetic PDA/GNS@aPD-L1 NPs functionalized with an anti-PD-L1 single-chain variable fragment. These NPs integrate the immune checkpoint blockade with photothermal ablation for targeted tumor therapy. This approach combines PD-1/PD-L1 checkpoint blockade with photothermal ablation, effectively reversing the immunosuppressive TME, inhibiting tumor growth, and prolonging survival. In vivo studies revealed that PDA/GNS@aPD-L1 NP therapy promoted DC maturation, increased $CD8^+$ T-cell infiltration, reduced immune-suppressor cell populations (e.g., regulatory T cells and myeloid-derived suppressor cells (MDSCs)), and induced the release of immune-activating cytokines (e.g., interferon-γ and tumor necrosis factor-α). DCs play a central role in innate and adaptive anti-tumor immunity. However, lipid accumulation in tumor-associated DCs can lead to immune tolerance and reduce tumor responsiveness to various therapies. Xu et al. [147] harnessed polycaprolactone-polyethyleneimine (PCL-PEI) NPs to create a lipid-reprogramming NP, TS-PP@FU, loaded with acetyl coenzyme A carboxylase inhibitor (TOFA) and X-frame-binding protein mRNA shear

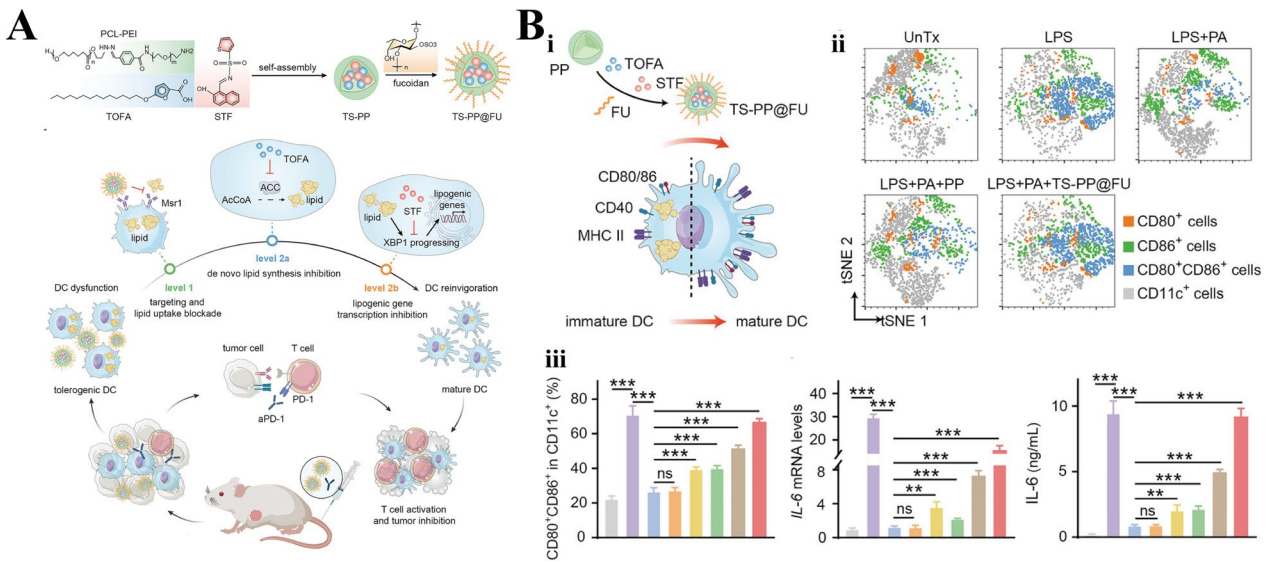


Fig. 5 Biomaterial tools targeting DCs in the TME. **A** Schematic illustration of the hierarchical lipid rewiring of NPs for targeted TADC reinvigoration. **B** (i) Scheme of TS-PP@FU preparation and effects on DC maturation. (ii) t-SNE maps of $CD80^+$, $CD86^+$, $CD80^+CD86^+$, and other $CD11^+$ DCs displayed in orange, green, blue, and gray, respectively. (iii) Ratios of $CD80^+CD86^+$ DCs (gated on $CD11c^+$ cells) after indicated treatment. The mRNA and secretion levels of IL-6 in DCs after indicated treatment [147]. Copyright 2023, Wiley

inhibitor (STF) in the hydrophobic core, and the lipid uptake inhibitor Fucoidan (FU), on the hydrophilic NP surface, attached via electrostatic interaction (Fig. 5A). Upon administration, FU on the NP surface targets the lipid transporter receptor MSR1 on TADCs, inhibiting exogenous lipid uptake. Simultaneously, TOFA and STF, released upon NP internalization, inhibit endogenous lipid uptake and transcription of lipid synthesis-related genes, respectively. This multipronged approach can effectively reprogram lipid metabolism in TADCs and holds promise for enhancing anti-tumor immune responses (Fig. 5B).

Targeting NK cells: Liu et al. [148] introduced an advanced nanoplatform for liver cancer immunotherapy (Fig. 6B). This platform integrated photothermal therapeutic agents (PTAs), DNA enzymes, and artificially engineered NK cells. PTAs, namely Mn-CONASHs, with their two-dimensional structures, were crafted using tetrahydroxyanthraquinone and Mn^{2+} ligands adsorbed with polyetherimide and DNAzyme. The DNAzyme@Mn-CONASHs demonstrated efficient photothermal conversion. The TME enhanced their T1 MRI signal and heat tolerance. Importantly, artificially engineered NK cells, modified with the TLS11a-aptamer for hepatocellular carcinoma specificity, effectively removed residual tumor cells after PTT. Li et al. [149] presented a strategy to boost the anti-tumor potential of over-transfected natural killer T (NKT) cells through PTT pretreatment of tumor tissues. Using the FDA-approved polymeric material PEG-PLGA–coated conjugated polymer PBIBDF-BT as a photosensitizer (NPs@PBT), they generated a thermal effect using an 808-nm near-infrared light. PTT-treated tumor tissues upregulated the expression of NKT cell-associated chemokines, facilitating the recruitment of NKT cells. Furthermore, PTT treatment induced the expression of pro-inflammatory cytokines and DC maturation at the tumor site, promoting NKT cell activation. These activated NKT cells trigger a cascade of immune responses and enhance the cytotoxic activity of NK and $CD8^+$ T cells. PTT combined with NKT cell transfusion exhibits potent antitumor efficacy against in situ tumors. Importantly, this combination therapy induces immune memory formation and prevents tumor metastasis and recurrence. The NPs@PBT platform effectively accumulated at the tumor site and demonstrated a strong photothermal switch. This approach significantly enhanced the recruitment and transfusion of NKT cells, thereby overcoming their limited infiltration capacity in solid tumors (Fig. 6A).

Targeting Tregs: Treg cell-mediated immunosuppression in the TME poses a significant challenge in cancer immunotherapy and is often associated with poor prognosis in various cancer types. Consequently, strategies to address the role of Tregs in cancer therapy have gained increasing attention. These include blocking Treg recruitment within tumors, inhibiting Treg function via ICB, and directly depleting Treg cells. Qu et al. [150] developed TME-targeting hybrid NPs by tLyp1 peptide conjugation. These NPs

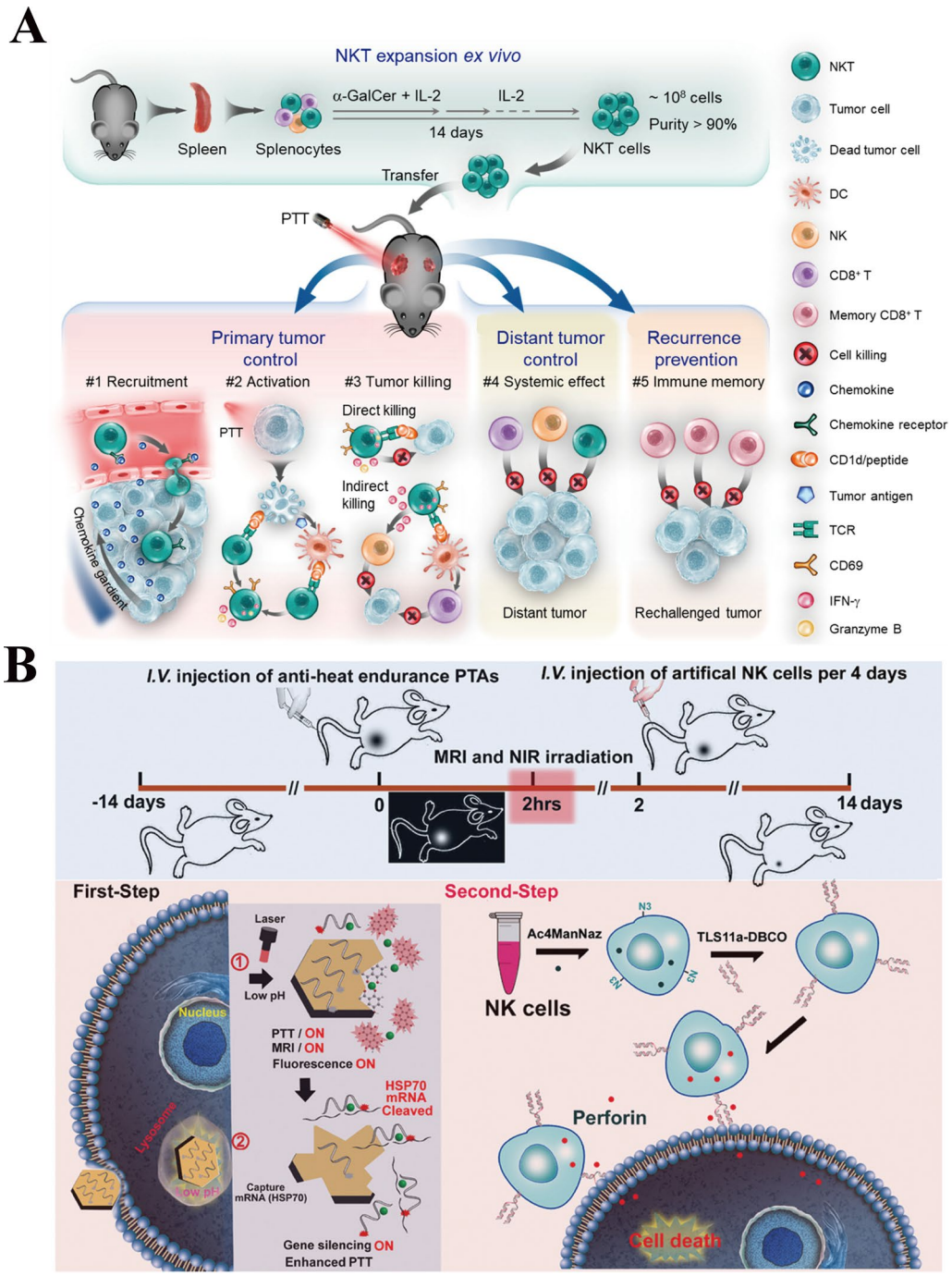


Fig. 6 Biomaterial tools targeting NK cells in the TME. **A** Schematic illustration showing that PTT improved the tumor recruitment and antitumor efficacy of adoptively transferred NKT cells [149]. Copyright 2021, American Chemical Society. **B** Schematic illustration of artificially engineered NK cells combined with the antiheat endurance strategy for improving the therapeutic efficiency of PTT [148]. Copyright 2019, Wiley

demonstrate exceptional stability and precise targeting of Treg cells. Their therapeutic efficacy against tumors is based on inhibiting STAT3 and STAT5 phosphorylation, leading to the downregulation of Treg cell activity in synergy with imatinib. In vivo studies further indicated that the combination of tLyp1-hNPs loaded with IMT and an anti-CTLA4 antibody successfully activate a potent anti-tumor immune response achieved by suppressing Treg cells, which exert immune inhibition and simultaneously promote $CD8^+$ T-cell activation.

In a recent study by Son et al., an innovative strategy harnessing mannan-based hollow nanoparticles with pathogen-mimicking properties emerged as a potent modulator of immune responses in the context of TMEs [16]. This approach, which holds immense promise for cancer immunotherapy, effectively curbs the regulatory T cell population while stimulating anti-tumor responses orchestrated by TH17 cells. The mechanism behind this immunomodulation centers on the activation of pattern recognition receptors, specifically Dectin-2 and Toll-like receptor 4, within DCs. This activation process plays a pivotal role in steering the differentiation of $CD4^+$ T cells toward the TH17 phenotype. Crucially, the intra-tumoral administration of these nanoparticles in murine models demonstrates remarkable outcomes. Simultaneously, a noteworthy increase occurs in the prevalence of TH17 cells, $CD8^+$ T cells, NK cells, and macrophages with an M1-like phenotype. ICB therapies have significantly advanced cancer treatment by releasing cytotoxic T lymphocytes (CTLs) from the "immunosuppressive brake," enhancing T-cell infiltration into the TME, and improving the recognition and killing of tumor cells [151]. Researchers are now exploring NPs for more efficient drug delivery. For example, Bu et al. [152] conjugated αPD-L1 onto hyperbranched poly (amidomine) dendrimers to create G7-αPD-L1. In vitro binding kinetics revealed that G7-αPD-L1 exhibited higher binding affinity to PD-L1 protein than free αPD-L1. In vivo imaging demonstrated that 72 h post-administration, G7-αPD-L1 showed 2.5-fold greater accumulation at the tumor site than free αPD-L1. Moreover, delivering PD-L1 siRNA through ionizable lipid NPs (LNPs) and polycation micelles possessing positively charged moieties effectively reduced PD-L1 expression in tumors in vivo [153].

Delivery of immunosuppressive molecule antagonists via *nanoparticles:* Small molecules possessing immunosuppressive properties, such as indoleamine-2,3-dioxygenase (IDO), have emerged as potential targets of interest. IDO plays a pivotal role in catalyzing the conversion of tryptophan (Trp) into kynurenine (Kyn). This metabolic shift significantly affects the survival and function of CTLs [154]. Furthermore, when IDO is expressed on APCs, such as macrophages and DCs, it effectively induces immune tolerance to tumor antigens by suppressing T cell proliferation. Consequently, the targeted inhibition of IDO presents a promising avenue for ameliorating the immunosuppressive TME and reinstating effector CTL activity. In a recent study, researchers introduced a light-induced NP (LINC) for immunotherapeutic purposes [155]. Using fluorescence imaging as a guide, an initial near-infrared (NIR) laser irradiation triggers the production of ROS, cleaving PEG and facilitating enhanced NP retention and deep tumor penetration. Subsequent NIR laser irradiation activates LINC, effectively eliciting an immune response and facilitating the infiltration of CTLs within the tumor. Moreover, delivery of NLG919 via LINC inhibits IDO-1 activity, ultimately reversing the immunosuppressive TME. Ding et al. devised a hybrid nanomedicine, "RPMANB NPs," engineered to co-deliver the IDO inhibitor NLG919 and a chemotherapeutic pro-drug to maximize therapeutic benefits [156]. RPMANB NPs exhibit favorable pharmacokinetics and accumulate within tumors owing to their meticulous surface engineering. Within cancerous tissues/cells, the loaded NLG919 is released in response to the collapse of the metal–organic framework platform triggered by high phosphate concentrations. This release effectively thwarts IDO activity and, in the presence of NIR light, activates the potent chemotherapeutic agent through highly efficient plasma-driven catalysis. This strategy elicits ICD and avoids side effects typically associated with systemic chemotherapy. In vivo investigations demonstrated that chemoimmunotherapy substantially suppresses tumor growth, fostering the accumulation of cytotoxic T lymphocytes within the tumor and downregulating Tregs.

Biomaterial applications for tumor hypoxia modulation

Tumor hypoxia, a distinctive feature of the TME, underlies inherent resistance to conventional cancer treatments such as chemotherapy, radiotherapy, PDT, and immunotherapy. Two primary strategies have emerged to ameliorate hypoxic TME and enhance the effectiveness of cancer therapies.

Oxygen delivery via *specialized carriers:* Numerous studies have focused on developing various nano-oxygen carriers, including hemoglobin- and perfluorinated compound-based oxygen carriers [157, 158]. Hb is primarily responsible for intracellular oxygen transport within erythrocytes. However, due to its susceptibility to decomposition and toxicity concerns, modifications are necessary to enhance its oxygen delivery capabilities [159]. One approach involves stimulating the erythrocyte antioxidant system and crosslinking hemoglobin with superoxide dismutase using glutaraldehyde. However, hemoglobin chemically binds to oxygen molecules, limiting its ability to release all dissolved oxygen into the surrounding tissues. In contrast, PFCs are physically soluble in oxygen, while hemoglobin releases only 26% of the oxygen released by PFCs under the same dissolved oxygen conditions [160]. Consequently, nano-oxygen carriers based on PFCs have emerged as promising candidates for clinical oxygen delivery systems owing to their superior oxygen-carrying and oxygen-releasing capabilities, as well as their high histocompatibility and safety. Recent advancements have led to the development

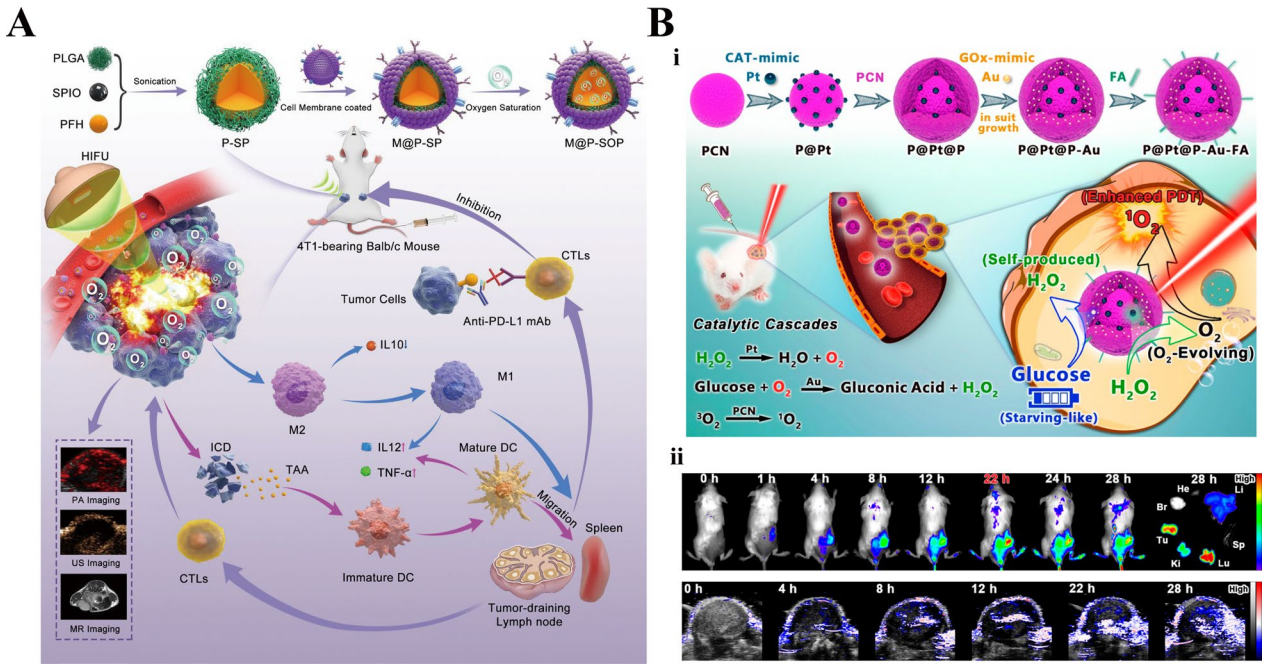


Fig. 7 Biomaterials tools targeting hypoxia in TME. **A** Schematic illustration of the preparation of M@P-SOP and the synergistic effects and mechanism of M@P-SOP-augmented HIFU in combination with anti-PD-L1 blockade against primary and distant tumors [161]. Copyright 2023, BMJ. **B** (i) Schematic illustration of the catalytic cascade-enhanced synergistic cancer therapy driven by dual inorganic nanozymes-engineered porphyrin metal – organic frameworks (PCNs)a. (ii) In vivo fluorescence imaging of 4T1 tumor-bearing mice with i.v. injection of P@Pt@P – Au – FA. Photoacoustic (PA) imaging under the oxy-hemo mode showed a significant improvement in tumor oxygenation after i.v. injection of P@Pt@P – Au – FA. [169]. Copyright 2019, American Chemical Society

of a multifunctional hybrid nanoplatform designated M@P-SOP, aimed at enhancing high-intensity focused ultrasound (HIFU) facilitation and alleviating hypoxia in cancer immunotherapy [161]. This perfluorinated nanocarrier oxygen delivery system offers several key advantages. First, the meticulously engineered M@P-SOP nano-capsules possess multifunctional attributes that greatly enhance HIFU ablation efficiency while reducing ultrasound energy requirements. Furthermore, the properties of perfluorohexane (PFH) within this carrier enable oxygen generation during HIFU irradiation, thereby modifying the acoustic energy conversion within the tumor (Fig. 7A). This alteration enhances the deposition of ultrasound energy in the focused region. Additionally, PFH within the carrier contributes to mitigating the immunosuppressive hypoxic microenvironment of the tumor, leading to the modulation of TAMs and the promotion of immunostimulatory M1 subtype macrophages, thereby bolstering the immune response.

Multifunctional nanoplatforms for in-situ oxygen generation: Abnormal tumor cell metabolism leads to elevated concentrations of H_2O_2 within tumor tissues, often reaching several hundred micromoles [162]. The localized catalytic breakdown of H_2O_2 within tumors generates oxygen molecules, promoting a reduction in tumor hypoxia. Enhancing the hypoxic microenvironment via catalytic H_2O_2 production in the tumor milieu amplifies the effectiveness of immunotherapy. A recent study devised a light-triggered *in-situ* gel system utilizing photosensitizer-modified catalase within a polyethylene glycol diacrylate (PEGDA) polymer matrix [163]. Upon local injection of a mixture containing Ce6-CAT/RPNPs/PEGDA into the tumor and subsequent exposure to 660 nm red light, the ROS generated by the Ce6 photo-initiator triggers the polymerization of PEGDA. Following the light-triggered in situ gelation, catalase (CAT) is physically embedded within the hydrogel. The retained CAT triggers the decomposition of endogenous hydrogen peroxide in the tumor, ensuring sustained relief from tumor hypoxia, enhancing the efficacy of PDT and reversing the immunosuppressive TME. Subsequently, tumor cell debris generated by PDT-induced ICD serves as a source of tumor-associated antigens, along with RPNPs as immune adjuvants, stimulating a robust anti-tumor immune response. In vivo experiments revealed that multi-round Gel-PDT significantly inhibited various subcutaneous tumors in mice, such as colon cancer tumors in CT26 mice and breast cancer tumors in 4T1

mice. Combining anti-CTLA4 treatment with intratumoral hydrogel injection resulted in a potent systemic anti-tumor immune response, suppression of metastatic tumors, and induction of long-term immune memory.

Considering the limitations of endogenous hydrogen peroxide production, Sung et al. developed an implantable oxygen-producing reservoir. This reservoir utilizes calcium chloride ($CaCl_2$) as a crosslinking agent and encapsulates calcium peroxide (CaO_2) and CAT within alginate [164]. Upon subcutaneous implantation near the tumor, the CaO_2 within the reservoir reacts with environmental osmotic water to produce calcium hydroxide and hydrogen peroxide. CAT co-coated within the reservoir subsequently breaks the hydrogen peroxide into molecular oxygen, effectively oxygenating the tumor. This oxygen-producing reservoir substantially enhances the response rate to intravenous Adriamycin (DOX) in human hepatocellular carcinoma solid tumors. Additionally, manganese dioxide NPs (MnO_2 NPs) modified with HA can produce oxygen by reacting with hydrogen peroxide in the TME. This reprogramming of M2 TAMs into anti-tumor M1 macrophages enhances their immunotherapeutic impact [165]. In another study, indocyanine green (ICG)-loaded lipid-encapsulated zinc peroxide (ZnO_2) NPs (ZnO_2@Lip-ICG) were prepared. Upon irradiation with near-infrared light (808 nm), the outer lipid layer of the ICG generates heat, increasing the local temperature and accelerating the release of ZnO_2. This leads to the apoptosis of tumor cells, with ZnO_2 rapidly producing oxygen in the TME (pH 6.5). This, in turn, alleviates tumor hypoxia, bolsters the PDT effect of ICG, and effectively inhibits tumor proliferation [166]. Research also suggests that using liposomal carriers for the sequential delivery of catalase and exogenous H_2O_2 to tumors can more effectively alleviate tumor hypoxia, significantly enhancing tumor therapy combined with radiation and anti-CTLA-4 immunotherapy [167]. Various peroxidase-based smart nanoreactors and synthetic nanoscale catalysts have shown similar potential for increasing tumor responsiveness to combined immunotherapy and PDT (Fig. 7B) [163, 168, 169] (Fig. 4B). Nonetheless, a study by Sheen et al. introduced mouse models of tumors treated with sustained intra-tumoral CAT, but did not observe significant differences in tumor growth or survival compared to untreated mice [170]. Gene expression analyses of enzyme-treated and untreated tumors showed no substantial differences in the expression of genes associated with the intended therapeutic mechanism. Consequently, these findings should be considered when evaluating CAT as a therapeutic agent against cancer.

Biomaterial applications for neutralizing tumor acids

In solid tumors, an acidic TME not only facilitates local invasion and metastasis but also contributes to treatment resistance and immune evasion [171]. Thus, developing biomaterials capable of modulating the pH within the TME is of the utmost importance. Various nano-systems have been developed to address these challenges to regulate the external pH of the TME. Notably, inorganic NPs such as calcium carbonate ($CaCO_3$) [172, 173], calcium phosphate (CaP) [174], and MnO_2 [172], which exhibit solubility in acidic conditions, have emerged as promising candidates for pH-responsive cancer therapies.

$CaCO_3$ is a nontoxic mineral that is simple and cost-effective to produce and has been successfully applied as a carrier for drugs, genes, and proteins [175]. It gradually decomposes into Ca^{2+} and CO_2 within a mildly acidic environment (pH ~ 6.8), concurrently regulating the pH by consuming H^+. Recently, Ding et al. [173] developed a pH-sensitive $CaCO_3$ nanocarrier loaded with TCL and the immune adjuvant CpG for triple-negative breast cancer (TNBC) immunotherapy (Fig. 8A). In vitro cellular experiments revealed that $CaCO_3$@TCL/CpG reduced lactate levels, inhibited M2 macrophage polarization, and enhanced M1 macrophage polarization (Fig. 8B). Subsequent in vivo experiments involving 4T1-loaded mice demonstrated efficient tumor vaccine aggregation at the tumor site and upregulation of the M1/M2 macrophage ratio. This enhanced inflammatory microenvironment within the tumor induces ICD, exposing tumor cells to calreticulin (CALR), and subsequently promoting DC maturation with the aid of immune adjuvants (Fig. 8C). This significantly enhances antigen presentation by T cells and elicits a robust anti-tumor response. Furthermore, because $CaCO_3$ synergizes with MnO_2 for anti-tumor effects, they are jointly encapsulated in cancer cell membranes to create pH-responsive nanomodulators. Controlled intelligently through pH-responsive and depletion mechanisms, $CaCO_3$ overloads intracellular calcium in tumor cells, leading to increased ICD and the generation of ROS. Mn^{2+}, in addition, further reshapes the TME by alleviating hypoxia, promoting ROS production, and enhancing immune cell proliferation and maturation, thereby effectively activating the immune system. This strategy results in the reprogramming of the immunosuppressed TME, inducing macrophage polarization and DC maturation through antigen cross-presentation, thereby enhancing the ability of the immune system to combat tumors effectively [172].

CaP is a widely used pH-responsive biomaterial for siRNA and drug delivery. Qing et al. [174] employed highly biocompatible CaP to encapsulate outer membrane vesicles (OMVs) within a pH-sensitive nanoshell.

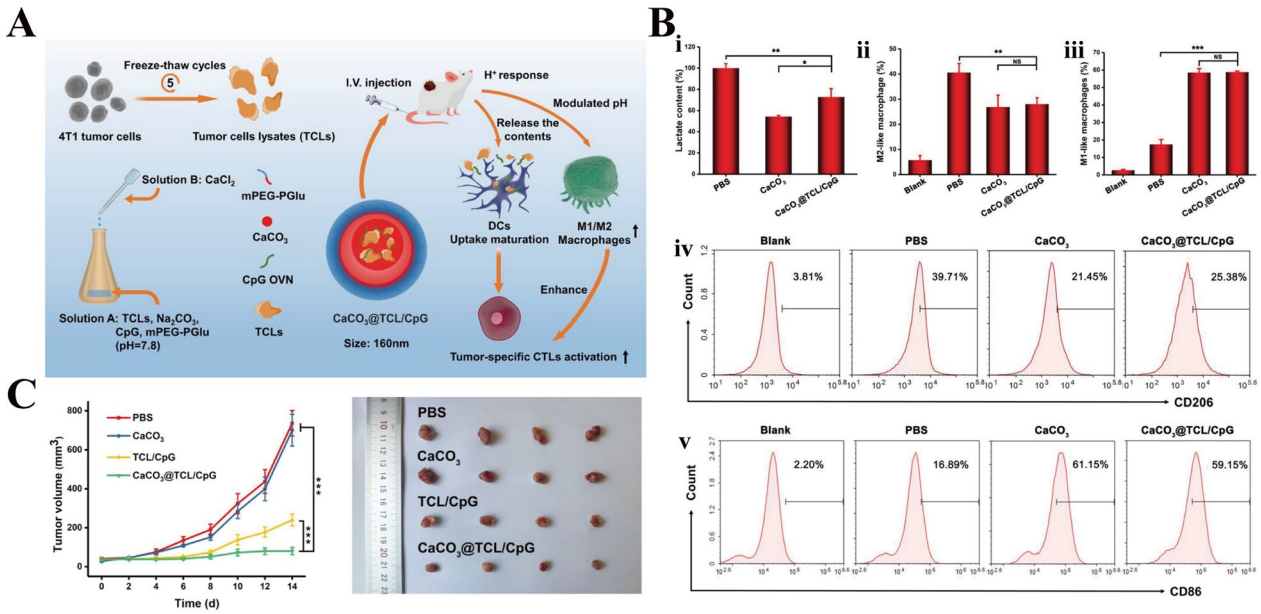


Fig. 8 Biomaterial tools targeting tumor acidity in the TME. **A** Schematic illustration of the preparation of tumor antigen-presenting nanoparticles (CaCO3@TCL/CpG) enabling enhanced antitumor immune response by activating DCs and upregulating M1/M2 TAMs polarization. **B** Quantitative analysis of extracellular lactate after various treatments. ii, iv) Proportions of M2-like TAMs or iii, v) M1-like TAMs measured by flow cytometry and analyzed statistically (gated on $CD11b^+$ and $F4/80^+$ cells). **C** Same dosage of CaCO3@TCL/CpG significantly inhibited tumor growth [173]. Copyright 2023, Wiley

This approach not only overcame the toxicity associated with intravenous injection of OMVs and antibody-dependent clearance but also contributed to the neutralization of the acidic TME, improving the antitumor effect. In a separate study, Ding et al. adopted a rapid microemulsion method to prepare alkaline sodium bicarbonate NPs ($NaHCO_3$-NPs)—a simple, non-toxic inorganic nanomaterial—for cancer immunotherapy [176]. The alkaline $NaHCO_3$ was shown to regulate lactate metabolism through acid–base neutralization, consequently reversing the weakly acidic immunosuppressive TME. Furthermore, the nanomaterial releases substantial amounts of Na^+ within tumor cells, inducing a surge in intracellular osmotic pressure. This activation triggers pyroptosis and ICD, releasing damage-associated molecular patterns and inflammatory factors, thus improving the immune response.

Biomaterial applications for ROS modulation

Reducing ROS: In solid tumors, the management of ROS is pivotal for restoring anti-tumor immune responses and enhancing the efficacy of immunotherapy. Disrupting the ROS balance holds potential as an immunotherapeutic strategy. Elevated ROS levels are a hallmark of tumors, whereas applying ROS-responsive biomaterials reduces ROS levels to stimulate anti-tumor immune responses and facilitate the controlled delivery of immunotherapeutic agents [177]. Furthermore, nanomaterials can be engineered to deliver exogenous hydrogen or promote endogenous hydrogen generation, effectively scavenging ROS and contributing to TME immunomodulation [178]. Chen et al. pioneered the development of a biologically responsive ICB therapy that relies on an ROS-sensitive protein complex [179]. Following intra-tumoral administration of the ROS-responsive aPD1@aCD47 complex, aCD47 is released, activating the recognition of cancer cells by the innate immune system and promoting a T-cell response. The subsequent release of aPD1 blocks PD1, thereby increasing the assault of allogeneic-responsive T cells on cancer cells. This study also explored the correlation between ROS levels and immune responses in various immune cells in the TME. In in vivo B16F10 melanoma models, the intra-tumoral injection of the drug significantly reduced ROS levels within the TME. This reduction significantly decreased M2-type TAMs and Tregs while augmenting tumor-infiltrating lymphocytes (TILs) and CTLs. Reduced ROS levels effectively reduce the number of immunosuppressive cells and enhance the infiltration of active T cells. Furthermore, an ROS-responsive hydrogel delivered anti-PD-L1 antibodies and the chemotherapeutic agent gemcitabine into the TME. Following implantation into the tumor, ROS facilitate a gradual degradation of the hydrogel, thereby sequentially

releasing the chemotherapeutic agent and anti-PD-L1. This decrease in ROS levels reduced MDSCs in the TME and improved the therapeutic efficacy of anti-PD-L1 in a mouse model of B16 tumors [180]. Gong et al. synthesized nanoscale CaH_2 particles by liquid-phase exfoliation technology. CaH_2 nanoparticles react with water to produce abundant hydrogen. Hydrogen reduces ROS levels and hydrolyzes CaH_2 to $Ca(OH)_2$, thereby neutralizing pH and improving the anti-tumor immune response of CTLA4 antibody therapy [181].

Elevating ROS: While ROS have been associated with cancer progression, the notion that antioxidant therapy limits tumor advancement has not been substantiated. Moreover, limiting the ROS levels may inadvertently promote cancer progression [182]. Clinically, the challenge remains that approximately half of patients are unresponsive to ICB therapy owing to inadequate T-cell infiltration within the tumor and an immunosuppressive microenvironment [183, 184]. One approach to overcome this hurdle involves the induction of ICD, a strategy that effectively activates tumor antigen-specific T cells, enhances the migration of cytotoxic T cells to the tumor, and transforms immune cold tumors into immunologically active "hot" tumors [41]. Among the various ICD inducers, photosensitizers capable of generating ROS upon light excitation offer significant advantages. Ding et al. developed a novel polymeric NP with surface mimetic protein secondary structures (SPSS NPs) capable of degrading PD-L1 within lysosomes using a lysosome-targeted chimeric (LYTAC)-like mechanism. This approach results in self-synergistic tumor immunity (Fig. 9A) [185]. SP3 NPs exhibit a high ROS generation efficiency and act as photosensitizers, inducing phototoxicity in tumor cells. Treatment of the colon cancer CT26 cell line with SP3 NPs followed by laser irradiation led to high ROS levels within CT26 cells, resulting in dose-dependent cell death and further stimulation of ICD in tumor cells (Fig. 9B). To

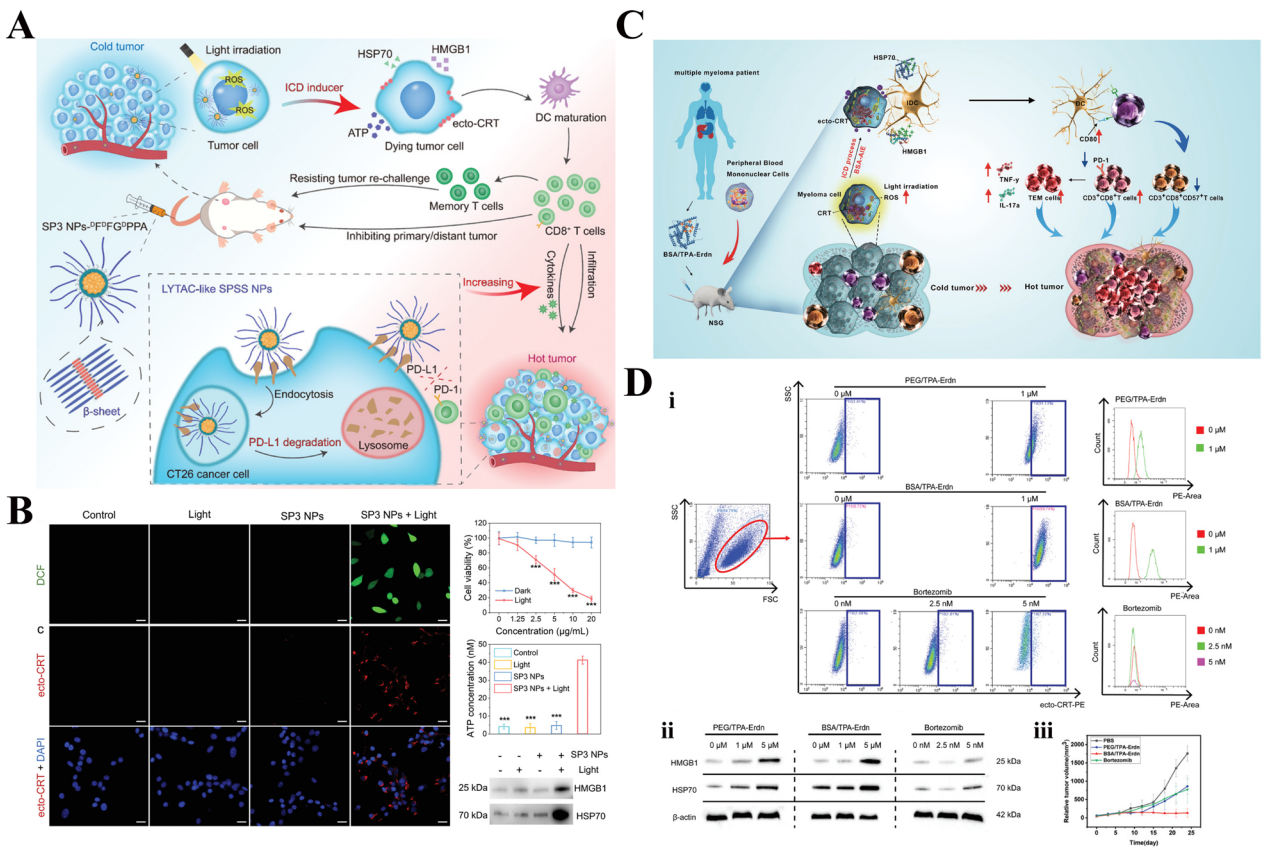


Fig. 9 Biomaterial tools targeting ROS in the TME. **A** Schematic illustration of SPSS NPs as lysosome-targeting chimeras for self-synergistic cancer immunotherapy. **B** Evaluation of the intracellular ROS generation property of SP3 NPs using 2′,7′-dichlorodihydrofluorescein diacetate (DCFDA). NP-mediated PDT strongly induced the ICD of tumor cells, an important prerequisite for enhancing tumor antigen presentation and T-cell activation [185]. Copyright 2022, Wiley. **C** Schematic of BSA/TPA-Erdn-mediated ICD immunotherapy for MM treatment. **D** (i) Expression of ecto-CRT protein in RPMI-8226 cells after treatment with PEG/TPA-Erdn, BSA/TPA-Erdn, or Bortezomib, as determined by flow cytometry. Cells in PEG/TPA-Erdn and BSA/TPA-Erdn were subjected to white light irradiation. (ii) Western blot analysis of HMGB1 and HSP70 protein abundance in RPMI-8226 cells after different treatments. (ii) Tumor growth curves in different groups [186]. Copyright 2023, Wiley

augment the anti-tumor activity of SP3 NP, researchers synthesized a D-type PD-L1 peptide antagonist (DPPA), a short peptide that binds to tumor-cell PD-L1 and obstructs the PD-L1 signaling pathway. The introduction of FFG, with self-assembling ability, into the N-terminus of DPPA induced the formation of a secondary structure with β-folding (DFDFGDPPA). The modified NPs (SPSS NPs) exhibited high affinity for PD-L1. In a CT26-homozygous mouse model, this PDT utilizing SP3 NPs was synergized with tumor immunotherapy, yielding excellent anti-tumor effects. In fact, 60% of the tumors in the treated mice were eliminated, and the mice survived for more than 55 days. Liu et al. introduced a novel strategy to enhance ICD immunotherapy by utilizing aggregation-induced emission (AIE) photosensitizer-loaded bovine serum albumin (BSA) NPs (BSA/TPA-ERDN) (Fig. 9C) [186]. When injected intravenously into mice, this agent generates large amounts of ROS within the TME, thereby inducing an ICD immune response. Through experiments utilizing the NSG mouse model, they further demonstrated that such an ROS generator could activate functional T cells in the monocytes of patients with multiple myeloma (MM), effectively enhancing the efficacy of immunotherapy (Fig. 9D).

The efficacy of ROS-modulated therapies varies significantly based on the tumor type, location, nature, and stage of progression; therefore, the intricate regulation and interactions within different tumors must be understood to facilitate the modulation of ROS in the development and refinement of current tumor therapies.

Biomaterial applications for blood vessel normalization

Blood vessel normalization is an important strategy for enhancing cancer therapy. This approach has the potential to bolster immune cell infiltration, facilitate drug penetration into tumor tissues, and mitigate hypoxia, a factor that influences macrophage polarization [23]. Achieving blood-vessel normalization involves innovative biomaterial-based strategies, often in combination with immunotherapy and anti-angiogenic treatments. Huang et al. demonstrated the remarkable capability of low-dose VEGFR2 antibody (DC101) to reprogram the immunosuppressive TME. This reprogramming transforms TAMs from the M2 to the M1 phenotype, consequently promoting the infiltration of $CD4^+$ and $CD8^+$ T cells and ultimately inducing active immunity [187]. Chen and collaborators engineered a multitargeted liposome system, enriched with anti-PD-L1 NPs and mannose ligands, to enable the concurrent delivery of mTOR inhibitors (rapamycin) and anti-angiogenic drugs (regorafenib) [63]. This innovative system, validated in a CT26 colon-tumor mouse model, emerged as a powerful approach to prevent metastasis, enhance immunotherapy, and improve drug penetration. Similarly, by leveraging the regulatory function of nitric oxide (NO) in angiogenesis and vascular homeostasis, Sung and his team developed a nano-delivery system termed NanoNO [188]. NanoNO, characterized by precise tumor targeting and stable NO release, effectively normalizes tumor vasculature. This improves drug delivery efficiency and increases anticancer efficacy, particularly in hepatocellular carcinoma models. Additionally, NanoNO reprograms immunosuppressive TAMs into an immunostimulatory phenotype, boosts the presence of tumor-infiltrating T cells, and synergistically enhances anticancer effects when combined with vaccines. Wang et al. conducted a comprehensive evaluation of STING-activating NPs (STANs) across multiple tumor models [189, 190]. STANs effectively normalize vascular integrity, alleviate hypoxia, and enhance the expression of T-cell adhesion molecules. This normalization increases T-cell infiltration, significantly improving the efficacy of immune checkpoint inhibitors and adaptive cell therapy.

Biomaterial applications for disrupting the tumor ECM

The TME predominantly comprises the ECM, which accounts for up to 60% of the solid tumor mass [191]. This intricate and dynamic three-dimensional network of biological macromolecules, including collagen, proteoglycans, laminin, and HA, plays a crucial role in tumor development, migration, and metastasis, significantly impacting drug delivery [59, 192]. Targeting the tumor ECM in advanced cancer stages has emerged as a promising therapeutic strategy.

Mild hyperthermia is an approach to alleviate the interstitial pressure in the dense ECM within tumors, leading to increased blood perfusion and immune cell infiltration. For example, the encapsulation of indocyanine green in PLGA NPs for initial photothermal ablation, followed by NIR light irradiation, enhances blood flow and facilitates CAR-T cell infiltration. Additionally, PTT triggers the release of inflammatory cytokines within tumors, activating robust anti-tumor immune responses. An illustrative study involving mice bearing the human melanoma WM115 cell line illustrated that this approach significantly boosts the anti-tumor activity of CAR T-cell therapy [193]. A groundbreaking study by Eikenes et al. demonstrated the effective use of collagenase in treating human osteosarcoma-transplanted tumors in mice, substantially reducing the IFP. This reduction greatly enhanced the transient permeability and intraluminal penetration of monoclonal antibodies and liporubicin [194]. Gong et al. [195] enhanced the tumor vascular density and the percentage of dilated blood vessels by employing a polyethylene glycol-based HAase. This, in turn, promoted tumor blood perfusion and the accumulation of subsequently administered

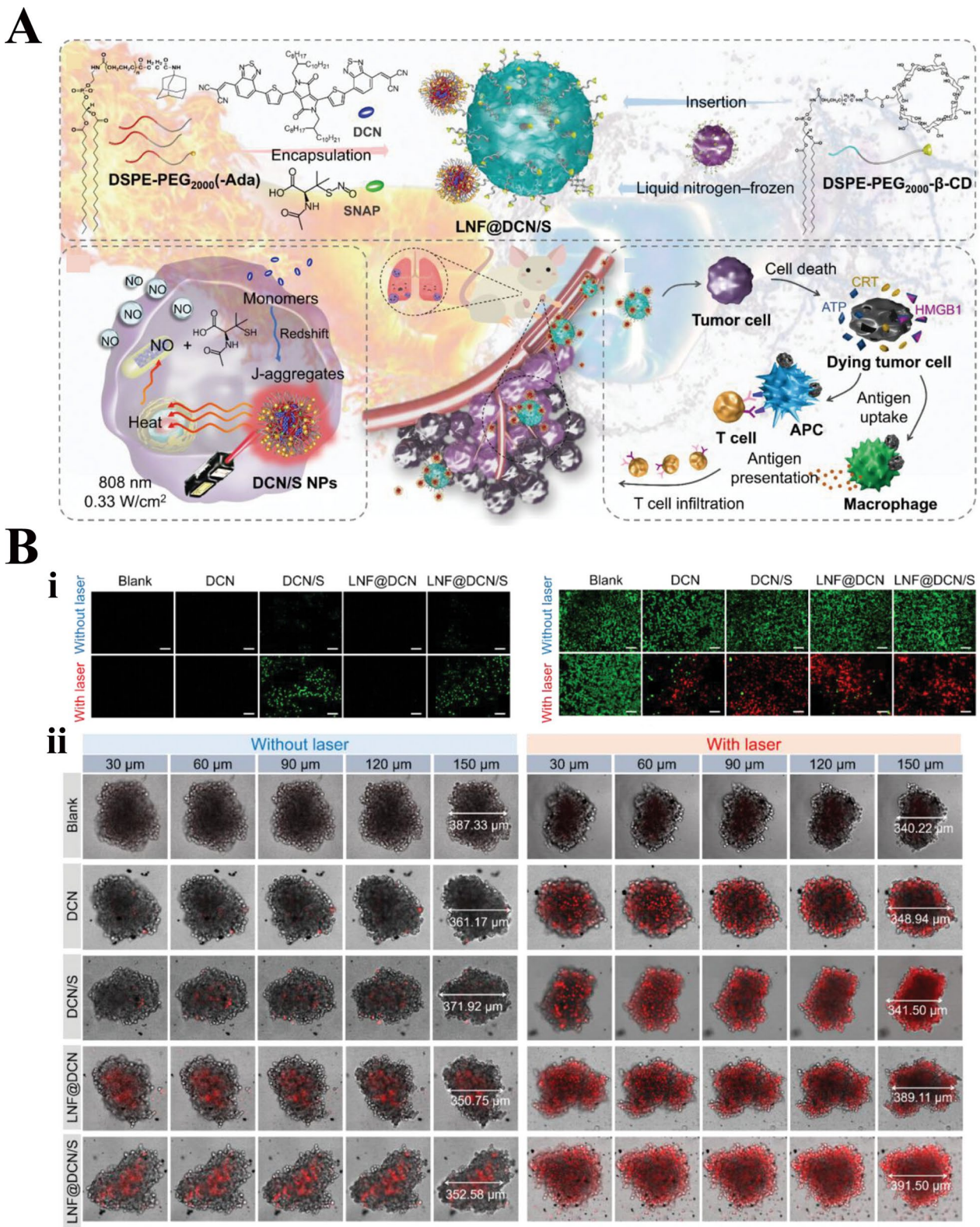


Fig. 10 Biomaterial tools targeting ECM in the TME. **A** Schematic illustration of "ice cell and fire nanomedicine" drug delivery platform for personalized anticancer therapy. **B** (i) DAF-FM DA (green) staining fluorescence imaging of 4T1 cells to detect cellular NO and Calcein-AM/PI double-staining images of 4T1 cells after different treatments. (ii) Confocal images of 4T1 multicellular spheroids with PI staining at different depths after treatment [197]. Copyright 2023, Wiley

Ce6-coupled nanomicelles, thereby effectively alleviating intra-tumoral hypoxia. The combination of these effects significantly enhances the efficacy of PDT.

Researchers have also explored the combination of PTT with biochemical enzymes to trigger tumor ECM disruption. Mohapatra et al. [196] developed a NO-releasing hydrogel system to deliver immune modulators to tumors. Upon irradiation with infrared light, NO release is triggered, activating matrix metalloproteinases (Pro MMPs) within the tumor tissue. This activation results in the degradation of the dense ECM, enabling deep transport of IDO inhibitors into the tumor tissue. The combination of NO Gel and NLG919 inhibited IDO expression in tumor cells and tissues, promoting an anti-tumor immune response. IDO inhibition also suppresses PTT-mediated MDSCs in tumor invasion. A supramolecular conjugate has been designed that combines photothermal, gas therapy, and immunotherapy. This approach effectively ablates deep tumor tissues while stimulating an immune response to suppress distant tumors and lung metastasis (Fig. 10A) [197]. By co-loading a novel diketopyrrole-based photosensitive agent (DCN) with an NO precursor (SNAP) and NIR-absorbing DCN into amphiphilic polymers, significant heat-induced NO release was generated, facilitating the degradation of the dense tumor ECM (Fig. 10B). This process enhances the depth of immune-cell infiltration within the tumor. Furthermore, anchoring DCN/SNAP NPs to liquid nitrogen-frozen cancer cells effectively triggered an anti-tumor immune response, enhancing macrophage and CTL functions. Notably, a single treatment enhanced the anti-tumor immune response and effectively inhibited distant tumor and lung metastases.

Conclusion

Tumor cells employ various mechanisms, including establishing an immunosuppressive microenvironment, inhibiting immune cells, hypoxia, and acidification to evade immune system attacks. Collectively, these factors hamper the activity and infiltration of immune cells, thereby diminishing the effectiveness of the treatment. The TME has emerged as a critical target for shaping tumor responses to immunotherapy, and modulating the TME has the potential to enhance the efficacy of immunotherapy. Specifically, through the strategic utilization of compatible biomaterial platforms, therapeutic drugs or materials with TME-modulating properties can be designed to complement immunotherapy, mitigate immunosuppression within the TME, and improve immune-cell infiltration and function.

Biomaterials, propelled by continuous advancements in materials science and delivery technologies, are poised to significantly impact the targeting of TMEs. Biomaterials offer distinct advantages over individual immunotherapies, as they enhance drug delivery efficiency and bolster anti-tumor effects while mitigating side effects. Their applications extend to the development of cancer vaccines, T-cell amplification, T-cell regulation, and management of immunosuppressive TMEs. By engineering biomaterials with tailored biological activity, biocompatibility, and degradability, it is possible to guide, modulate, and fortify immunotherapy within the TME. One integral strategy involves the delivery of immune modulators and drugs via biomaterials. The synergistic pairing of immune checkpoint inhibitors with biomaterial carriers amplifies drug infiltration and release within tumors, ultimately improving immunotherapy efficacy. Moreover, biomaterials serve as valuable tools for normalizing tumor blood vessels, enhancing drug permeability, promoting immune cell infiltration, and reducing hypoxia, all of which contribute to improved immunotherapy effectiveness. Additionally, biomaterials disrupt the ECM of tumor cells, breaking down barriers to drug delivery and consequently enhancing treatment efficacy.

While strategies to remodel the TME have enticing advantages, they wield a double-edged sword. For instance, while disrupting the tumor ECM facilitates the deep penetration and perfusion of nanoDDS in solid tumors, it may inadvertently provide impetus to tumor metastasis. Similarly, while elevated ROS levels effectively inhibit tumor progression and enhance immunotherapy efficacy, they may also promote genetic mutations, cell proliferation, and angiogenesis, ultimately fostering tumor invasion and metastasis. Moreover, despite its potential to increase blood perfusion and alleviate tumor hypoxia, the normalization of tumor vasculature introduces a paradox by potentially reducing the permeability to large particles through the ERP effects. As we navigate the intricate landscape of cancer therapeutics, it becomes clear that achieving victory in the fight against cancer requires a keen understanding of the TME's complexity and the design of efficient and comprehensive biomaterials.

However, the clinical application of biomaterials presents challenges that must be addressed. Ensuring safety, large-scale manufacturing, batch quality control, and long-term stability are crucial hurdles that must be overcome to enhance the clinical potential of biomaterials. The design and preparation of biomaterials must adhere to stringent controls to guarantee both safety and effectiveness, with consideration given to mitigating unnecessary side effects associated with immunogenicity.

Using biocompatible synthetic biomaterials with low immunogenicity and toxicity, such as liposomes, LNPs, degradable polymer NPs, and microneedles, is promising. Finally, transitioning biomaterials from laboratory to clinical settings necessitates addressing regulatory and quality-control challenges. Natural biomaterials, such as extracellular vesicles, HA, chitosan, and collagen, face the complex task of balancing their functionality, large-scale production, and quality control to unlock their clinical potential. Overall, using biomaterials in immunotherapy is promising and can overcome some limitations of immunotherapy, however, its own limitations must be overcome to ensure safe and effective clinical application.

Abbreviations

APCs	Antigen-presenting cells
ROS	Reactive oxygen species
TADCs	Tumor-associated dcs
TME	Tumor microenvironment
ACC	Acetyl-coa carboxylase
AIE	Aggregation-induced emission
CAFs	Cancer-associated fibroblasts
CAR-T	Chimeric antigen receptor T-cell therapy
CAT	Catalase
CSF1	Colony-stimulating factor 1
CTLs	Cytotoxic T lymphocytes
DCs	Dendritic cells
ECM	Extracellular matrix
EPR	Enhanced permeation and retention
FDA	Food and Drug Administration
HA	Hyaluronic acid
Hb	Hemoglobin
HIF-1α	Hypoxia-inducible factor-1α
HIFU	High-intensity focused ultrasound
ICB	Immune checkpoint blocker
ICD	Immunogenic cell death
ICG	Indocyanine green
IDO	Indoleamine-2,3-dioxygenase
IFP	Interstitial fluid pressure
IONPs	Iron oxide nanoparticles
MDSCs	Myeloid-derived suppressor cells
MHC	Major histocompatibility complex
MONs	Manganese oxide nanoparticles
MS-Ap-PAMP	Mesoporous silica, apatite, and Ancer-derived pamps
NIR	Near-infrared
NK	Natural killer
NO	Nitric oxide
NP	Nanoparticle
PCL-PEI	Poly(ε-caprolactone)-block-polyethyleneimine
PDT	Photodynamic therapy
PEG	Poly (ethylene glycol)
PEG-b-PLGA	Poly(ethylene glycol)-b-poly(lactic-co-glycolic acid)
PFCs	Perfluorocarbons
RT	Radiation therapy
SF	Silk fibroin
TAMs	Tumor-associated macrophages
TCRs	T-cell receptors
TEX	Tumor-derived exosomes
Th1	T-helper 1
TILs	Tumor-infiltrating lymphocytes
Tregs	Regulatory T cells
VEGF	Vascular endothelial growth factor
ZnO NPs	Zinc-oxide nanoparticles

Acknowledgements
Not available.

Author contributions
FY collected and analyzed articles, and wrote the manuscript. TQ, LS and LL reviewed the manuscript. WB, YQ and ZY assisted in manuscript and provided some helpful suggestions.

Funding
This work was supported by the National Natural Science Foundation of China (No. 82173341); the Natural Science Foundation of Hunan province (No. 2021JJ40845); the new medical technology of the Second Xiangya Hospital of Centra South University in 2022.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study doesn't contain any animal and human experiments.

Consent for publication
All authors agreed to publish this manuscript.

Competing interests
The authors declare no competing interests.

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Received: 16 January 2024 Accepted: 9 November 2024
Published online: 27 November 2024

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