

# Tumor Microenvironment Modulating Functional Nanoparticles for Effective Cancer Treatments

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**Abstract** Cancer is one of the major diseases that threaten human life worldwide. Despite advances in cancer treatment techniques, such as radiation therapy, chemotherapy, targeted therapy, and immunotherapy, it is still difficult to cure cancer because of the resistance mechanism of cancer cells. Current understanding of tumor biology has revealed that resistance to these anticancer therapies is due to the tumor microenvironment (TME) represented by hypoxia, acidity, dense extracellular matrix, and immunosuppression. This review demonstrates the latest strategies for effective cancer treatment using functional nanoparticles that can modulate the TME. Indeed, preclinical studies have shown that functional nanoparticles can effectively modulate the TME to treat refractory cancer. This strategy of using TMEs with controllable functional nanoparticles is expected to maximize cancer treatment efficiency in the future by combining it with various modern cancer therapeutics.

**Keywords** Tumor microenvironment · Nanoparticles · Cancer treatments · Drug delivery · Biomaterials

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## 1 Introduction

Cancer is a significant global life-threatening disease that is expected to increase the number of cases and deaths due to the gradual aging of the population [1, 2]. Numerous efforts have been dedicated to solving this problem via various cancer treatments, such as surgery, chemotherapy, and immunotherapy. However, treatment efficacy is unsatisfactory due to limitations imparted by specific characteristics of the tumor environment [3–5]. Therefore, it is necessary to understand tumor microenvironment (TME) to improve the unsatisfactory treatment efficacy.

TME is the environment surrounding the center, edge, or periphery of a tumor composed of non-malignant cells, blood vessels, lymphoid organs or lymph nodes, nerves, intercellular components, and metabolites. It is distinguished by hypoxic, acidic, and immunosuppressive status with a unique extracellular matrix, which differs from normal tissues [6]. The TME is tightly associated with tumor development, progression, and metastasis, and simultaneously exhibits high resistivity to various cancer

treatments [7, 8]. Therefore, numerous methods (e.g., oxygen delivering and acidity neutralization) have been reported to significantly increase the effectiveness of cancer treatments by effectively modulating the TME with the precise delivery of therapeutic agents [9].

Unlike direct tumor cell killing strategies, TME modulation is an alternative method of cancer treatment with reduced toxicity and can improve the efficacy of conventional cancer therapies such as chemotherapy and radiotherapy [10]. However, non-specific delivery of TME modulating agents with high-dosage may also cause deleterious side effects [11–13]. Consequently, nanoparticle-based tumor-specific drug delivery systems have been utilized for TME modulating agents intensively to circumvent and minimize side effects while enhancing therapeutic effects [14].

In general, nanoparticles refer to particles with diameters of 100 nm or less. To date, various types of nanoparticles have been developed, including liposomes, micelles, inorganic nanoparticles, and polymer nanoparticles [15, 16]. Nanoparticles can be effectively permeabilized and retained in cancer tissues via the enhanced permeability and retention (EPR) effect. When new blood vessels are made to meet the demands for nutrition and oxygen due to the abnormally rapid growth rate of cancer tissues, they have a leaky structure and poor lymphatic drainage compared to normal blood vessels. As a result, nanoparticles are well permeated from blood vessels to cancer tissues. These nanoparticles cannot easily escape and get accumulated in the tissues [17, 18]. Through the EPR effect, nanoparticles could passively target tumors by encapsulating therapeutics to selectively deliver and accumulate in the tumor, thereby reducing the side effects caused by systemic exposure of anticancer drugs and maximizing the therapeutic effect [19].

With the rapid advancement of nanotechnology and the understanding of TME importance, numerous studies have reported on TME-tailored nanoparticle strategies to reduce side effects resulting from imprecise drug delivery and simultaneously modulate the TME further to promote effective cancer treatment [20–22]. This review will highlight representative strategies to modulate the TME while precisely delivering therapeutic agents to the cancer site for enhanced cancer treatment. The TME modulation strategies with functional nanoparticles were summarized in Table 1. We believe that the development of TME-tailored nanoparticles will bring nanomedicines a step closer to clinical usage, which will transform patient care.

## 2 Modulation of TME based on nanoparticles for improving cancer treatment efficacy

### 2.1 Strategy for modulation of hypoxic TME

Tumor hypoxia (hypoxic TME) is a typical characteristic of the majority of most solid tumors. Under such conditions, there is an inadequate supply of oxygen and nutrients due to the rapid proliferation of cancer cells and abnormal blood vessel structures in the tumor tissues [35]. Hypoxic TME has a relatively low pH (hydrogen ion concentration exponent) with a significantly increased reactive oxygen species (ROS) level than normal tissues. Such unique characteristics increase tumor invasiveness, metastasis, angiogenesis, and multidrug resistance [25, 36]. In addition to the reduced therapeutic efficacy of anticancer drugs, hypoxic TME strengthens resistance to oxygen-involved treatments, such as photodynamic therapy (PDT) and radiation therapy [9]. Therefore, modulation of hypoxic TME is an ideal strategy to increase the effectiveness of conventional cancer treatment [14, 37, 38]. Hyperbaric oxygen therapy can cause multiple side effects due to oxygen toxicity caused by non-selective delivery [39]. Therefore, precise tumor targeting strategies have been reported to ensure precise oxygen transfer or oxygen generation at the tumor site [40, 41].

#### 2.1.1 Oxygen delivery

Cancer cells adapt to the hypoxic TME by overexpressing hypoxia-inducible factor (HIF-1 $\alpha$ ), which participates in the transcriptional activity of multidrug resistance gene 1 (MDR1), which encodes P-glycoprotein (P-gp), which exports different anticancer drugs in cancer cells [42]. Increased P-gp expression confers resistance to anticancer drugs. Tian et al. engineered hemoglobin-encapsulated biomimetic oxygen-nanocarriers (DHCNPs) to overcome anticancer drug resistance by modulating hypoxic TME [23] (Fig. 1A). This study demonstrated effective reduction of HIF-1 $\alpha$ , MDR 1, and P-gp expression by modulating the hypoxic TME through selective delivery of oxygen-containing hemoglobin encapsulated nanoparticles to the tumor site (Fig. 1B, C). As a result, hypoxia-induced chemoresistance disappeared by inhibition of HIF-1 $\alpha$ -induced P-gp expression, and cancer cells were killed by doxorubicin (DOX), a type of anticancer drug, delivered with hemoglobin, thereby effectively inhibiting tumor growth.

An alternative to incorporating hemoglobin is perfluorocarbon (PFC) which modulates hypoxic TME via efficient oxygen delivery to the tumor site. PFC is an inert and biocompatible synthetic molecule with high oxygen

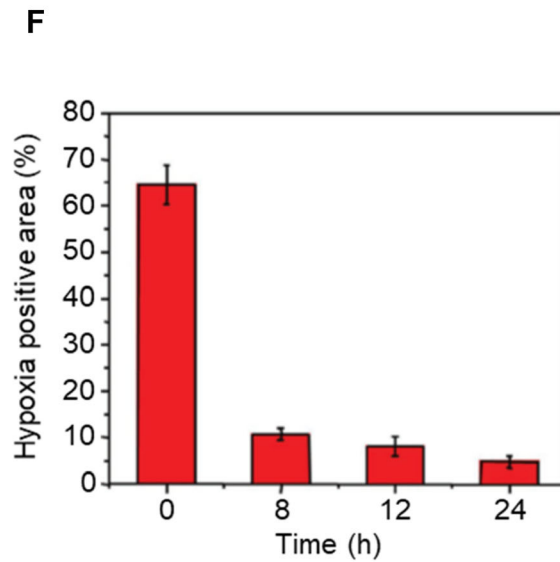
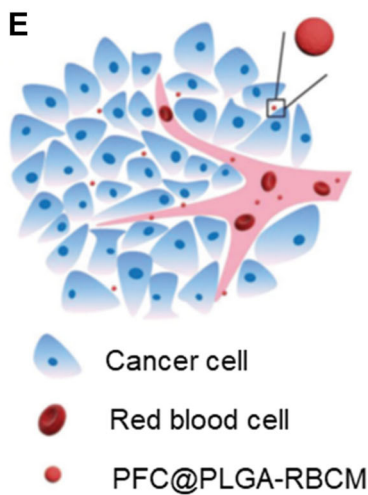
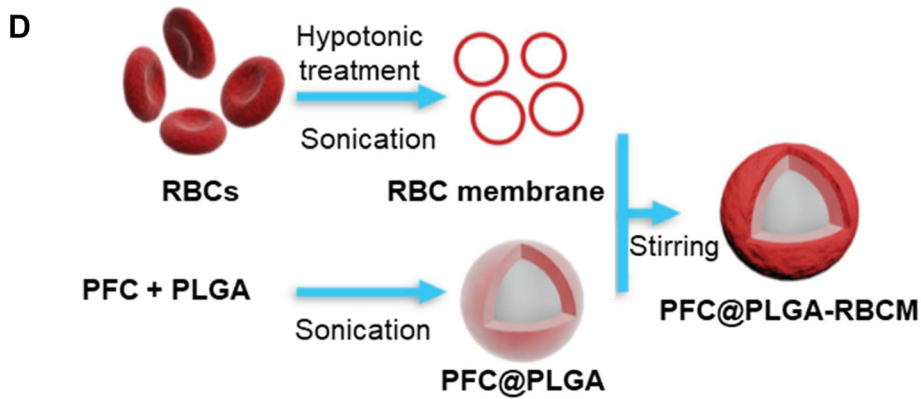
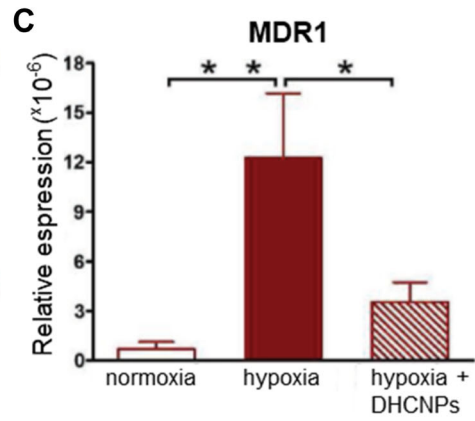
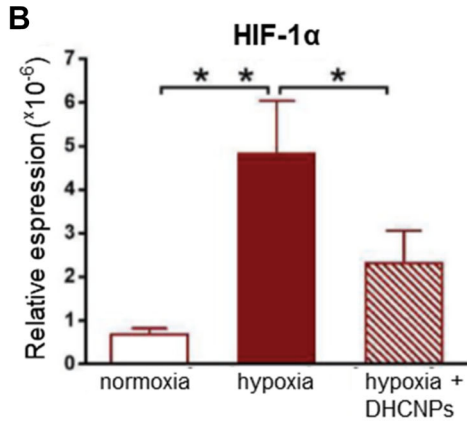
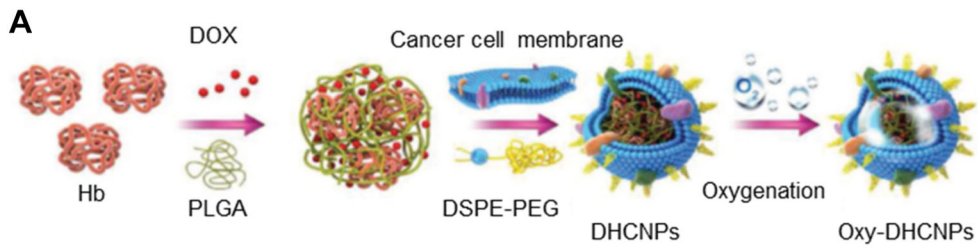
**Table 1** Nanoparticle-based TME modulation strategies

| Types of TME          | Modulation strategy  | Types of nanoparticles  | Advantage  | References |
|-----------------------|--|---|--|------------|
| Hypoxic TME           | Oxygen delivery  | Hemoglobin & DOX encapsulating cancer cell membrane camouflaged nanocarrier     | Overcome hypoxia-induced chemotherapy resistance   | [23]       |
|                       |  | Perfluorocarbon encapsulating red blood cell membrane-coated PLGA nanoparticles | Overcome hypoxia-induced radiotherapy resistance   | [24]       |
|                       | Oxygen generation  | Ce6-loaded MnO <sub>2</sub> nanoparticles                                       | Overcome hypoxia-induced photodynamic therapy resistance   | [25]       |
| Acidic TME            | Alkaline buffer delivery                                   | Sodium bicarbonate loaded liposomes   | Overcoming drug resistance by enhancing cellular drug penetration                                    | [26]       |
|                       | Nanoparticle-based buffering                               | Nano-CaCO <sub>3</sub> nanoparticles  | Acidic TME neutralization  | [27]       |
|                       | Reduction of lactate production                            | Vesicular cationic lipid-assisted nanoparticles                                 | Increased infiltration of CD8 <sup>+</sup> T cells and decreased numbers of immunosuppressive cells, | [28]       |
| Tumor ECM             | Collagen degradation                                       | Collagenase-loaded liposomes (collagozomes)                                     | Increased drug penetration   | [29]       |
|                       | Hyaluronic acid degradation                                | Hyaluronidase-conjugated dextran nanoparticles                                  | Increased drug penetration & enhanced PDT treatment  | [30]       |
|                       | High intensity focused ultrasound (Pulsed-HIFU) technology | Glycol chitosan nanoparticles   | Increased drug penetration   | [31]       |
| Immunosuppressive TME | TAM repolarization   | CpG oligodeoxynucleotide encapsulated ferritin nanoparticles                    | Increased expression of pro-inflammatory cytokines and M1 marker                                     | [32]       |
|                       | MDSC depletion   | Conjugated micelle system encapsulated RGX-104 and PTX                          | MDSC depletion and CTL activation  | [33]       |
|                       | Treg inhibition  | Engineered cellular nanovesicles presenting the PD-1 receptor on the membrane   | Treg and tumor growth inhibition through blocking PD-1/PD-L1   | [34]       |

solubility and is used as an oxygen carrier [43]. Using these PFC characteristics, Gao et al. developed a PFC-encapsulated nanocarrier coated with a red blood cell (RBC) membrane (PFC@PLGA-RBCM) to modulate hypoxic TME and improve the effectiveness of radiotherapy [24] (Fig. 1D). The RBCM-coated nanoparticles exhibited prolonged blood circulation compared to the naked PFC@PLGA nanoparticles. Furthermore, since PFC@PLGA-RBCM (about 290 nm) is smaller than the RBCs (microscale), it has the advantage to quickly diffuse into the tumor tissue and be oxygenated (Fig. 1E), thereby effectively modulating hypoxic TME. In PFC@PLGA-RBCM-treated mice, hypoxia area stained with immunofluorescence decreased from 66.8% to 4.7% after 24 h treatment. (Fig. 1F). Hypoxia-alleviated TME overcame the resistance to radiation therapy and demonstrated effective suppression of cancer growth.

### 2.1.2 Oxygen generation

Hypoxic TME also exhibits relatively low pH and high H<sub>2</sub>O<sub>2</sub> concentrations compared to normal tissues [36]. Recent studies on tumor hypoxia have reported MnO<sub>2</sub> nanoparticles to generate oxygen in situ in response to the TME [37, 41]. The precise delivery of MnO<sub>2</sub> nanoparticles to hypoxic TME enables the continuous production of oxygen (O<sub>2</sub>) and Mn<sup>2+</sup> by decomposing H<sub>2</sub>O<sub>2</sub> to modulate the TME [44]. Based on this principle, Zhu et al. engineered a MnO<sub>2</sub> nano-vehicle conjugated with a Ce6 photosensitizer (Ce6@MnO<sub>2</sub>-PEG) for hypoxic TME modulation potentiated PDT enhancement [25]. The intravenously injected nano-vehicles were observed to accumulate selectively and continuously produce O<sub>2</sub> and Mn<sup>2+</sup> by decomposing H<sub>2</sub>O<sub>2</sub>, which significantly suppressed tumor hypoxia (Fig. 2A). Hypoxia positive areas by immunofluorescence staining demonstrate that i.v. injection of Ce6@MnO<sub>2</sub>-PEG could greatly suppress tumor hypoxia (Fig. 2B, C). Furthermore, Ce6@MnO<sub>2</sub>-PEG



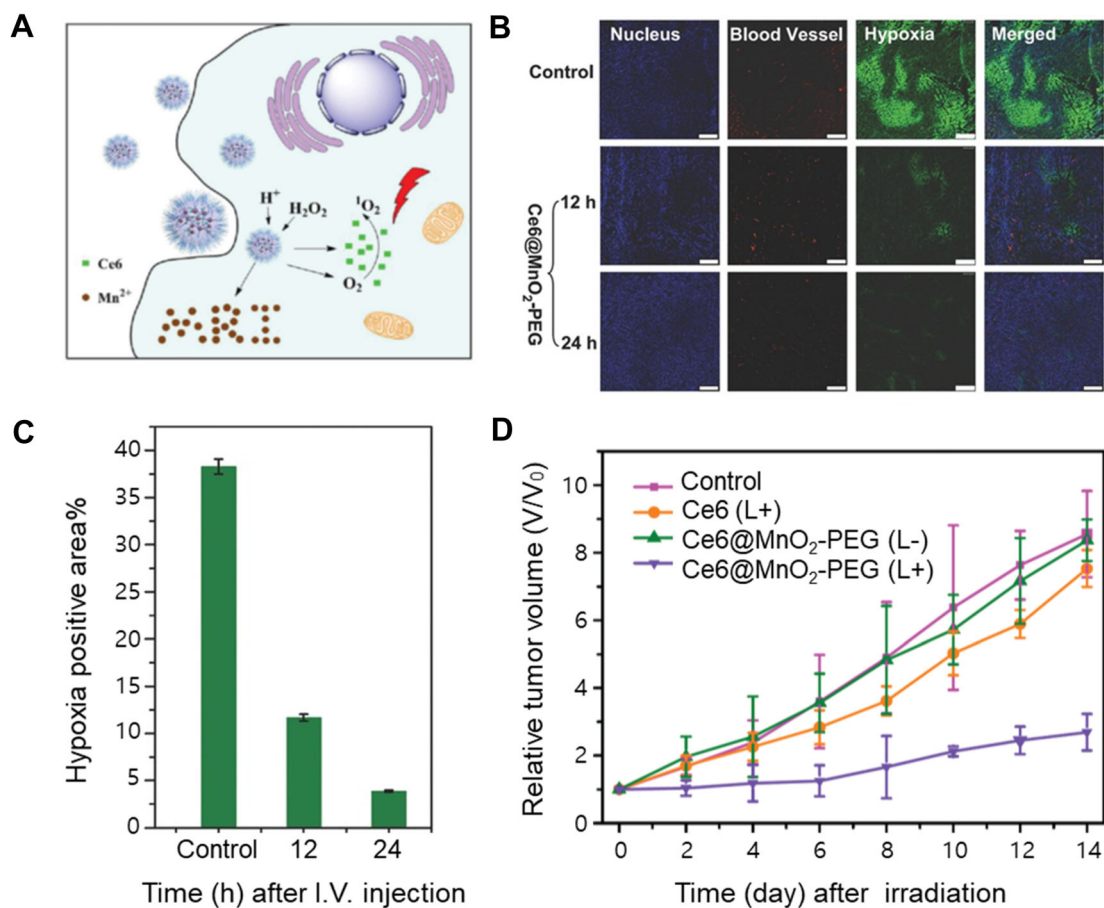
**Fig. 1** Modulation of the hypoxic tumor microenvironment through oxygen delivery using functional nanoparticles. **A** Synthetic process of DHCNP containing hemoglobin (oxygen transporter) and doxorubicin (anticancer agent). **B, C** Changes in the expression levels of HIF-1 $\alpha$ , MDR1 in cancer cells (MCF-7) after DHCNP treatment. **D** The engineering process of nanoparticles (PFC@PLGA-RBCM) encapsulated with perfluorocarbon and coated with cell membranes of red blood cells. **E** Schematic illustration of PFC@PLGA-RBCM nanoparticles: PFC@PLGA-RBCM nanoparticles are smaller than RBC in size can quickly diffuse into the tumor and effectively deliver oxygen. **F** Changes in hypoxia-positive area over time, as confirmed through immunofluorescence staining after nanoparticle treatment. Reproduced from [23, 24] with permission from Wiley-VCH

injection with laser irradiation showed an obvious inhibitory effect of tumor growth (Fig. 2D). Hence, this strategy applies to treatments requiring increased O<sub>2</sub> quantities, including PDT.

## 2.2 Strategy for modulation of acidic TME

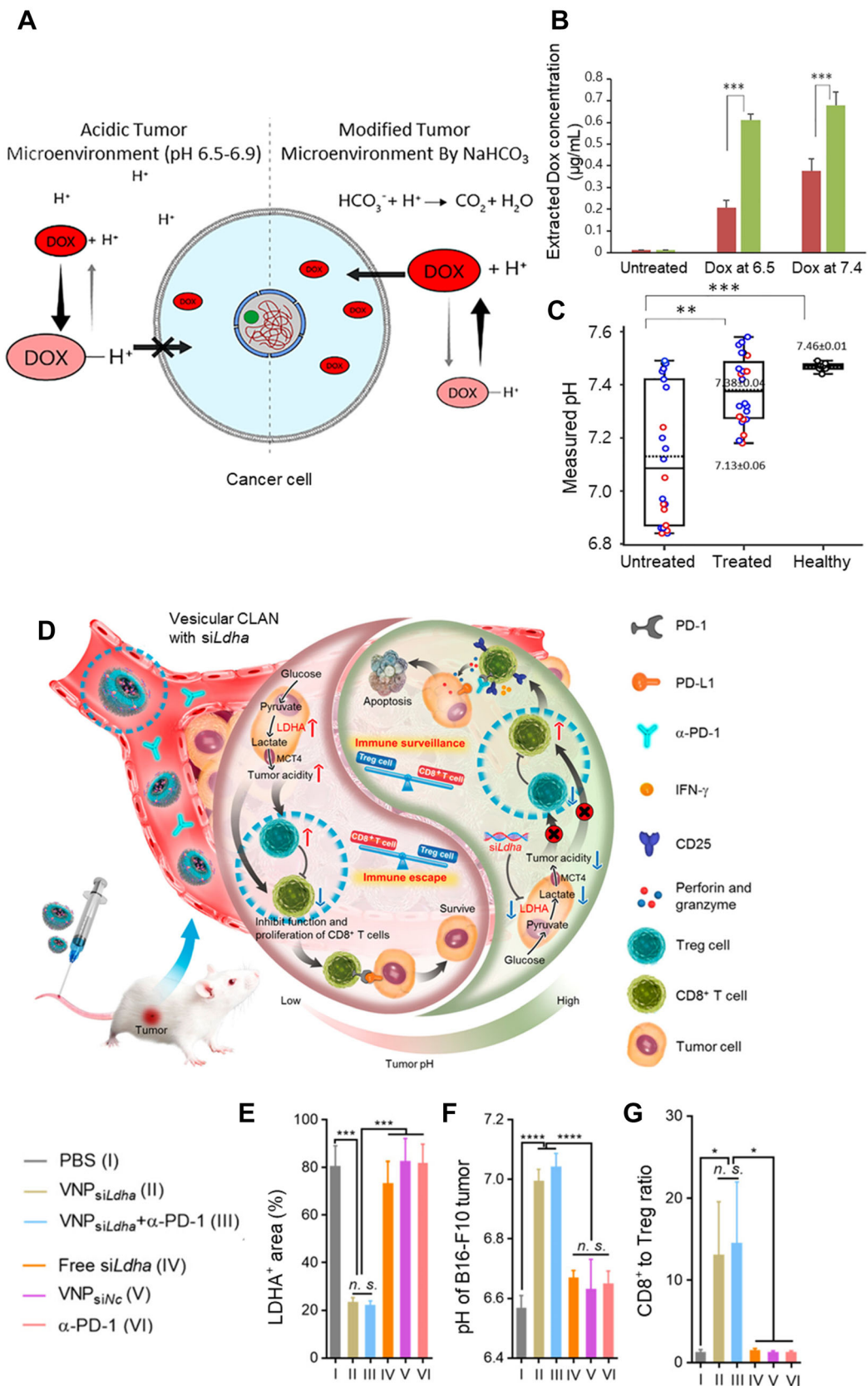
One of the significant causes of the acidic physicochemical composition of TME is low perfusion, which simultaneously limits oxygen delivery and removal of acidic waste products from metabolic activities. Unlike normal cells that obtain energy through oxidative phosphorylation, tumor cells in hypoxia generate energy from oxygen-independent glycolysis by adapting to insufficient oxygen supply (called the Warburg effect) [45, 46]. In this process, tumor cells produce and release a large number of acidic products, such as lactic acid, resulting in an acidic extracellular environment (pH 6.5–6.8) that is distinct from normal tissues (pH 7.4) [10, 45, 47].

This acidic TME is involved in proliferation, metastasis, and increased expression of P-gp, a multidrug resistance protein, resulting in multidrug resistance [9, 48, 49]. In



**Fig. 2** Modulating the hypoxic TME through oxygen generation using MnO<sub>2</sub> encapsulated nanoparticles and improved cancer treatment effect. **A** Schematic illustration of cellular uptake of Ce6@MnO<sub>2</sub>-PEG nanoparticles and O<sub>2</sub> generation within cells. **B** Representative immunofluorescence images of tumor after hypoxia staining. The blood vessels, nuclei, and hypoxic areas were stained by anti-CD31 antibody (red), DAPI (blue), and anti-pimonidazole

antibody (green), respectively. **C** The relative hypoxia positive area. **D** Tumor growth curve in various groups: when hypoxia was modulated using nanoparticles (Ce6@MnO<sub>2</sub>-PEG), photodynamic therapy (L +) showed a much superior tumor growth inhibitory effect compared to the comparative group (Ce6) that did not. Reproduced from [25] with permission from Wiley-VCH



**Fig. 3** Modulation of the acidic TME and improved cancer treatment effect using functional nanoparticles. **A** Mechanism of increasing the uptake of doxorubicin into the acidic TME modulated by bicarbonate. **B** Graph of doxorubicin absorption concentration of cancer cells according to pH around tumor cells and bicarbonate treatment: The bicarbonate-treated group (green) showed more doxorubicin absorption than did not (red). **C** In the in vivo mouse model, the results of measuring the pH of the tumor tissue with the group treated with the liposome containing bicarbonate (the red dot measured the center of the tumor, and the blue circle measured the surrounding tissue of the tumor). **D** Schematic illustration of siRNA-encapsulated nanoparticle mediated acidic TME modulation and activation of T cell immune response: Nanoparticle-mediated knockdown of LDHA reversed tumor acidic TME, reducing the number of immunosuppressive cells, increasing CD8<sup>+</sup> T cell infiltration, and restoring antitumor function. **E** Quantitative expression of LDHA in tumor tissue through immunohistochemical staining. **F** pH values of B16-F10 tumor tissues measured on day 19 after treatment. pH values were measured in vivo using pH microneedle probe. **G** Ratios of CD8<sup>+</sup> T cells to Treg (Foxp3<sup>+</sup>) cells through immunohistochemical quantitative analysis. Reproduced from [26, 28] with permission from Elsevier, American Chemical Society

addition, low extracellular pH generally limits drug efficacy by ionizing weakly basic drugs such as DOX, making it difficult for cellular transport (called the ion trapping effect) [50]. Thus, acidic TME neutralization strategies have been proposed to enhance the efficacy of conventional chemotherapy [51]. A basic buffer solution is an option to neutralize the acidic TME; however, treatment with a systemic basic buffer solution rather than a tumor-specific pH modulation could cause severe side effects such as metabolic alkalosis [52].

### 2.2.1 Alkaline buffer delivery

To solve this problem, Abumanhal et al. synthesized a tumor-targeted liposomal nano platform which was encapsulated with a basic buffer solution to reduce the side effects caused by systemic exposure of the buffer solution and concurrently overcome the ion trapping effect by improving the acidic TME [26]. The basic sodium bicarbonate (NaHCO<sub>3</sub>) buffer solution used in this study produces bicarbonate (HCO<sub>3</sub><sup>-</sup>), which reacts with H<sup>+</sup> around the tumor to generate H<sub>2</sub>O and carbon dioxide (CO<sub>2</sub>) (HCO<sub>3</sub><sup>-</sup> + H<sup>+</sup> ⇌ H<sub>2</sub>CO<sub>3</sub> ⇌ CO<sub>2</sub> + H<sub>2</sub>O) [53]. Consequently, HCO<sub>3</sub><sup>-</sup> in liposome nanoparticles elevated the tumor pH, protecting DOX from the ion trapping effect. Ultimately, non-ionized DOX was effectively absorbed into the cells (Fig. 3A, B). Collectively, the liposomal nanoplateforms with sodium bicarbonate buffer effectively increased the pH in the TME to normal tissue levels in vivo (Fig. 3C), which improved the cell absorption effect of DOX and thus demonstrated an excellent tumor growth inhibitory effect.

### 2.2.2 Nanoparticle-based buffering

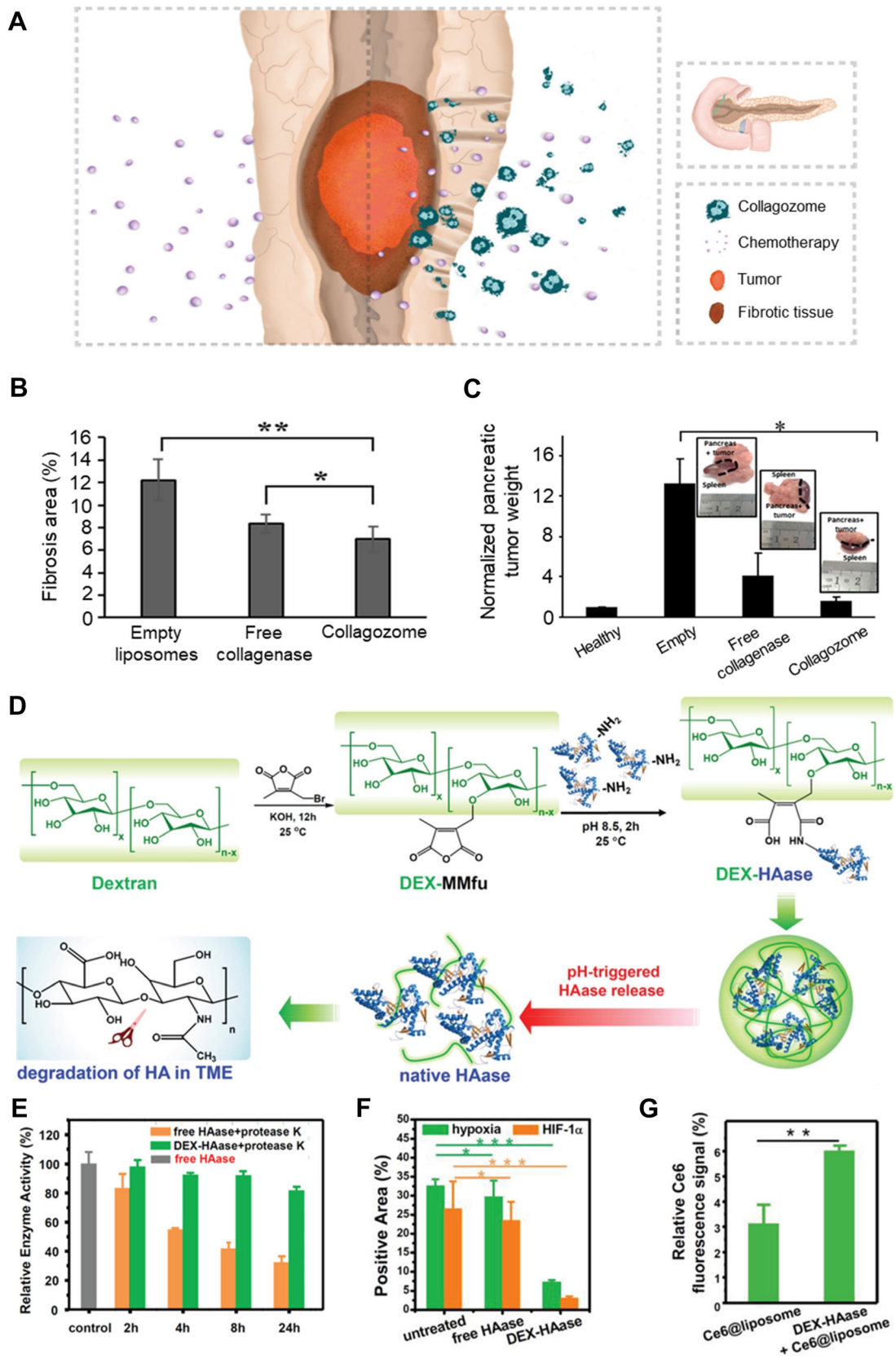
Furthermore, inhibition of tumor growth and metastasis by neutralizing acidic TME through nanoparticle-based buffering has been proposed [54]. CaCO<sub>3</sub> nanoparticles have a high payload and buffering capacity to effectively deliver drugs and modulate acidic TME by forming bicarbonate (HCO<sub>3</sub><sup>-</sup>) and decomposing under weakly acidic conditions [27]. Using these characteristics, a strategy that responds to the acidic TME and rapidly decomposes to deliver tumor-specific drugs was introduced [55]. Som et al. prepared nano-CaCO<sub>3</sub> (CaCO<sub>3</sub> nanoparticles) neutralizing acidic TMEs to inhibit tumor growth [27]. Nano-CaCO<sub>3</sub> prepared by gas diffusion method gradually increased tumor pH over time due to selective accumulation in the tumor after intravenous injection in an HT-1080 tumor-bearing mouse model. Repeated daily administration of nano-CaCO<sub>3</sub> significantly inhibited tumor growth compared to that in the control group.

### 2.2.3 Reduction of lactate production

Emerging evidence demonstrates the immunosuppressive role of acidic TME by interfering with effective anti-tumor T-cell immune responses [56]. CD8<sup>+</sup> T cells tend to become anergic and apoptotic when exposed to an acidic environment [57]. In addition, excess lactic acid improves the function of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), thereby suppressing the anti-tumor immune response [58, 59]. Thus, it can neutralize tumor acidity by inhibiting lactate production to restore anti-tumor T cell function and immune response [60]. Zhang et al. developed siRNA-encapsulated vesicular cationic lipid-assisted nanoparticles (CLAN) to modulate acidic TME by silencing lactate dehydrogenase A (LDHA), which causes acidity of the tumor as it converts pyruvate into lactic acid and accelerates glycolysis (Fig. 3D) [28]. In this study, siLdha (siRNAs against *Ldha*)-encapsulated vesicular CLAN (VNP<sub>siLdha</sub>) mediated systematic knockdown of LDHA in tumor cells, resulting in reduced lactic acid production and neutralization of the TME (Fig. 3E, F). In the in vivo experiment, neutralization of tumor acidity reduced the number of immunosuppressive cells, whereas infiltration of CD8<sup>+</sup> T cells increased, which significantly inhibited tumor growth (Fig. 3G).

## 2.3 Strategy for modulation of ECM in TME

The extracellular matrix (ECM) is a network of non-cellular components such as structural proteins (mainly collagen), glycoproteins, proteoglycans, and polysaccharides [61]. These extracellular matrices exist in all tissues and





◀**Fig. 4** Modulation of extracellular matrix through enzymatic degradation using functional nanoparticles. **A** Drug penetration is restricted by the dense extracellular matrix layer of the tumor tissue, resulting in drug resistance of the tumor (left). In contrast, modulating the extracellular matrix layer through collagozome treatment can increase the effectiveness of chemotherapy by increasing the drug tumor penetration (right). **B** The ratio of the fibrosis area according to each treated group in the mouse model. As collagenase decomposes collagen fibers, the fibrosis area is decreased, and the group treated with collagozome showed the least fibrosis area. **C** Comparison of tumor weight when treated with anticancer drug (paclitaxel) nanoparticles after treatment of each group. **D** Synthesis of DEX-HAase and proposed mechanism. DEX-HAase linked by a pH-responsive linker (MMfu) showed specific decomposition of HA in TME through pH-triggered free HAase release in acidic TME. **E** Relative enzymatic activity of free HAase and DEX-HAase against protease digestion. **F** Hypoxia relief and downregulation of HIF-1 $\alpha$  positive areas by ECM degradation after DEX-HAase treatment. **G** Increased intratumor penetration of Ce6-Liposome by ECM degradation after DEX-HAase treatment. Reproduced from [29, 30] with permission from American Chemical Society, Wiley–VCH

organs, providing essential physical support for cellular components, and play an essential role in tissue morphogenesis, differentiation, and homeostasis maintenance [62, 63].

ECM is disturbed in tumors. The tumor matrix promotes cancer growth, survival, and invasion, and modifies fibroblast and immune cell behavior to induce metastasis and impair treatment [64]. Compared to normal tissue, it has much more collagen fibers and hyaluronic acid, making it denser and increasing the interstitial fluid pressure, which acts as a physical barrier preventing the penetration of drugs or nanoparticles [65, 66]. To address this issue, a collagen-degrading enzyme (collagenase) has been used to improve tumor tissue permeability for enhanced chemotherapy treatments [31]. However, intravenous injection of collagenase resulted in rapid degradation and early deactivation by proteases in the bloodstream, which caused severe toxicity by non-selective action on normal tissues [67, 68].

### 2.3.1 Collagen and hyaluronic acid degradation

Encapsulating collagenase in nanoparticles could protect the cargo enzymes from proteases in the bloodstream and reduce their side effects in normal tissues [68]. Zinger et al. improved the treatment efficacy of chemotherapy by increasing the penetration of anticancer drugs by effectively degrading the ECM of the TME using collagenase-encapsulated liposome nanoparticles (Fig. 4A) [29]. The collagenase maintained enzymatic activity for a long time by encapsulation in liposomes, and it effectively accumulated in the tumor and continuously degraded collagen, thereby modulating the ECM of TME (Fig. 4B). When Gd-

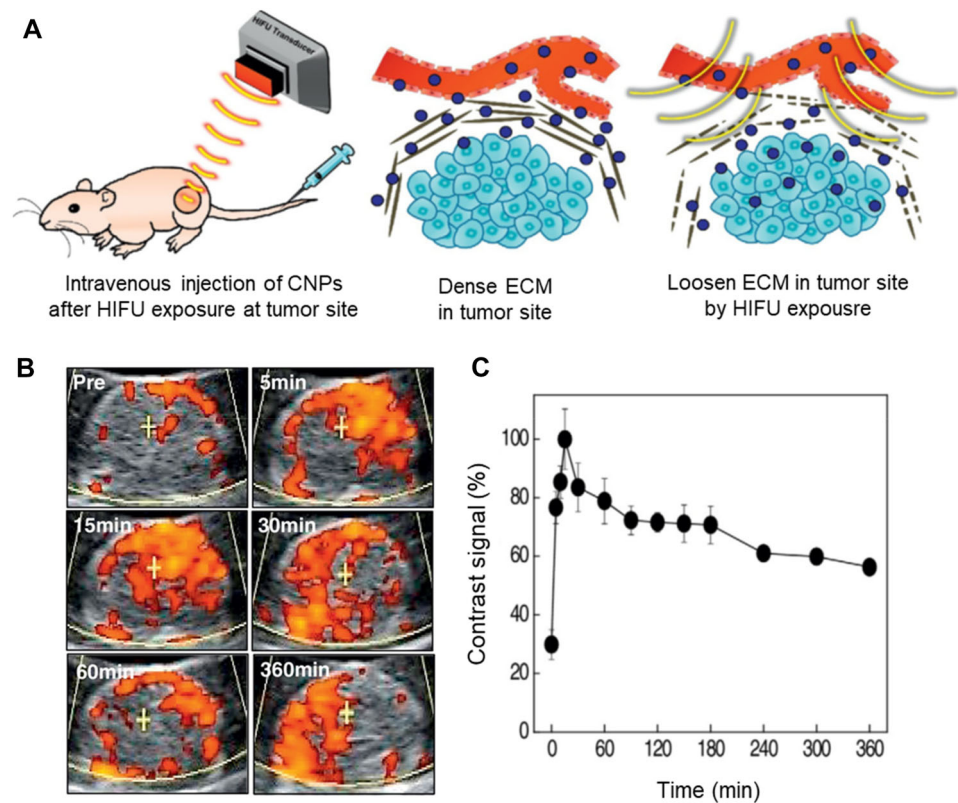
loaded liposomes were used, more than twofold enhancement of pancreatic uptake was observed in collagen-treated PDAC mice compared to free enzyme. When PDAC tumor-bearing mice were pretreated with collagosomes, empty liposomes, or free collagenase and then treated with paclitaxel micelles, the collagozome-treated group showed the best therapeutic efficacy. (Fig. 4C).

Hyaluronidase (HAase) is a hydrolysis enzyme that degrades hyaluronic acid. Hyaluronic acid (HA) is a significant component of the ECM and is abundant in the TME [69]. HAase has been studied to enable tumor ECM degradation, which increases tumor penetration of drugs with enhancing the therapeutic efficacy [31, 70, 71]. Wang et al. demonstrated that DEX-HAase nanoparticles conjugated with HAase and dextran, a biocompatible polymer, can effectively modulate the ECM of the TME via a pH-responsive linker to increase penetration of oxygen and other therapeutic agents, thereby improving the therapeutic effect of PDT [30]. Using biocompatible natural polymer dextran, the formulated DEX-HAase nanoparticles demonstrated improved enzyme stability, reduced immunogenicity, and increased blood half-life after intravenous injection (Fig. 4D). Through protection against degradation by proteases and efficient passive tumor accumulation, the DEX-HAase within the acidic TME separates and releases the native HAase, which later causes the breakdown of HA, loosening the ECM structure, and enhancing the penetration of oxygen and other therapeutic agents (Fig. 4E–G). Hence, DEX-HAase nanoparticles greatly relieve tumor hypoxia and promote the therapeutic effect of nanoparticle-based PDT and are accompanied by a reversal of immunosuppressive TME, enhancing cancer immunotherapy.

### 2.3.2 High intensity-focused ultrasound (Pulsed-HIFU) technology

In addition to biochemical enzymes, a strategy for modulating ECM using physical methods (*i.e.*, PDT and ultrasound) was also studied [72]. Lee et al. disassembled the stiff ECM structure using high-intensity focused ultrasound (Pulsed-HIFU) technology; ECM modulation was performed to confirm the improved penetration of nanoparticles and tumor targeting (Fig. 5A) [31]. In the ECM-rich A549 tumor-bearing mouse model, after exposure to pulsed-HIFU, the collagen structure of the tumor tissue could be directly degraded without damaging the peripheral tissue. As a result, the blood flow in the blood vessels of the tumor tissue rapidly increased to 4.9 times after 15 min of treatment and to 2.9 times after 6 h (Fig. 5B, C). Nanoparticle penetration into the loosened tumor ECM increased 2.6 times compared to tumor tissues not treated with Pulsed-HIFU. These results show that ECM

**Fig. 5** Modulation of extracellular matrix through High intensity focused ultrasound (Pulsed-HIFU) technology using nanoparticles. **A** Schematic illustration of ECM remodeling strategy using HIFU for deep penetration of nanoparticles. **B** Time-dependent blood flow images of tumor blood vessels in ECM-rich A549 tumor-bearing mice after Pulsed-HIFU exposure (orange: blood flow of blood vessels, gray: tumor region). **C** Quantitative contrast signals of time-dependent blood flow. Reproduced from [31] with permission from Elsevier



disassembly and modulation of collagen structures by Pulse-HIFU is a promising strategy to enhance the penetration and tumor targeting of nanoparticles in ECM-rich tumor tissues.

#### 2.4 Strategy for modulation of immunosuppressive TME

Tumor tissue constitutes an immunosuppressive TME by recruiting immunosuppressive cells such as TAMs, MDSCs, and regulatory T cells (Tregs) [73]. TME interacts with tumor cells through various immune cells during tumor growth, mediates immune tolerance, and affects immunotherapy efficacy. Therefore, inhibiting TME immune suppression can improve the therapeutic outcomes of cancer immunotherapy [74].

It has been reported that nanoparticles can avoid physiological barriers such as endonuclease degradation and renal clearance to release cargo-containing drugs, antigens, and adjuvants to their intended target sites [75]. Therefore, immunosuppressive TME modulation using nanoparticles is a promising treatment strategy.

Macrophages are the constituent cells of the mononuclear phagocyte system (MPS) and play various roles in homeostasis, inflammation, and wound healing. In cancer, TAM, a vital component of the TME, is involved in tumor

growth, progression, and metastasis and is associated with a worse patient prognosis [76].

TAM produces various growth factors, proteases, and immunosuppressive cytokines that are required for tumor survival [77]. In general, macrophages can be divided into classically activated M1 and alternatively activated M2-type macrophages according to their activation status and function [78, 79]. M1 macrophages secrete pro-inflammatory cytokines and chemokines and promote leukocyte recruitment and activation to help eliminate tumor cells, whereas M2 type TAMs are anti-inflammatory, which induce immune suppression and promote tumor progression through a variety of mechanisms, including immune-suppressing cytokine production, cytotoxic T cell activity inhibition, promotion of regulatory T cell stimulation, and B cell signaling inhibition [80].

##### 2.4.1 TAM repolarization

To improve cancer treatment efficacy, a strategy has been proposed to modulate the polarization of immunosuppressive M2 macrophages to immune-supportive M1 macrophages [81]. Shan et al. effectively inhibited tumor growth by modulating M2 phenotype polarization of TAM to M1 phenotype by using ferritin nanoparticles (M2pep-rHF-CpG) encapsulated with CpG oligodeoxynucleotide (CpG ODNs), a toll-like receptor 9 (TLR9) agonist that can shift

the polarity of M2 macrophages to the M1 phenotype [32]. Naked CpG ODNs do not cross the cell membrane and are easily removed by nucleases. However, when administered systemically, it can trigger an inflammatory response via non-specific stimulation. Thus, encapsulating CpG ODNs in nanoparticles could protect CpG from nucleases in the bloodstream and TAM-specific delivery using M2 targeting peptide (M2pep) could reduce side effects (*i.e.*, inflammation) caused by systemic action of TLR agonists. Thus, M2pep-rHF-CpG nanoparticles repolarized M2 TAMs to the M1 type and effectively suppressed tumor growth in 4T1 tumor-bearing mice after *i.v.* injection.

#### 2.4.2 MDSC depletion

MDSCs are a heterogeneous population of bone marrow-derived cells [82]. MDSCs are one of the major components of the immunosuppressive TME that accumulate in the tumor site and play a vital role in drug resistance, tumor angiogenesis, metastasis, and immunosuppression [83, 84]. In addition, MDSCs activate Tregs and suppress other immune cells by releasing IL-10, ARG1, NOS2, and indoleamine 2,3-dioxygenase (IDO). Thus, MDSC depletion can dramatically improve cancer immunotherapy [85].

The liver-X nuclear receptor (LXR) induces the transcriptional activity of apolipoprotein E (ApoE) and impairs MDSC survival. MDSC depletion by LXR enhances the activation of cytotoxic T lymphocytes (CTL) and enhances cancer immunotherapy [86]. Wan et al. used a conjugated micelle system to encapsulate RGX-104, an LXR agonist, to induce cancer cell apoptosis and regulate the tumor immune environment, which ultimately enhances the anti-tumor effect of CTL through MDSC depletion [33]. In this study, a dual pH-sensitive conjugated micelle system (PAH/RGX-104@PDM/PTX) was developed to deliver RGX-104 and paclitaxel (PTX), an anticancer drug, to the perivascular region and tumor, respectively (Fig. 6A). MDSC depletion and CTL were activated by RGX-104 released in response to acidic TME, and PTX was released from the endosome/lysosome to effectively kill the tumor cells (Fig. 6B, C). PAH/RGX-104@PDM/PTX showed excellent tumor accumulation and penetration and was able to inhibit tumor growth by 74.88%.

#### 2.4.3 Treg inhibition

Tregs are immunosuppressive T cells capable of inhibiting the activity of anti-tumor T effector cells. Tregs play a role in preventing autoimmune diseases through immune tolerance to autoantigens, but in the TME, they can suppress immune cells and weaken anticancer immune activity [85]. Thus, one can also functionally inhibit or eliminate Tregs to induce anti-tumor immunity [87, 88].

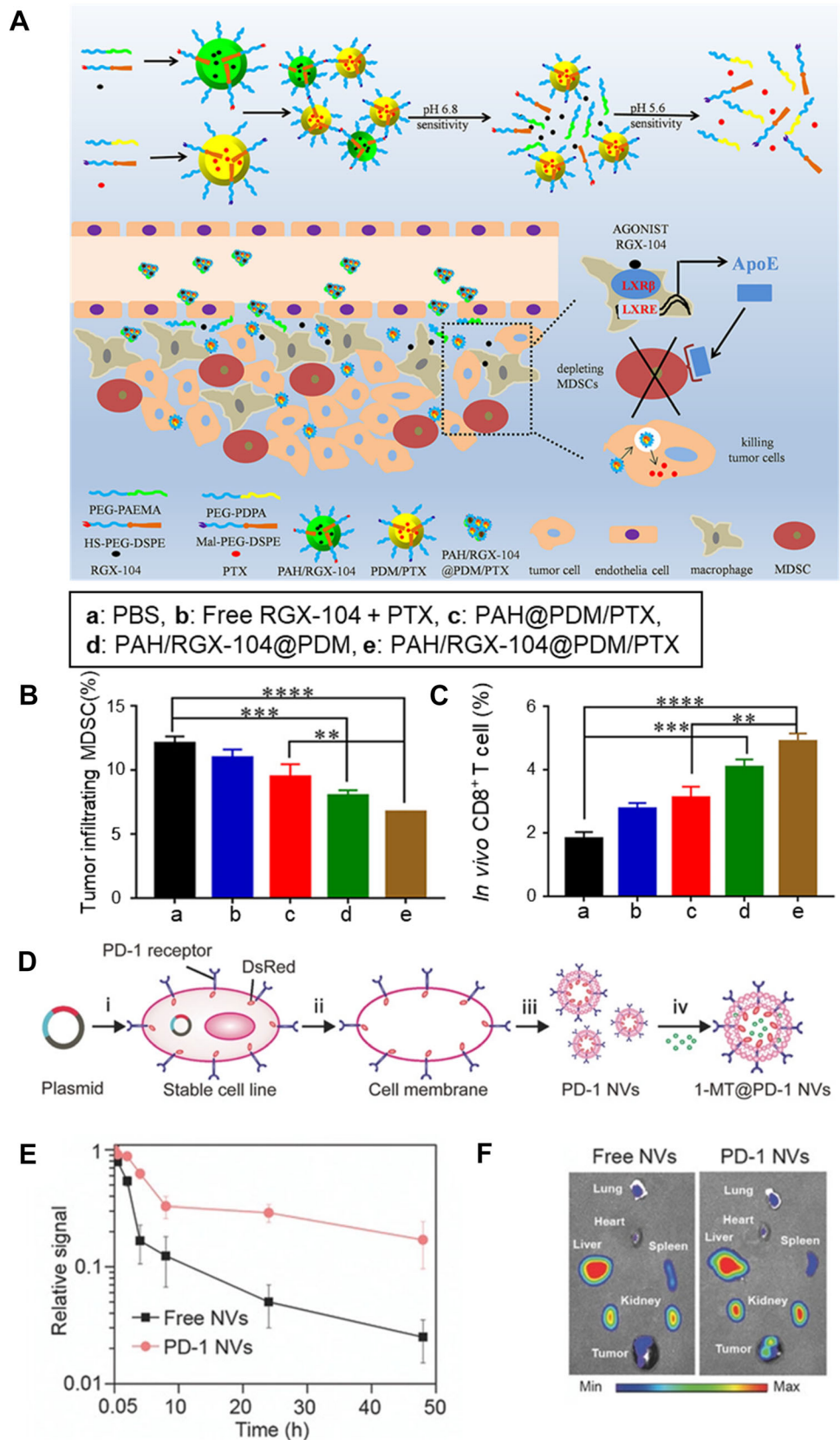
Programmed cell death protein-1 (PD-1), expressed in Tregs, binds to the tumor cell receptor programmed cell death ligand-1 (PD-L1), inactivating the T-cell immune response and contributing to tumor immune evasion [89]. Anti-PD-1 (aPD-1), an immune checkpoint inhibitor (ICI), can activate T-cell immune responses against tumor cells by blocking the binding of PD-1 and PD-L1 [90]. Therefore, blocking PD-1/PD-L1 using ICI is a promising treatment method for inducing T cell-mediated tumor death [91]. Lan et al. significantly enhanced the immune response against melanoma tumors using 1-methyl-tryptophan (1MT)-loaded cellular nanovesicles (NVs) that present the PD-1 receptor on the membrane [34] (Fig. 6D). PD-1 NV exhibits long circulation and can effectively bind to PD-L1 in melanoma cancer cells (Fig. 6E, F). In addition, 1MT, an inhibitor of indoleamine 2,3-dioxygenase (IDO), can be loaded into PD-1 NV to disrupt other immune tolerance pathways in the TME effectively. PD-1 NVs inhibited tumor growth and prolonged survival time in mice compared to free anti-PD-L1 Ab.

### 3 Summary and perspective

The tumor microenvironment (TME) is highly complex, and the unique atmosphere of tumor tissues that contributes to the tumor development, progression, and metastasis. Although the hypoxic, acidic, immunosuppressive, and unique ECM of TME differentiates itself from the normal tissues, the flexible tumor cells can adapt to the diverse TME and develop high resistance to various therapies, including chemotherapy, photodynamic, and radiation therapy. Given the pivotal role of the TME, TME modulation strategies have garnered increasing attention from researchers to achieve improved cancer treatment. Nevertheless, non-specific delivery of TME-modulating agents and chemotherapeutic drugs resulted in severe side effects. Therefore, functional nano-vehicles with high delivery accuracy to tumor sites have been incorporated to maximize treatment efficacy while minimizing side effects.

TME can generally be classified into (1) hypoxic TME, (2) acidic TME, (3) abnormal ECM, and (4) immunosuppressive TME. Since these limits a variety of treatments, various modulation strategies are being studied to efficiently treat them. The hypoxic TME could be relieved using oxygen-containing nanocarriers or *in situ* oxygenation inside the tumor. The acidic TME could be regulated by neutralizing tumor pH by delivering basic buffer solution, nanoparticle-based buffering, or inhibiting lactate production, which may provide additional benefits in tumor growth inhibition. Remodeling of abnormal ECM in TME via enzymatic degradation or ultrasound has become an effective strategy to support the treatment of various types

**Fig. 6** Immunosuppressive TME modulation through MDSC depletion and Treg inhibition using functional nanovesicles. **A** Schematic illustration of the structure of the conjugated micelles system and the construction and transformation of PAH/RGX-104 @ PDM/PTX. **B** The level of MDSC in tumor tissues after treatment with different formulations. **C** The amount of CD8<sup>+</sup> T cells in tumor tissues after treatment with different formulations. **D** Schematic illustration of PD-1 blockade cellular NVs for cancer immunotherapy. **E** Fluorescence of Cy5.5 labeled free NV and PD-1 NV after intravenous injection. **F** In vivo distribution of PD-1 NV and free NV as indicated by the in vivo imaging system (IVIS). Reproduced from [33, 34] with permission from Elsevier, Wiley–VCH



of cancer. Moreover, modulating immunosuppressive TME by targeting specific immune cells via nanomedicines can improve the effectiveness of cancer immunotherapy. Thus, TME modulation using various functional nanoparticles can be utilized as pre-conditioning for chemotherapy and immunotherapy for cancer treatment.

Due to advances in tumor biology, a better understanding of TME will contribute to the development of effective anticancer drugs. In addition, recently, studies on the interaction between nanomedicine and TME have been actively conducted, revealing the delivery process of nanoparticles to tumors through systemic injection. New functional nanoparticles designed based on these fundamental research results are expected to overcome TME and maximize the therapeutic effect of various intractable cancers. Recently, gene therapy and vaccine technologies using nanoparticles encapsulated with mRNA or siRNA have been approved in the clinic. The nanoparticle-based genetic engineering techniques such as lipid nanoparticles for TME modulation has a bright prospect. Tumor-specific delivery of genetic materials capable of modulating TME can induce successful immunotherapy by activating immunosuppressive immune cells and triggering the self-sustaining cancer immunity cycle. Taken all together, we believe that the combination of TME modulating nanoparticles introduced in this review and various anticancer or immunotherapeutic agents will be an effective cancer treatment option.

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**Author's contribution** SS and JL collected data and evidence. SS and JH drew the figures. FL, DL, and WP formulated the study concept and design. SS, JL, and WP wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

#### Declarations

**Conflict of interest** The authors declare no conflict of interest.

**Ethical statement** There are no animal experiments carried out for this article.

#### References

- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7–34.
- Jung KW, Won YJ, Kong HJ, Lee ES. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2016. *Cancer Res Treat*. 2019;51:417–30.
- Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. *Nat Rev Cancer*. 2013;13:714–26.
- Brown JM, Wilson WR. Exploiting tumour hypoxia in cancer treatment. *Nat Rev Cancer*. 2004;4:437–47.
- Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell*. 2017;168:707–23.
- Jin MZ, Jin WL. The updated landscape of tumor microenvironment and drug repurposing. *Signal Transduct Target Ther*. 2020;5:166.
- Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med*. 2013;19:1423–37.
- Trédan O, Galmarini CM, Patel K, Tannock IF. Drug resistance and the solid tumor microenvironment. *J Natl Cancer Inst*. 2007;99:1441–54.
- Yang S, Gao H. Nanoparticles for modulating tumor microenvironment to improve drug delivery and tumor therapy. *Pharmacol Res*. 2017;126:97–108.
- Liu J, Chen Q, Feng L, Liu Z. Nanomedicine for tumor microenvironment modulation and cancer treatment enhancement. *Nano Today*. 2018;21:55–73.
- Wingelaar TT, van Ooij PAM, Brinkman P, van Hulst RA. Pulmonary oxygen toxicity in navy divers: a crossover study using exhaled breath analysis after a one-hour air or oxygen dive at nine meters of sea water. *Front Physiol*. 2019;10:10.
- Liu J, Tian L, Zhang R, Dong Z, Wang H, Liu Z. Collagenase-encapsulated pH-responsive nanoscale coordination polymers for tumor microenvironment modulation and enhanced photodynamic nanomedicine. *ACS Appl Mater Interfaces*. 2018;10:43493–502.
- Torchilin V. Tumor delivery of macromolecular drugs based on the EPR effect. *Adv Drug Deliv Rev*. 2011;63:131–5.
- Xu J, Shi R, Chen G, Dong S, Yang P, Zhang Z, et al. All-in-one theranostic nanomedicine with ultrabright second near-infrared emission for tumor-modulated bioimaging and chemodynamic/photodynamic therapy. *ACS Nano*. 2020;14:9613–25.
- Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. *Annu Rev Med*. 2012;63:185–98.
- Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer*. 2017;17:20–37.
- Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res*. 1986;46:6387–92.
- Gerlowski LE, Jain RK. Microvascular permeability of normal and neoplastic tissues. *Microvasc Res*. 1986;31:288–305.
- Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol*. 2015;33:941–51.
- Chung CH, Lu KY, Lee WC, Hsu WJ, Lee WF, Dai JZ, et al. Fucoidan-based, tumor-activated nanoplatform for overcoming hypoxia and enhancing photodynamic therapy and antitumor immunity. *Biomaterials*. 2020;257:120227.
- Zhang Y, Ho SH, Li B, Nie G, Li S. Modulating the tumor microenvironment with new therapeutic nanoparticles: a promising paradigm for tumor treatment. *Med Res Rev*. 2020;40:1084–102.
- Tan T, Hu H, Wang H, Li J, Wang Z, Wang J, et al. Bioinspired lipoproteins-mediated photothermia remodels tumor stroma to improve cancer cell accessibility of second nanoparticles. *Nat Commun*. 2019;10:3322.

23. Tian H, Luo Z, Liu L, Zheng M, Chen Z, Ma A, et al. Cancer cell membrane-biomimetic oxygen nanocarrier for breaking hypoxia-induced chemoresistance. *Adv Funct Mater.* 2017;27:1703197.
24. Gao M, Liang C, Song X, Chen Q, Jin Q, Wang C, et al. Erythrocyte-membrane-enveloped perfluorocarbon as nanoscale artificial red blood cells to relieve tumor hypoxia and enhance cancer radiotherapy. *Adv Mater.* 2017;29:1701429.
25. Zhu W, Dong Z, Fu T, Liu J, Chen Q, Li Y, et al. Modulation of hypoxia in solid tumor microenvironment with MnO<sub>2</sub> nanoparticles to enhance photodynamic therapy. *Adv Funct Mater.* 2016;26:5490–8.
26. Abumahal-Masarweh H, Koren L, Zinger A, Yaari Z, Krinsky N, Kaneti G, et al. Sodium bicarbonate nanoparticles modulate the tumor pH and enhance the cellular uptake of doxorubicin. *J Control Release.* 2019;296:1–13.
27. Som A, Raliya R, Tian L, Akers W, Ippolito JE, Singamaneni S, et al. Monodispersed calcium carbonate nanoparticles modulate local pH and inhibit tumor growth in vivo. *Nanoscale.* 2016;8:12639–47.
28. Zhang YX, Zhao YY, Shen J, Sun X, Liu Y, Liu H, et al. Nanoenabled modulation of acidic tumor microenvironment reverses anergy of infiltrating T cells and potentiates anti-PD-1 therapy. *Nano Lett.* 2019;19:2774–83.
29. Zinger A, Koren L, Adir O, Poley M, Alyan M, Yaari Z, et al. Collagenase nanoparticles enhance the penetration of drugs into pancreatic tumors. *ACS Nano.* 2019;13:11008–21.
30. Wang H, Han X, Dong Z, Xu J, Wang J, Liu Z. Hyaluronidase with pH-responsive dextran modification as an adjuvant nanomedicine for enhanced photodynamic-immunotherapy of cancer. *Adv Funct Mater.* 2019;29:1902440.
31. Lee S, Han H, Koo H, Na JH, Yoon HY, Lee KE, et al. Extracellular matrix remodeling in vivo for enhancing tumor-targeting efficiency of nanoparticle drug carriers using the pulsed high intensity focused ultrasound. *J Control Release.* 2017;263:68–78.
32. Shan H, Dou W, Zhang Y, Qi M. Targeted ferritin nanoparticle encapsulating CpG oligodeoxynucleotides induces tumor-associated macrophage M2 phenotype polarization into M1 phenotype and inhibits tumor growth. *Nanoscale.* 2020;12:22268–80.
33. Wan D, Yang Y, Liu Y, Cun X, Li M, Xu S, et al. Sequential depletion of myeloid-derived suppressor cells and tumor cells with a dual-pH-sensitive conjugated micelle system for cancer chemoimmunotherapy. *J Control Release.* 2020;317:43–56.
34. Zhang X, Wang C, Wang J, Hu Q, Langworthy B, Ye Y, et al. PD-1 blockade cellular vesicles for cancer immunotherapy. *Adv Mater.* 2018;30:e1707112.
35. Vaupel P, Kallinowski F, Okunieff P. Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumors: a review. *Cancer Res.* 1989;49:6449–65.
36. Sharma A, Arambula JF, Koo S, Kumar R, Singh H, Sessler JL, et al. Hypoxia-targeted drug delivery. *Chem Soc Rev.* 2019;48:771–813.
37. Fu C, Duan X, Cao M, Jiang S, Ban X, Guo N, et al. Targeted magnetic resonance imaging and modulation of hypoxia with multifunctional hyaluronic acid-MnO<sub>2</sub> nanoparticles in glioma. *Adv Healthc Mater.* 2019;8:e1900047.
38. Liu Y, Jiang Y, Zhang M, Tang Z, He M, Bu W. Modulating hypoxia via nanomaterials chemistry for efficient treatment of solid tumors. *Acc Chem Res.* 2018;51:2502–11.
39. Wingelaar TT, van Ooij PAM, van Hulst RA. Oxygen toxicity and special operations forces diving: hidden and dangerous. *Front Physiol.* 2017;8:1263.
40. Wang Y, Wu W, Mao D, Teh C, Wang B, Liu B. Metal-organic framework assisted and tumor microenvironment modulated synergistic image-guided photo-chemo therapy. *Adv Funct Mater.* 2020;30:2002431.
41. Revuri V, Cherukula K, Nafujjaman M, Vijayan V, Jeong YY, Park IK, et al. In situ oxygenic nanopods targeting tumor adaptation to hypoxia potentiate image-guided photothermal therapy. *ACS Appl Mater Interfaces.* 2019;11:19782–92.
42. Chen J, Ding Z, Peng Y, Pan F, Li J, Zou L, et al. HIF-1 $\alpha$  inhibition reverses multidrug resistance in colon cancer cells via downregulation of MDR1/P-glycoprotein. *PLoS One.* 2014;9:e98882.
43. Castro CI, Briceno JC. Perfluorocarbon-based oxygen carriers: review of products and trials. *Artif Organs.* 2010;34:622–34.
44. Liu J, Zhang W, Kumar A, Rong X, Yang W, Chen H, et al. Acridine orange encapsulated mesoporous manganese dioxide nanoparticles to enhance radiotherapy. *Bioconjugate Chem.* 2020;31:82–92.
45. Feng L, Dong Z, Tao D, Zhang Y, Liu Z. The acidic tumor microenvironment: a target for smart cancer nano-theranostics. *Natl Sci Rev.* 2018;5:269–86.
46. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? *Nat Rev Cancer.* 2004;4:891–9.
47. Park W, Chen J, Cho S, Park SJ, Larson AC, Na K, et al. Acidic pH-triggered drug-eluting nanocomposites for magnetic resonance imaging-monitored intra-arterial drug delivery to hepatocellular carcinoma. *ACS Appl Mater Interfaces.* 2016;8:12711–9.
48. Lin G, Chen S, Mi P. Nanoparticles targeting and remodeling tumor microenvironment for cancer theranostics. *J Biomed Nanotechnol.* 2018;14:1189–207.
49. Wojtkowiak JW, Verduzco D, Schramm KJ, Gillies RJ. Drug resistance and cellular adaptation to tumor acidic pH microenvironment. *Mol Pharm.* 2011;8:2032–8.
50. Mahoney BP, Raghunand N, Baggett B, Gillies RJ. Tumor acidity, ion trapping and chemotherapeutics: I. Acid pH affects the distribution of chemotherapeutic agents in vitro. *Biochem Pharmacol.* 2003;66:1207–18.
51. Ihraiz WG, Ahram M, Bardaweel SK. Proton pump inhibitors enhance chemosensitivity, promote apoptosis, and suppress migration of breast cancer cells. *Acta Pharm.* 2020;70:179–90.
52. Faes S, Dormond O. Systemic buffers in cancer therapy: the example of sodium bicarbonate; stupid idea or wise remedy? *Med Chem.* 2015;5:540–4.
53. Silva AS, Yunes JA, Gillies RJ, Gatenby RA. The potential role of systemic buffers in reducing intratumoral extracellular pH and acid-mediated invasion. *Cancer Res.* 2009;69:2677–84.
54. Som A, Raliya R, Paranandi K, High RA, Reed N, Beeman SC, et al. Calcium carbonate nanoparticles stimulate tumor metabolic reprogramming and modulate tumor metastasis. *Nanomedicine (Lond).* 2019;14:169–82.
55. Zhang Y, Cai L, Li D, Lao YH, Liu D, Li M, et al. Tumor microenvironment-responsive hyaluronate-calcium carbonate hybrid nanoparticle enables effective chemotherapy for primary and advanced osteosarcomas. *Nano Res.* 2018;11:4806–22.
56. Huber V, Camisaschi C, Berzi A, Ferro S, Lugini L, Triulzi T, et al. Cancer acidity: an ultimate frontier of tumor immune escape and a novel target of immunomodulation. *Semin Cancer Biol.* 2017;43:74–89.
57. Calcinotto A, Filipazzi P, Grioni M, Iero M, De Milito A, Ricupito A, et al. Modulation of microenvironment acidity reverses anergy in human and murine tumor-infiltrating T lymphocytes. *Cancer Res.* 2012;72:2746–56.
58. Yang X, Lu Y, Hang J, Zhang J, Zhang T, Huo Y, et al. Lactate-modulated immunosuppression of myeloid-derived suppressor cells contributes to the radioresistance of pancreatic cancer. *Cancer Immunol Res.* 2020;8:1440–51.
59. Choi SY, Collins CC, Gout PW, Wang Y. Cancer-generated lactic acid: a regulatory, immunosuppressive metabolite? *J Pathol.* 2013;230:350–5.

60. Brand A, Singer K, Koehl GE, Koltitzus M, Schoenhammer G, Thiel A, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell Metab.* 2016;24:657–71.
61. Giussani M, Triulzi T, Sozzi G, Tagliabue E. Tumor extracellular matrix remodeling: new perspectives as a circulating tool in the diagnosis and prognosis of solid tumors. *Cells.* 2019;8:81.
62. Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. *J Cell Sci.* 2010;123:4195–200.
63. Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK. Extracellular matrix structure. *Adv Drug Deliv Rev.* 2016;97:4–27.
64. Kai F, Drain AP, Weaver VM. The extracellular matrix modulates the metastatic journey. *Dev Cell.* 2019;49:332–46.
65. Netti PA, Berk DA, Swartz MA, Grodzinsky AJ, Jain RK. Role of extracellular matrix assembly in interstitial transport in solid tumors. *Cancer Res.* 2000;60:2497–503.
66. Whatcott CJ, Han H, Posner RG, Hostetter G, Von Hoff DD. Targeting the tumor microenvironment in cancer: why hyaluronidase deserves a second look. *Cancer Discov.* 2011;1:291–6.
67. Diener B, Carrick L Jr, Berk RS. In vivo studies with collagenase from *Pseudomonas aeruginosa*. *Infect Immun.* 1973;7:212–7.
68. Villegas MR, Baeza A, Vallet-Regí M. Hybrid collagenase nanocapsules for enhanced nanocarrier penetration in tumoral tissues. *ACS Appl Mater Interfaces.* 2015;7:24075–81.
69. Chen E, Han S, Song B, Xu L, Yuan H, Liang M, et al. Mechanism investigation of hyaluronidase-combined multistage nanoparticles for solid tumor penetration and antitumor effect. *Int J Nanomedicine* 2020;15:6311–24.
70. Guan X, Chen J, Hu Y, Lin L, Sun P, Tian H, et al. Highly enhanced cancer immunotherapy by combining nanovaccine with hyaluronidase. *Biomaterials.* 2018;171:198–206.
71. Mardhian DF, Storm G, Bansal R, Prakash J. Nano-targeted relaxin impairs fibrosis and tumor growth in pancreatic cancer and improves the efficacy of gemcitabine in vivo. *J Control Release.* 2018;290:1–10.
72. Izi M, Maksoudian C, Manshian BB, Soenen SJ. The use of alternative strategies for enhanced nanoparticle delivery to solid tumors. *Chem Rev.* 2021;121:1746–803.
73. Duan Q, Zhang H, Zheng J, Zhang L. Turning cold into hot: firing up the tumor microenvironment. *Trends Cancer.* 2020;6:605–18.
74. Gao S, Yang D, Fang Y, Lin X, Jin X, Wang Q, et al. Engineering nanoparticles for targeted remodeling of the tumor microenvironment to improve cancer immunotherapy. *Theranostics.* 2019;9:126–151.
75. Saeed M, Gao J, Shi Y, Lammers T, Yu H. Engineering nanoparticles to reprogram the tumor immune microenvironment for improved cancer immunotherapy. *Theranostics.* 2019;9:7981–8000.
76. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. *Nat Rev Clin Oncol.* 2017;14:399–416.
77. Jeong H, Kim S, Hong BJ, Lee CJ, Kim YE, Bok S, et al. Tumor-associated macrophages enhance tumor hypoxia and aerobic glycolysis. *Cancer Res.* 2019;79:795–806.
78. Galván-Peña S, O'Neill LA. Metabolic reprogramming in macrophage polarization. *Front Immunol.* 2014;5:420.
79. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol.* 2008;8:958–69.
80. Sylvestre M, Crane CA, Pun SH. Progress on modulating tumor-associated macrophages with biomaterials. *Adv Mater.* 2020;32:e1902007.
81. Gionfriddo G, Plastina P, Augimeri G, Catalano S, Giordano C, Barone I, et al. Modulating tumor-associated macrophage polarization by synthetic and natural PPAR $\gamma$  ligands as a potential target in breast cancer. *Cells.* 2020;9:174.
82. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol.* 2009;9:162–74.
83. Gabrilovich DI. Myeloid-derived suppressor cells. *Cancer Immunol Res.* 2017;5:3–8.
84. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The nature of myeloid-derived suppressor cells in the tumor microenvironment. *Trends Immunol.* 2016;37:208–20.
85. Park W, Heo YJ, Han DK. New opportunities for nanoparticles in cancer immunotherapy. *Biomater Res.* 2018;22:1–10.
86. Tavazoie MF, Pollack I, Tanqueco R, Ostendorf BN, Reis BS, Gonsalves FC, et al. LXR/ApoE activation restricts innate immune suppression in cancer. *Cell.* 2018;172:825–40.
87. Taylor NA, Vick SC, Iglesia MD, Brickey WJ, Midkiff BR, McKinnon KP, et al. Treg depletion potentiates checkpoint inhibition in claudin-low breast cancer. *J Clin Invest.* 2017;127:3472–83.
88. Ou W, Thapa RK, Jiang L, Soe ZC, Gautam M, Chang J-H, et al. Regulatory T cell-targeted hybrid nanoparticles combined with immuno-checkpoint blockade for cancer immunotherapy. *J Control Release.* 2018;281:84–96.
89. Kumagai S, Togashi Y, Kamada T, Sugiyama E, Nishinakamura H, Takeuchi Y, et al. The PD-1 expression balance between effector and regulatory T cells predicts the clinical efficacy of PD-1 blockade therapies. *Nat Immunol.* 2020;21:1346–58.
90. Tang J, Yu JX, Hubbard-Lucey VM, Neftelinov ST, Hodge JP, Lin Y. Trial watch: the clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. *Nat Rev Drug Discov.* 2018;17:854–5.
91. Webb ES, Liu P, Baleeiro R, Lemoine NR, Yuan M, Wang Y. Immune checkpoint inhibitors in cancer therapy. *J Biomed Res.* 2018;32:317.

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