

Polymeric Nanomedicines for Comprehensive Regulation of Tumor Microenvironment

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Abstract Cancer immunotherapy, which harnesses the host immune system to combat cancer, has advanced into preclinical and clinical trials. However, the tumor microenvironment (TME) usually promotes tumor angiogenesis and induces immune tolerance. Recently, polymeric nanomedicines with comprehensive regulation of the TME have attracted research interest. Compared with others, polymeric nanomedicines have outstanding characteristics, including facile preparation, improved tumor penetration, longer blood circulation, and better bioavailability. In particular, polymeric nanomedicines hold great potential for integrating combined treatments and imaging methods to concurrently modulate and trace the functional processes of multiple immune cells. This review summarizes the advances in polymeric nanomedicine-based strategies for TME regulation, including the regulation of TME stromal cells, the immune microenvironment matrix, and vasculature. Furthermore, the development of comprehensive polymeric nanomedicine-based theragnostic platforms integrated with imaging segments is briefly introduced.

Keywords Polymeric nanomedicines; TME regulation; Cocktail cancer immunotherapy; Theranostic nanoplatforms

Citation: Li, H. X.; Wu, R. Y.; Mao, X. T.; Zhou, X. R.; Hao, K.; Tian, H. Y. Polymeric nanomedicines for comprehensive regulation of tumor microenvironment. *Chinese J. Polym. Sci.* 2026, 44, 2427–2452.

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1 INTRODUCTION

Cancer remains a major public health threat and one of the leading causes of death worldwide. Great efforts have been devoted to understanding cancer at the cellular and molecular levels as well as diverse therapeutic strategies.^[1,2,3] Immunotherapy, such as immune checkpoint therapy, which has been clinically used in recent years, has limited application owing to the low response rate of patients.^[4] With growing insights into the role of tumor microenvironment (TME) in tumor progression, researchers have found that the dynamic crosstalk between cancer cells and the TME greatly contributes to tumor formation and progression.^[5] In general, the TME comprises three core components: tumor cells, tumor stromal cells, and extracellular matrix (ECM). Tumor stromal cells are further divided into immune and non-immune subsets, including macrophages, lymphocytes (T cells, B cells), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) etc., while the latter includes cancer-associated fibroblasts (CAFs), endothelial cells, and peri-

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Invited Review

Received February 28, 2026; Accepted March 18, 2026; Published online June 10, 2026

cytes. ECM mainly consists of collagen, fibronectin, hyaluronan, laminin, and other macromolecules.^[6,7] Tumor cells interact with surrounding stromal cells *via* cytokines and chemokines to drive tumor progression and clonal evolution, while the TME dynamically adapts to evolving environmental and oncogenic cues during cancer development.^[8,9] Therefore, medicines enabling *in situ* regulation of the TME are urgently needed. However, the penetration and efficacy of current immunotherapeutic drugs are hindered by the heterogeneity of the TME.^[10]

Polymeric nanomedicines have the advantages of facile preparation, improved tumor penetration, longer blood circulation and multiple types of therapeutic drugs co-delivery, etc.^[11] Till now, over 200 polymeric nanomedicines products are undergoing clinical approval or investigation. For example, liposomes (Doxil), protein-based nanoparticles (Abraxane), polymeric micelles (Apealea), liposomal gene delivery formulations (NCT02369198), and polymeric micellar (NK105/NC-6004).^[12] In spite of the monumental successes, several limitations remain with single-target regulation. For instance, destroying the ECM only partially enhances drug penetration, while resident immunosuppressive cells in the TME still provide a favorable microenvironment for tumor stromal reformation. Therefore, tremendous effort has been devoted to integrating multiple therapeutic drugs or genes into “all-in-one” polymeric nanocarriers. Beyond polymeric nanocarriers integrated with functional segments for effective cancer therapy, companion diagnosis targeting the dynamically evolving TME is crucial. It enables the real-time monitoring of therapeutic outcomes, timely adjustment of dosages, and minimization of adverse side effects. To achieve this, numerous immune-related molecules have been exploited as biomarkers for monitoring using nanoprobe. For instance, Granzyme B, a functional enzyme secreted by cytotoxic T lymphocytes, has been used to track immune responses during cancer immunotherapy.^[13] Micro ribonucleic acid-21 (miRNA-21), a highly abundant microRNA in solid tumors that suppresses phosphatase production, serves as a key biomarker for early tumor detection.^[14,15] Lactic acid has been reported to promote the polarization of macrophages toward the M2 phenotype, making it a key targeting molecule for reporters specific to M2 macrophages in TME.^[16] Therefore, there is an urgent need to systematically summarize multi-dimensional TME regulation strategies based on polymeric nanomedicines and to provide insights into the development of integrated theranostic platforms for enhanced cancer immunotherapy.

In this review, we first provide an overview of the basic fundamental design and construction strategies of polymeric nanomedicines for TME regulation, ranging from the targeted modulation of critical stromal cells to the intervention of major physiological barriers that hinder tumor therapy. In combination with the recent advances in multimodal TME-cocktail therapy achieved by our group and the cutting-edge progress in nanoprobe technologies for tracking and evaluating anti-tumor immune responses, we further envisage the development of integrated theranostic nanoplatforms. Such platforms are designed to co-assemble functional therapeutic nanomedicines and imaging modules, enabling the simultaneous execution of precise cancer immunotherapy and dy-

namic *in situ* monitoring of immune responses within the TME (Scheme 1). Collectively, advances in polymeric nanomedicines and theranostic platforms provide a promising foundation for translating preclinical mechanistic studies into clinically relevant exploratory evidence.

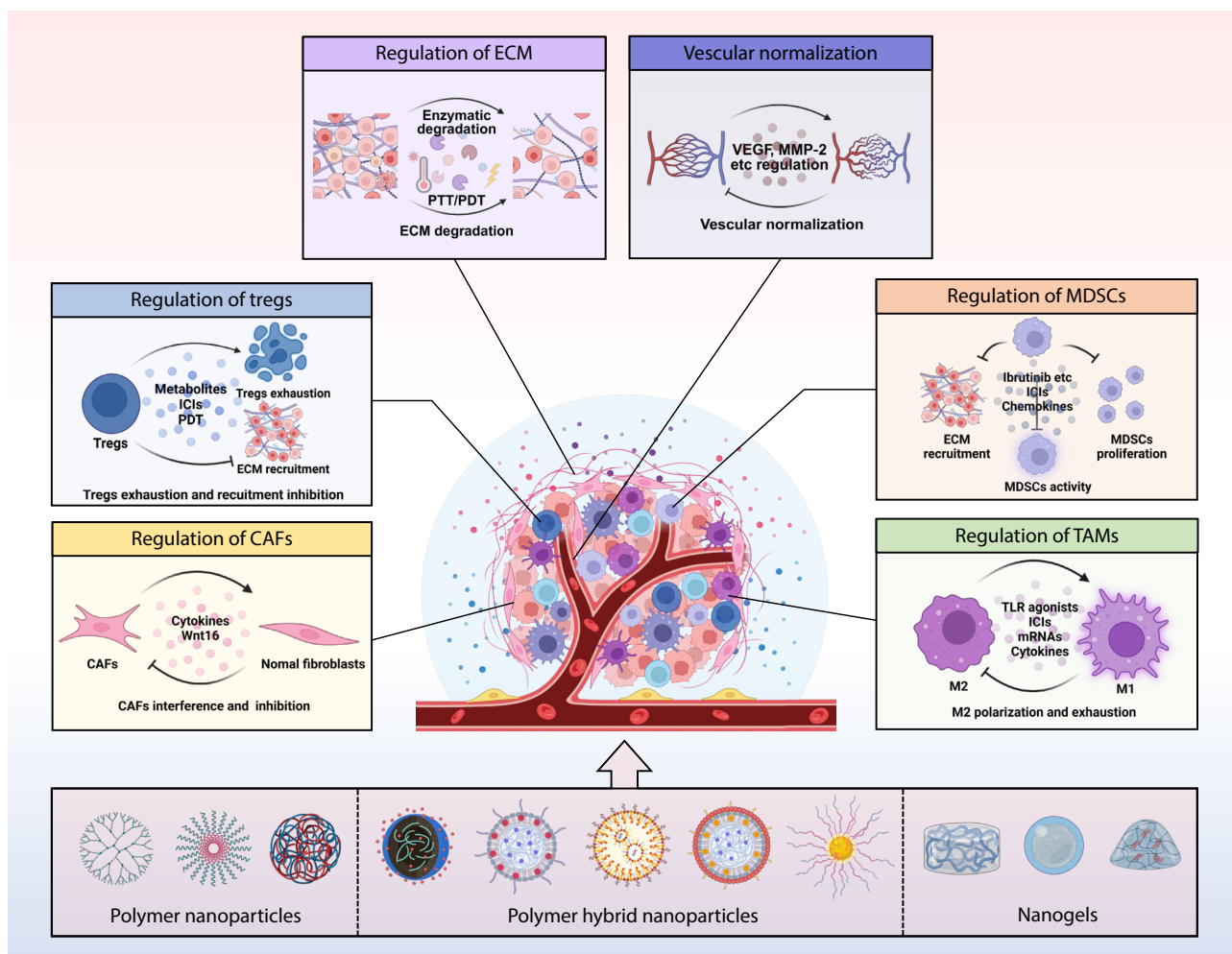
2 POLYMERIC STRATEGIES FOR MODULATING TME STROMAL CELLS

The TME is characterized by a dense immunosuppressive network, and the typical features of the cold TME include infiltration of M2 macrophages, MDSCs, Tregs, and CAF; downregulation of pro-inflammatory signals accompanied by elevated immune inhibitory molecules; hypoxic stress that impairs immune cell function; and disordered glucose, lipid, and amino acid metabolism.^[7,17,18] Thus, reprogramming this immunosuppressive status by targeting heterogeneous stromal components has emerged as a promising therapeutic approach. Reversing this immunosuppressive status through modulation of stromal cells represents a critical therapeutic strategy. Among the various stromal populations, tumor-associated macrophages (TAMs) constitute up to 50% of the tumor mass and promote progression by secreting immunosuppressive mediators, trophic factors, and invasion-facilitating enzymes.^[19–21] TAMs also inhibit T cell activation and induce regulatory T cell differentiation. Consequently, polymeric nanomedicines have been extensively developed to regulate stromal cells and remodel the immunosuppressive TME.

2.1 Reprogramming TAMs

Macrophages exhibit high phenotypic plasticity and are typically polarized into two functionally distinct subsets: pro-inflammatory (M1) and pro-tumor (M2). M1 macrophage polarization is induced by pathogen-associated molecular patterns (PAMPs) and cytokines (Interleukin-2 (IL-2), IFN- γ , and TNF- α) during type 1 immunity, whereas M2 polarization is triggered by IL-4 and IL-13 during type 2 immunity.^[22] Phenotypically, M1 macrophages overexpress CD80, CD86, and MHC II, whereas M2 macrophages overexpress CD68, CD163, and CD206 on the cell surface.^[23] Functionally, M1 macrophage polarization is associated with macrophage-dependent tumor killing, whereas M2 polarization suppresses inflammation, which may support tumor progression. Thus, emerging polymeric nanomedicine therapies aim to deplete M2 macrophages or reprogram them to M1-phenotype macrophages.

Han *et al.* reported that vitamin C-loaded lipid nanoparticles (LNPs) consisting of lecithin poly(ethylene glycol) (PEG)-modified poly(lactic-co-glycolic acid) (PLGA) can efficiently induce oxidative toxicity and polarization of M1 macrophages in the TME for intensive immune checkpoint blocking therapy (Fig. 1a). Although Vitamin C (Vc) is an essential dietary nutrient, it may promote M1 macrophage polarization induced by H₂O₂.^[24] Some small-molecule traditional Chinese medicines have unique advantages in terms of immune modulation. Polymeric delivery carriers can effectively regulate the macrophage phenotype. Cao *et al.* derived EVs from ginseng (GDNP) to alter M2-like polarization, both *in vitro* and *in vivo*, to promote cancer immunotherapy. GDNP-induced M1 polarization was found to depend on Toll-like receptor (TLR)-4 and myeloid differentiation antigen 88 (MyD88)-mediated



Scheme 1 Immunosuppressive signals in the TME and their reprogramming strategies by polymeric nanomedicines. Created with BioRender.com.

signaling.^[25] Ruan *et al.* synthesized snowman-like tumor-targeting PLA/shellac-FA dimer nanoparticles (NPs) composed of paclitaxel (PTX) and curcumin (CUR). These engineered nanocarriers effectively reduced the proportion of TAMs in lymphocytes and reprogrammed M1/M2 polarization (Fig. 1b).^[26] Evidence suggests that curcumin modulates macrophage phenotypes by inhibiting the monoamine oxidase A/signal transducer and activator of transcription 6 (MAO-A/STAT6) signaling pathway. This represents a critical signaling axis involved in M2 macrophage polarization, which is driven by interleukin-4/interleukin-13 (IL-4/IL-13) secreted by tumor cells and fibroblasts.^[27]

Tumor suppression through macrophage phenotypic modulation can be achieved using two strategies: inhibiting the signaling pathways that promote the M2 phenotype or activating the pathways that drive M1 macrophage polarization. In this context, the nuclear factor kappa-B (NF- κ B) pathway plays a crucial role in the regulation of M1 macrophage polarization. TLR agonists are potent drivers for repolarizing TAMs from the pro-tumor M2 phenotype to the anti-tumor M1 phenotype. To ensure precise delivery and minimize systemic toxicity, various polymeric nanocarriers have been engineered to encapsulate the TLR7/8 agonists. For instance, Liu *et al.* utilized a radiosensitive peptide hydrogel (Smac-TLR7/8

hydrogel) for localized delivery to regulate TAMs repolarization (Fig. 1c), whereas Santos *et al.* designed peptide-guided lignin nanoparticles that carry TLR7/8a targeting CD206⁺ M2-TAMs in the TME of an aggressive triple-negative *in vivo* model of breast cancer. Furthermore, Shao *et al.* developed a mannose-decorated dendrimeric nanoscaffold with imidazoquinoline (IMDQ) capable of crossing the blood-brain barrier (BBB) to target M2-TAMs in glioblastoma, which improved the cytotoxic effects (Fig. 1d).^[28–30]

Cytokine-based polymeric nanosystems can also enable precise TAM regulation. Interleukin-2 (IL-12), a potent pro-inflammatory cytokine, promotes T helper cell type 1 (Th1) differentiation and T cell-mediated tumor killing.^[31] Chen *et al.* used HA-coated, mannan-conjugated MnO₂ particles to increase tumor oxygenation, modify pro-tumoral M2 TAMs to pro-inflammatory, anti-tumor M1 macrophages, and down-regulate hypoxia-inducible factor-1 α (HIF-1 α) and vascular endothelial growth factor (VEGF) in the tumor. In addition, MnO₂ NPs were designed for delivery to hypoxic regions by taking advantage of the hypoxic properties of tumor regions with high TAM accumulation.^[32] Shen *et al.* further designed a cationic polymer gene-delivery vector, poly[N-[2-(acryloyloxy) ethyl]-N-[p-acetyloxyphenyl]-diethylammonium chloride], to deliver the IL-12 plasmid. This vector efficiently transfected

both cancer cells and TAMs, turning them into local "factories" for sustained IL-12 production. The delivered IL-12 efficiently activates anti-tumor immune responses and remodels the TME, for example, by increasing the intratumoral M1/M2 macrophage ratio by more than fourfold.^[33]

Following the clinical success of messenger ribonucleic acid (mRNA) vaccines, mRNA-based polymeric nanomedicines have emerged as powerful tools for TAM reprogramming. Stephan *et al.* developed injectable polymeric nanoparticles delivering *in vitro*-transcribed mRNA encoding M1-polarizing factors, such as interferon regulatory factor 5 (IRF5) and its activating kinase (IKK β), to regulate TAM (Fig. 1e). In ovarian cancer, metastatic melanoma, and glioblastoma models, this nanosystem reduces M2-TAM density in tumors.^[34] Weiss *et al.* similarly used lipid-polymer hybrid nanoparticles (LNPs) to encapsulate RNA-encoded IL-12; intratumoral injection induces high IL-12 expression, activates type I interferon responses, and triggers immunogenic cell death (ICD), transforming the TME into an inflamed "hot" state and priming systemic anti-tumor immunity.^[35]

In summary, as the most abundant immune cell subset in the TME, macrophages play an indispensable regulatory role in anti-tumor immune responses. Currently, macrophage modulation strategies have gradually evolved from single-pathway modulation mediated by small-molecule drugs to more precise molecular approaches, such as mRNA delivery and gene editing. The success of these innovative strategies often relies on the continuous optimization and upgrading of polymeric nanoparticle-based targeted delivery systems. In the future, such precise macrophage regulatory strategies integrated with polymeric nanocarriers will become more efficient, offering greater potential for clinical translation.

2.2 Depleting and Differentiating MDSCs

In addition to macrophages, MDSCs represent another major immunosuppressive population within the TME, which requires effective modulation. MDSCs represent a heterogeneous population of immature myeloid cells that play a pivotal role in maintaining normal tissue homeostasis against systemic insults, such as infection and traumatic stress under physiological conditions. MDSCs have been divided into polymorphonuclear myeloid-de-

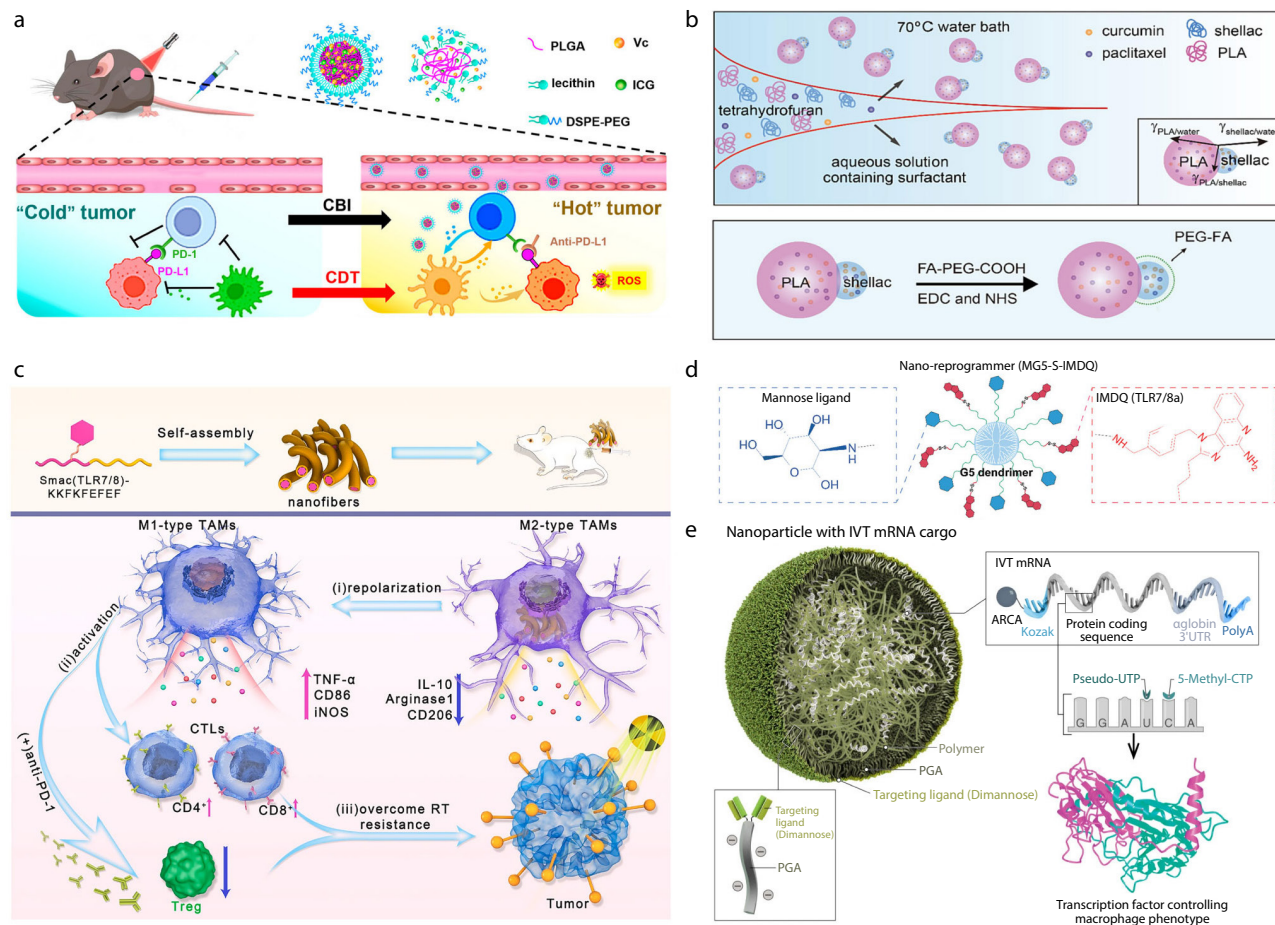


Fig. 1 Strategy of TAM regulation by polymeric nanomedicine: (a) Vitamin C-loaded LNPs for inducing the polarization of M1 macrophages in the TME (Reproduced with permission from Ref. [24]; Copyright (2022), American Chemical Society.); (b) Curcumin (CUR) nanoparticles reduce the proportion of TAMs in lymphocytes (Reproduced with permission from Ref. [26]; Copyright (2023), Elsevier B.V. All rights reserved.); (c) Toll like receptor agonist TLR7/8a to regulate TAMs repolarization from M2 type into M1 type (Reproduced with permission from Ref. [28]; Copyright (2021), The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co., Ltd.); (d) Imidazoquinoline (IMDQ) nanoparticles (MG5-S-IMDQ) penetrate BBB and selectively target M2-TAMs in the GBM (Reproduced with permission from Ref. [30]; Copyright (2025), Wiley-VCH GmbH.); (e) mRNA encoding IRF5 and IKK β to regulate TAM (Reproduced with permission from Ref. [34]; Copyright (2019), The Author(s)).

rived suppressor cells (PMN-MDSCs), which promote immune evasion in the early stage of tumor development, and monocytic MDSC (M-MDSCs), which further support tumor progression by promoting angiogenesis and metastasis in the later stage of the tumor.^[36–38] During tumor progression, the recruitment and spread of MDSCs is regulated by the TME, tumor-derived cytokines, and chemokines. Studies have shown that MDSCs and inflammatory monocytes are recruited to primary tumor tissues via the chemokines CCL1, CCL2, and CCL5. During tumor metastasis, MDSCs accumulate in the pre-metastatic niche through CXCL1 CXCL2 CXCL5 and S100A8/9,^[39] and construct a pre-metastatic niche with other stromal cells. Once localized in the TME, MDSCs exert their immunosuppressive and pro-metastatic functions through multiple mechanisms, downregulating IFN- γ to establish local immune tolerance and secreting matrix metalloproteinase 9 (MMP9) to promote vascular heterogeneity and tumor cell invasion.^[40] Targeting MDSCs to alleviate their immunosuppressive properties has emerged as a promising therapeutic strategy to enhance the efficacy of immune checkpoint inhibitors (ICIs) in cancer immunotherapy. This strategy can effectively enhance anti-tumor immune responses by synergizing with cancer vaccines. The core strategies for MDSC modulation in the TME and lymphoid organs include inhibiting their recruitment, blocking their differentiation and expansion, and abrogating their immunosuppressive functions.^[41]

Several FDA-approved drugs, such as gemcitabine, all-trans retinoic acid, curcumin, and ibrutinib, have been approved to reverse MDSC-mediated immunosuppression; however, the long-term use of free drugs leads to drug resistance, and the delivery efficiency *in vivo* is severely compromised by poor solubility and non-specific distribution. To address these limitations, polymeric nanomedicines have been engineered to encapsulate these drugs for targeted delivery to MDSCs, thereby significantly enhancing their bioavailability and therapeutic efficacy. Chen *et al.* described a strategy to formulate a Gem analog, gemcitabine monophosphate (GMP), into lipid-coated calcium phosphate (LCP) nanoparticles (LCP-GMP), which could effectively deplete MDSCs and inhibit tumor growth.^[42] All-trans retinoic acid (ATRA) is a classic small molecule that drives the differentiation of MDSCs into mature non-immunosuppressive myeloid cells. Zhou *et al.* used ATRA to target MDSCs in tumor-bearing mice and discovered that tumor-inflating programmed death-ligand 1⁺ (PD-L1⁺) MDSCs were more prevalent in cervical cancer patients. Blockade of PD-L1 expression in MDSCs with anti-PD-L1 antibody did not directly relieve the suppressive activity of MDSCs toward HeLa cells, whereas ATRA efficiently abrogated the suppressive activity of MDSCs.^[43] Ibrutinib, a dual inhibitor of Bruton's tyrosine kinase (BTK) and interleukin-2-inducible kinase (ITK), approved for chronic lymphocytic leukemia (CLL) treatment, has been shown to reduce MDSC accumulation in the spleen and tumor tissues of treated mice.^[44] Deng *et al.* synthesized nanocomplexes modified with a sialic acid (SA)–stearic acid conjugate on the surface to encapsulate IBR for targeted immunotherapy (Fig. 2a). An amphiphilic egg phosphatidylglycerol (EPG) structure and strong IBR-EPG interactions resulted in a high IBR-loading capacity and prolonged blood circulation. Thus, IBR-EPG effectively delivered IBR to the tumor, facilitating the subsequent inter-

nalization of IBR by TAMs through SA-mediated active targeting. This nanoplateform polarizes TAM phenotype and has the potential to downregulate MDSCs.^[45]

In addition to removing excess MDSCs or promoting their phenotypic differentiation, pharmacological strategies targeting the chemotaxis of MDSCs have also been developed to inhibit the invasion and migration of tumor cells. Florindo *et al.* combined cancer vaccines with an anti-programmed cell death protein 1 antibody (α PD-1), anti-OX40 antibody (α OX40), and ibrutinib for immunotherapy against melanoma-bearing mice. Groups administered either PD-1/OX40 + ibrutinib or trivalent treatment (man-NP+PD-1/OX40+ibrutinib) had significantly decreased tumor volumes (Fig. 2b).^[46] Pseudo-neutrophil cytokine sponges (pCSs) are covered with neutrophil plasma membranes that phenotypically and morphologically resemble polymorphonuclear MDSCs (PMN-MDSCs) (Fig. 2c). An *in vivo* study indicated that pCSs can suppress the expansion and trafficking of MDSCs and efficiently disrupt tumor progression.^[47] Particularly, antibodies such as anti-CXCR2 and anti-PD-1 have been shown to reduce the recruitment of MDSCs. In addition, MDSC-induced immunosuppression may be prevented by controlling the metabolism of L-arginine by enzymes such as ARG1 and NOS2.^[48] Alonso *et al.* created multilayer polymer nanocapsules to transport the chemokine CCL2 and two distinct RNAi sequences, shC/EBP and miR142-3p, which affect the CCAAT/enhancer-binding protein beta (C/EBP β) pathway (Fig. 2d). In MCA-203 fibrosarcoma tumor-bearing mice, the nanomedicine decreased C/EBP levels in MDSCs and monocyte differentiation into TAMs.^[49]

In conclusion, the modulation of MDSCs through polymeric nanomedicines effectively disrupts the immunosuppressive barrier, significantly enhancing the therapeutic efficacy of immunotherapies, such as immune checkpoint blockade and cancer vaccines. This approach also provides a strong foundation for the development of an integrated nanoplateform aimed at TME.

2.3 Inhibiting Tregs

Tregs, a CD4⁺ T cell subset that specifically expresses the transcription factor forkhead box P3 (FoxP3), play a pivotal role in regulating host immunity while mediating tumor immune resistance.^[50] As a "double-edged sword," Tregs maintain immune homeostasis by restricting the activation and proliferation of effector T cells, thereby preventing autoimmune disorders such as rheumatism.^[51] However, in the context of tumor progression, Tregs emerge as a central mediator of immunotherapy resistance, primarily by suppressing the function of activated immune cells, including dendritic cells (DCs) and macrophages.^[52] Accumulating evidence has confirmed that Treg infiltration within the TME promotes tumor growth and metastasis, ultimately leading to poor prognosis and reduced survival rates in patients.^[53]

To optimize Treg reprogramming or inhibit their immunosuppressive activity, extensive studies have deciphered the underlying mechanisms: (1) Tregs infiltrate DC niches to hinder DC maturation and priming, downregulate the expression of co-stimulatory molecules CD80 and CD86 on DC surfaces, and suppress macrophage pro-inflammatory responses while promoting their polarization toward the M2 pheno-

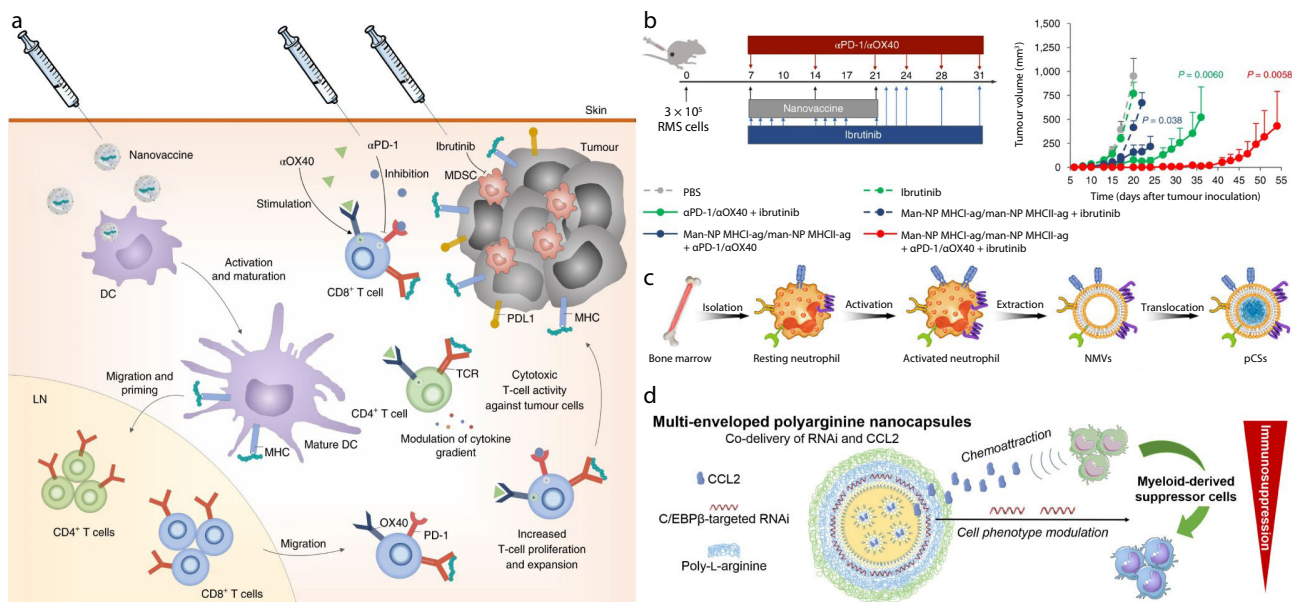


Fig. 2 Strategy of MDSCs regulation by polymeric nanomedicine: (a) IBR-EPG effectively delivered IBR to the tumor and downregulate MDSCs (Reproduced with permission from Ref. [45]; Copyright (2019), Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.); (b) Nanomedicines composed of multi-antibodies and ibrutinib effectively impair MDSCs tumor accumulation (Reproduced with permission from Ref. [46]; Copyright (2019), The Author(s), under exclusive licence to Springer Nature Limited.); (c) pCSs covered with neutrophil plasma membranes that resemble polymorphonuclear MDSCs phenotypically and morphologically (Reproduced with permission from Ref. [47]; Copyright (2020), American Chemical Society.); (d) Multilayer polymeric nanocapsules co-encapsulating CCL2, shC/EBP and miR142-3p effectively reduced C/EBP expression levels in MDSCs (Reproduced with permission from Ref. [49]; Copyright (2018), Elsevier B.V. All rights reserved.).

type;^[54] (2) Tregs highly express CD25 on their surface, which specifically binds interleukin-2 (IL-2) to block the interaction between IL-2 and effector T cells, resulting in effector T cell apoptosis;^[55] (3) T Tregs can directly kill effector T cells *via* the FasL-Fas signaling pathway or the secretion of granzyme B and perforin;^[56] (4) Tregs prevent effector T cell activation by sequestering anti-inflammatory cytokines IL-10 and transforming growth factor β (TGF- β), and promote angiogenesis by secreting VEGF. (5) Metabolically, Tregs express CD39 and CD73 on their surface, which catalyze the conversion of extracellular ATP to adenosine, an immune regulator that suppresses DC maturation.^[57]

The upregulation of immunosuppressive receptors or ligands on tumor and immune cells induces T cell exhaustion, suppresses T cell proliferation, and facilitates Treg infiltration.^[58] Thus, immune checkpoint blockade or gene knockout of checkpoints represents a promising strategy for Treg modulation. Jaafari *et al.* utilized liposomes as small interfering ribonucleic acid (siRNA) carriers to silence PD-1 expression in T cells, enhancing the siRNA targeting efficiency. In B16F10 tumor-bearing mice, siPD-1-loaded liposomes reduced Treg infiltration in the TME, while increasing the infiltration of T-helper 1 (Th1) and cytotoxic T cells.^[59] Compared with PD-1 and CD25, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a Treg-specific immune checkpoint that interacts with CD80 and CD86 ligands on DCs to inhibit their activation. Blockade or knockout of CTLA-4 can reduce unnecessary systemic inflammation while reprogramming the tumor immune microenvironment (TIME).^[60] Wang *et al.* constructed nanoparticles to transport the siRNA of cytotoxic T lymphocyte-associated molecule-4 (CTLA-4) (NPsiCTLA-4) with

efficient *in vivo* T cell penetration. In a B16F10 animal model (Fig. 3a), NPsiCTLA-4 treatment enhanced T cell activation and proliferation, significantly increasing the proportion of anti-tumor CD8⁺ T cells and decreasing the Treg ratio among tumor-infiltrating lymphocytes (TILs).^[61] An appealing strategy for activating host anti-tumor immunity is to target Tregs. It is necessary to specifically target intratumoral Tregs because they are present in many different organs and are important for preserving immunological homeostasis.^[62] A nanoparticle modified by tLyp1 was created by Kim *et al.* to target Treg cells in the TME. This hybrid nanoparticle improved the effects of imatinib by decreasing Treg cell suppression through the inhibition of STAT3 and STAT5 phosphorylation (Fig. 3b). When combined with checkpoint blockade using an anti-CTLA-4 antibody, an *in vivo* analysis demonstrated that the nanoparticles accumulate highly in tumors, which accelerates intratumoral CD8⁺ T cells and prolongs survival rate, improves tumor inhibition, reduces Treg cells, and reduces tumor progression.^[63]

Nanomedicine is often used to encapsulate metabolic regulatory drugs to regulate Tregs, realizing the precise delivery of medicines to the TME and longer circulation time.^[64] Kyoung *et al.* encapsulated fenofibrate into amphiphilic poly glutamic acid-based nanoparticles (F/ANs), and the nanoparticle interfaces were engineered with an anti-CD3e f(ab')₂ segment to target T cells (Fig. 3c). Under glucose-deficient conditions, aCD3/F/AN-treated T cells exhibited obvious mitochondrial cristae, membrane potential, and mitochondrial oxygen consumption rate. The proliferation of T-cells in a glucose-deficient environment that mimics the TME is supported by the activation of fatty acid metabolism by anti-CD3e

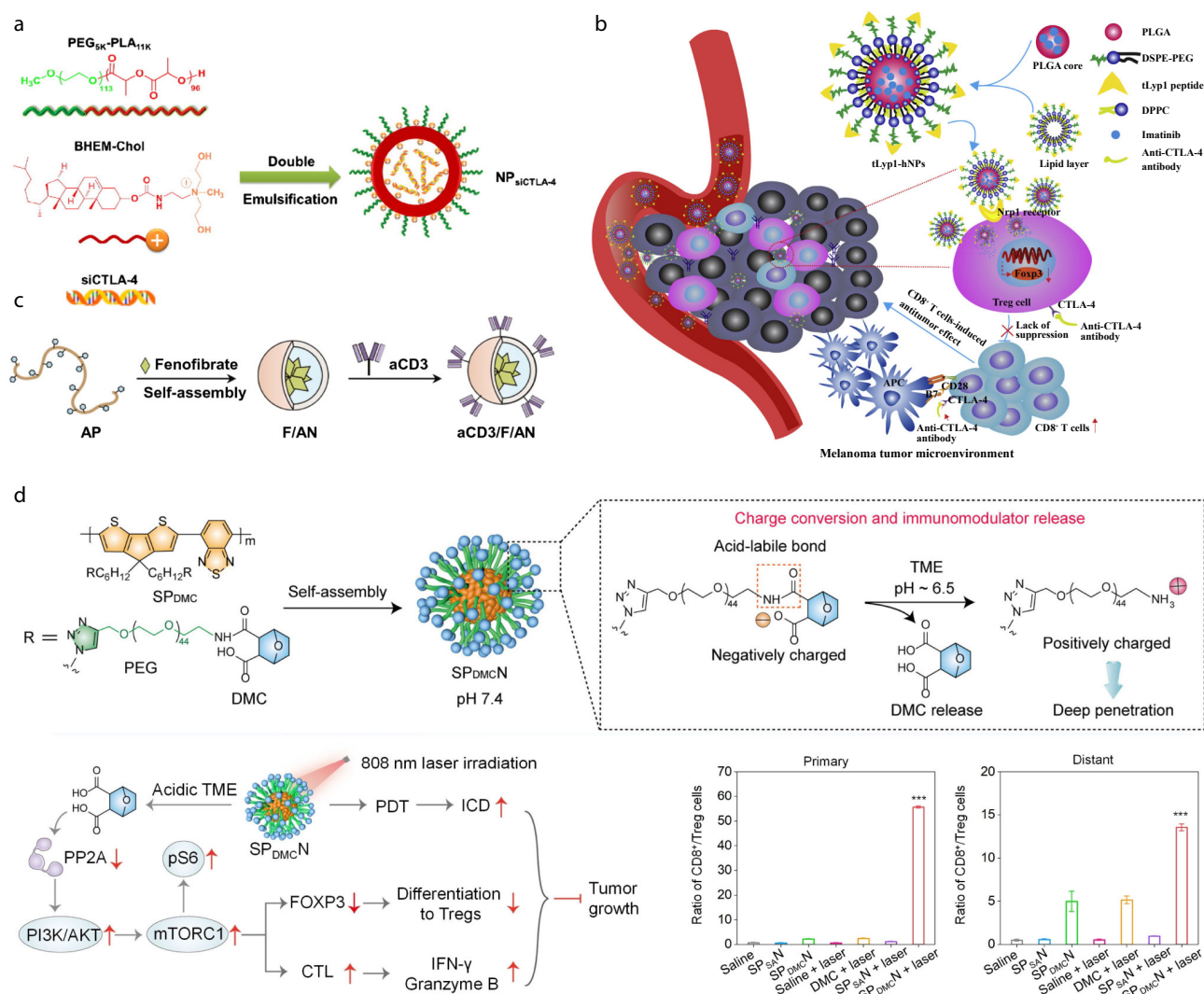


Fig. 3 (a) CTLA-4-siRNA-loaded nanoparticles (NPsiCTLA-4), which can efficiently penetrate into T cells, significantly facilitate T cell activation and proliferation (Reproduced with permission from Ref. [61]; Copyright (2016), Elsevier B.V. All rights reserved.); (b) tLyp1 peptide-conjugated hybrid nanoparticles for targeting Treg cells in TME and enhancing the effect of imatinib in downregulating Treg cell suppression (Reproduced with permission from Ref. [63]; Copyright (2018), Published by Elsevier B.V.); (c) Anti-CD3ε f(ab')₂-modified, fenofibrate-loaded poly(γ-glutamic acid) nanoparticles (aCD3/F/ANs) regulate mitochondrial morphology oxygen consumption rate in T cells under glucose deprivation (Reproduced with permission from Ref. [65]; Copyright (2021), The Author(s).); (d) A charge-reversal polymer nano-modulator (SP_{DMCN}) conjugating an immunomodulator (demethylcantharidin, DMC) activated TME inhibits protein phosphatase 2 (PP2A) activity and decreases Tregs differentiation (Reproduced with permission from Ref. [68]; Copyright (2021), Wiley-VCH GmbH.).

f(ab')₂ fragment-modified and fenofibrate-encapsulated amphiphilic nanoparticle (aCD3/F/ANs). This may ultimately transform Tregs or other exhausted T cells into cytotoxic T cells that kill melanoma cells.^[65] Xu *et al.* discovered that HPβCD facilitated the active loading of UA-liposomes. In plants and fruits, ursolic acid (UA) is a strong triterpenoid molecule that can modulate important cell signaling pathways, including STATs, NF-κB, and TRAIL. By preventing STAT5 phosphorylation and IL-10 release, CD4⁺CD25⁺Foxp3⁺ T cells were successfully modified in 4T1 tumor-bearing mice. This ultimately resulted in fewer MDSCs and Tregs persisting in the tumor tissues, which repaired the tumor-mediated immunosuppressive milieu.^[66]

Photodynamic therapy (PDT) combined with nanomedicines can also effectively inhibit Treg function.

Tang *et al.* developed TPE-BT-BBTD nanoparticles conjugated with anti-programmed death-ligand 1 (αPD-L1) on the surface to regulate Tregs in the TME. αPD-L1@TPE-BT-BBTD exhibited precise tumor accumulation and a higher immunosuppression reversal capability. Moreover, TPE-BT-BBTD has an absorption wavelength of 980 nm, which facilitates second near-infrared window (NIR-II) imaging-guided synergistic modulation of TME.^[67] A charge-reversal polymer nano-modulator (SP_{DMCN}) was developed by Pu *et al.* for photodynamic immunotherapy of cancer (Fig. 3d). The immunomodulator (demethylcantharidin, DMC) was conjugated to the side chains of the photodynamic polymer *via* an acid-labile linker. Upon photoirradiation, SP_{DMCN} generated abundant reactive oxygen species (ROS), induced ICD generation, and activated DCs, while DMC's phosphatase 2 (PP2A) inhibitor was

cleaved from the side chain in the TME, which inhibited Treg differentiation.^[68]

2.4 Inactivating CAFs

CAFs, a heterogeneous and complex cell population within the TME, promote tumor progression by secreting ECM proteins and basement membrane components, which in turn modulate the differentiation and functional activation of other immune cells and impair anti-tumor immunological responses. VEGFs, a key pro-angiogenic cytokine secreted by CAFs, drives tumor angiogenesis and fuels tumor development. Moreover, the abnormal ECM microenvironment shaped by CAFs, which is characterized by low oxygen tension, elevated interstitial fluid pressure, and aberrant alterations in ECM components, also creates a favorable niche for tumor growth and metastasis. CAFs are recognized as major immunosuppressive cell populations that infiltrate the TME.^[69] They not only crosstalk with other tumor-associated immunosuppressive cells *via* cytokine signaling but also are the primary source of microenvironmental barrier components in the TME. Therefore, we discuss CAFs as the final segment of stromal cell regulation, serving as a critical transitional node between the modulation of immunosuppressive immune cells and remodeling of the physical immune microenvironmental barrier in the TME.

Chen *et al.* developed salvinolic acid-B-loaded PEGylated liposomes (PEG-SAB-Lip) to inhibit CAF activation by suppressing TGF- β secretion. *In vivo* studies demonstrated that PEG-SAB-Lip treatment markedly upregulated the expression of Th1 cytokines and chemokines (CXCL9 and CXCL10), thereby effectively recruiting CD4⁺ T cells, CD8⁺ T cells, and M1-polarized macrophages into the tumor site, while downregulating the expression of Th2 cytokines and chemokines (CXCL13). The abundance of MDSCs, Tregs, and M2 macrophages was significantly reduced alongside CAF inactivation.^[70] He *et al.* engineered a multifunctional size-switchable nanoparticle, dendrigraft poly-L-lysine (DGL)/gemcitabine (GEM) @PP/gemcitabine (GA), which achieved deep tumor penetration and CAF-specific modulation. In stroma-rich pancreatic and breast cancer models, this nanoparticle responds to the overexpression of matrix metalloproteinase-2 (MMP-2) in the TME to release GEM-conjugated small DGL/GEM nanoparticles while retaining large 18 β -GA-loaded PP/GA nanoparticles at the tumor site (Fig. 4a). The released DGL/GEM nanoparticles penetrated deep into the tumor parenchyma and intracellularly released GEM to exert direct cytotoxic effects on tumor cells. In contrast, residual GA-loaded PP/GA nanoparticles accumulated around the tumor vasculature and were selectively internalized by CAFs, which in turn inhibited the secretion of Wnt16, a crucial drug resistance-related (DRP) protein.^[71] Huang *et al.* demonstrated that quercetin, a natural dietary flavonoid, potently suppressed Wnt16 expression in activated CAFs, leading to a significant reduction in CAF abundance and interstitial collagen deposition in the TME (Fig. 4b). Based on this finding, they developed a tailored lipid/calcium/phosphate nanoparticle formulation with high loading efficiency for quercetin phosphate, the prodrug of quercetin. In a stroma-rich bladder cancer model, quercetin phosphate-loaded nanoparticle exhibited a robust synergistic anti-tumor effect when combined with cisplatin-loaded nanoparticles.^[72]

3 OVERCOMING PHYSICAL BARRIERS: REMODELING ECM AND VASCULAR NORMALIZATION

The biological barrier in the TME hinders the deep penetration of nanodrugs. First, despite abundant peritumoral blood vessels, the central regions of the tumors lack sufficient blood vessels. Second, vascular density decreases with tumor progression. Angiogenesis helps tumors to generate blood vessels in the center; however, the vascular structure is heterogeneous, which slows the tumor blood flow and confines the infiltration of nanoparticles deep inside the tumor. Consequently, the extratumoral matrix pores shrink sharply and the internal pressure is high, preventing the infiltration of drugs and immune cells.^[73] Therefore, reprogramming the tumor ECM or blood vessels has been targeted to increase the penetration and distribution of nanomedicines.

3.1 Degradation and Remodeling of the ECM

The ECM is another main component of the immune microenvironment, which acts as a nest where tumors and associated cells grow, multiply, and communicate with each other. Generally produced by stromal fibroblasts, the matrix, such as highly cross-linked hyaluronic acid and collagen, severely hinders the penetration of nanoparticles into the TME. Owing to the high intratumoral interstitial pressure and thick ECM interactions with stromal cells in the TME,^[74] many nanoparticles were stuck in the perivascular areas and were unable to directly interact with tumor cells.^[75] Thus, regulation of the ECM holds great potential for TME reprogramming and tumor inhibition.

Gao *et al.* developed a two-step sequential delivery approach for pancreatic cancer therapy. The nanopatform was developed by incorporating gemcitabine (GEM) and a pH (low) insertion peptide (pHLIP) into magnetic nanoparticles (GEM-MNP-pHLIP). During the therapy, metformin (MET) was first injected to break down the thick stroma, allowing the GEM-MNP-pHLIP nanoparticles to penetrate deeply into the tumor. This technique significantly increased the treatment effectiveness in subcutaneous and orthotopic tumor mouse models.^[76] Many biological enzymes and factors can promote the tumor penetration of nanoparticles by disrupting the arrangement of the matrix or directly degrading the matrix; therefore, they are often assembled or wrapped in nanoparticles for therapeutic action. Liu *et al.* created DEX-HAase nanoparticles by modifying hyaluronidase (HAase) with dextran (DEX) *via* a pH-responsive traceless linker. DEX-HAase can release natural HAase in an acidic TME and loosen the ECM structure, resulting in the deep penetration of other loading drugs. The efficacy of nanoparticle-based PDT and anti-PD-L1 checkpoint blockade treatment was greatly enhanced after pretreatment with DEX-HAase.^[77] Wang *et al.* created an endogenous stimuli-responsive polypeptide nanoparticle by conjugating mPEG-Peptide1-Promedine and tLyP1-Peptide2-Promedine and incorporating a sequence of poly-cysteine, poly-histidine, and poly-leucine.^[78]

Photothermal and photodynamic therapies are effective means of ablating the TME matrix. Nanoparticles with photothermal effects can overcome the disadvantages of poor permeability and diffusivity of photosensitizers and can deeply dissolve tumor-related matrices.^[79] By using bLP-me-

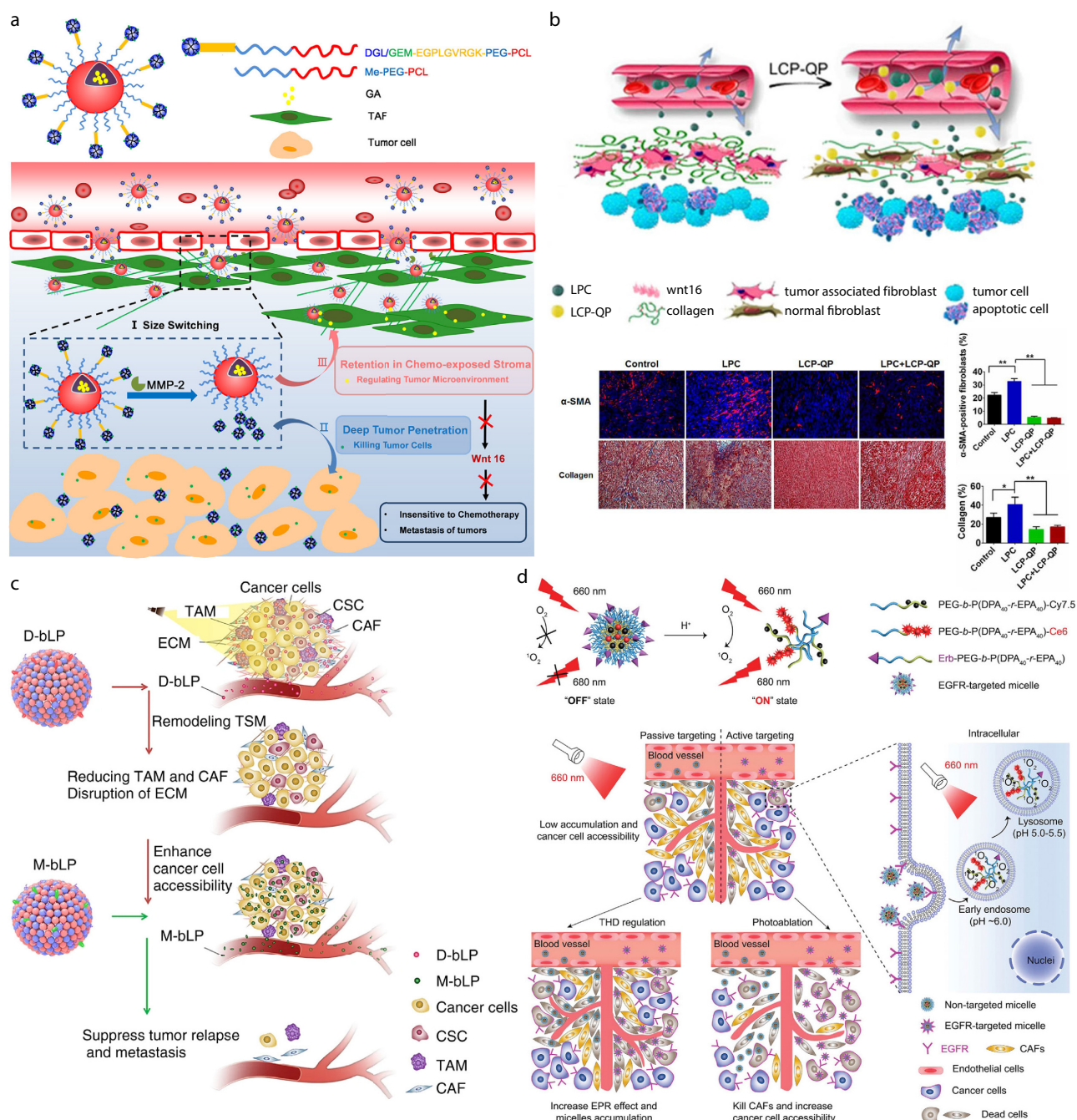
diated photothermal effects, Li *et al.* described a bioinspired lipoprotein (bLP) that can significantly disrupt various stromal cells and ECM components (Fig. 4c). This causes deep penetration of the entire tumor with a 27.0-fold increase in accessibility to cancer cells.^[80] Gelatin nanoparticles containing telmisartan (TM) were coupled with platinum nanoparticles (PtNPs) attached to paclitaxel (PTX) by Shen *et al.* MMP-2, which is overexpressed in the TME, mediates TM release, which further downregulates the expression of TGF- β . Moreover, the photothermal effect of PtNPs successfully ablated the ECM.^[81]

In addition to the traditional methods of enhancing tumor matrix penetration, nanomedicines can penetrate tumor le-

sions through active transcellular transport.^[82] Wang *et al.* fabricated an ultra-pH-sensitive nano-photosensitizer targeting epidermal growth factor receptors for anticancer therapy. *In vivo* studies revealed that nanoparticles facilitated the penetration of drugs into tumor regions. First, nanoparticle-encapsulated thalidomide modulated tumor vasculature. After photoirradiation, the tumor stroma was partially ablated, ensuring the penetration of the medications, which were further internalized via EGFR-mediated endocytosis (Fig. 4d).^[83]

3.2 Normalization and Anti-angiogenesis of Tumor Vasculature

The tumors are highly heterogeneous. In the TME, tumor blood



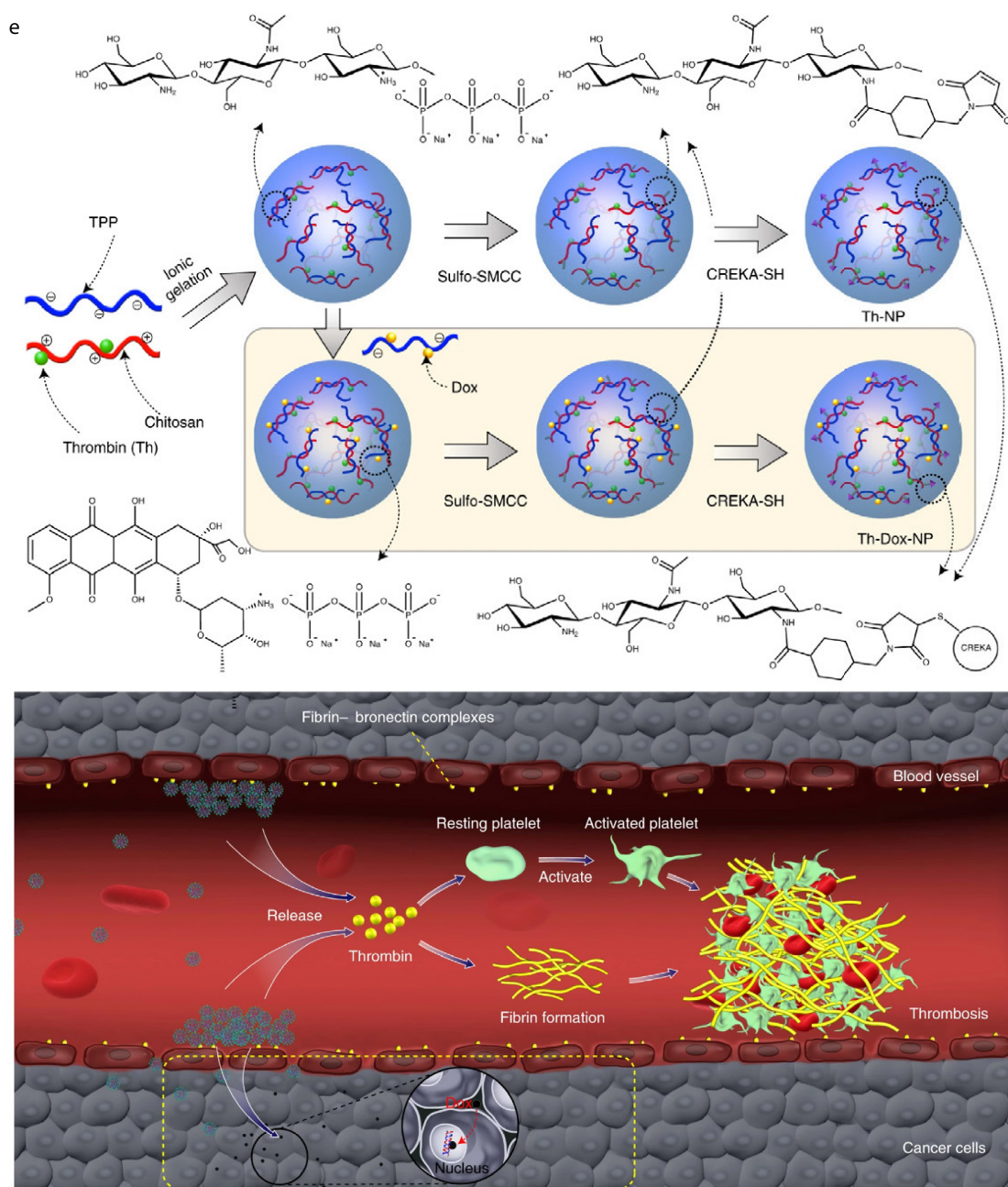


Fig. 4 (a) Size-switchable nanoparticle DGL/GEM@PP/GA for TAF targeting and deep tumor penetration (Reproduced with permission from Ref. [71]; Copyright (2019), American Chemical Society.); (b) Lipid/calcium/phosphate nanoparticles loaded with quercetin downregulate Wnt16 expression, thereby decreasing α -SMA-positive fibroblasts and collagen deposition (Reproduced with permission from Ref. [72]; Copyright (2017), American Chemical Society.); (c) Bioinspired lipoprotein (bLP) that can induce efficient photothermia to remodel tumor stromal microenvironments (TSM) and disrupted the multiple stromal cells and ECM components (Reproduced with permission from Ref. [80]; Copyright (2019), The Author(s).); (d) Tumor vasculature normalization by thalidomide enhances the accumulation of nanoparticles in tumors, which are retained in the tumor stromal bed (Reproduced with permission from Ref. [83]; Copyright (2020), The Authors. Advanced Science published by Wiley-VCH GmbH.); (e) Chitosan-based nanoparticles functionalized with a tumor-homing peptide target fibrin-fibronectin complexes overexpressed on tumor vessel walls and in tumor stroma (Reproduced with permission from Ref. [89]; Copyright (2020), The Author(s), under exclusive licence to Springer Nature Limited.).

vessels are structurally malformed and disorganized, with intercellular gaps often exceeding 100 nm between vascular endothelial cells.^[84] Such leaky vascular walls facilitate invasion and extravasation of tumor cells, thereby promoting tumor metastasis. This abnormal vascular phenotype also enables the efficient penetration of nanoparticles with a diameter of ap-

proximately 100 nm.^[85] To normalize the malformed tumor vasculature, nanomedicines have been widely developed for targeted cancer therapy to normalize the malformed tumor vasculature.

Cisplatin (DDP) was loaded into cRGD-folate-heparin nanoparticles (VE) and patched onto the surface of pro-

tamine (Pro) by Wang *et al.* By controlling the MMP-2/VEGF, AKT/mTOR/MMP-2/Laminin, and AKT/mTOR/EMT signaling pathways, they showed that the self-anti-angiogenesis ability of VE-DDP-Pro was ascribed to VE. This allows chemotherapeutics to successfully suppress the growth and metastasis of ovarian cancer.^[86] Zhang *et al.* developed a combined delivery strategy using cationic liposomes to encapsulate lactate oxidase/catalase (LOx/CAT) and VEGF siRNA (siVEGF) to synergistically suppress tumor proliferation and angiogenesis, followed by coating the nanoparticles with pegylated phenylboronic acid. This co-delivery system enabled the simultaneous release of siVEGF and LOx/CAT at the tumor site. In the 4T1 murine tumor model, lactate depletion and VEGF silencing effectively inhibited tumor progression and metastasis.^[87] Xu *et al.* developed ROS-responsive side-chain selenium-grafted polymers loaded with the photodynamic therapeutic agent Ce6 to form a nanoplatform for potential antiangiogenic therapies. Upon irradiation, ROS were generated quickly by Ce6, which could cleave the C-Se bonds on the side chains of the polymers to form organic selenic acid. The newly formed seleninic acid further downregulated the expression of VEGF and matrix metalloproteinase-2 (MMP-2), synergistically modulating the TME.^[88]

In addition to inhibiting angiogenesis, many researchers have developed nanoplatform-based metabolic regulation methods to block avenues for tumors to obtain nutrients. Nie *et al.* reported a combination of tumor infarction therapy and chemotherapy. Briefly, chitosan-based nanoparticles decorated with a tumor-homing peptide targeting fibrin-fibronectin complexes overexpressed on tumor vessel walls and in tumor stromal cells were synthesized and used to encapsulate the coagulation-inducing protease thrombin and the chemotherapeutic drug doxorubicin (Fig. 4e). This nanomedicine efficiently inhibited tumor growth and lowered tumor recurrence in subcutaneous and orthotopic tumor-bearing mice and rabbits.^[89]

4 REGULATING SOLUBLE SIGNALING AND METABOLIC MICROENVIRONMENTS

4.1 Modulation of Cytokines and Chemokines Networks

Cytokines and chemokines are communicators in the tumor community, mainly through interactions with receptors to achieve signal transduction to regulate the body's immune response. As a subfamily of cytokines, chemokines are responsible for lymphoid tissue growth and immune-cell trafficking. During tumor progression, chemokines can directly target non-immune cells in the TME, including stromal and vascular endothelial cells. Therefore, chemokines are considered crucial predictors of disease progression and have great potential for improving patient prognosis and treatment response. Cytokines and chemokines are also involved in various tumor development processes, including angiogenesis, metastasis, cancer cell proliferation, stemness, and invasiveness (Fig. 5a).^[90] Chemokine secretion has been proven to be frequently altered in the TME, and abnormal chemokine distribution may promote the differentiation and infiltration of immunosuppressive cells (such as Treg cells, MDSCs, and TAMs). Cytokines are a type

of tiny molecular polypeptide generated by diverse cells that may not only collaborate with other cytokines to promote each other in the body but can also block other cytokines, building a complex and orderly cytokine regulation network. Nanomedicine-targeting cytokines are widely used for TME regulation.^[91]

Nanoplatforms have been developed for both cytokine supplementation and chemokine blockade to reshape the immune-supportive TME. Weiss *et al.* used LNPs to encapsulate the mRNA encoding interleukin-12 (IL-12). After a single intratumoral injection of LNP caused significant IL-12 production, type I interferon response activation, and cancer cell ICD, the TME became extremely inflammatory, and systemic anti-tumor immunity was primed as a result.^[35] Liu *et al.* designed a platform for LNPs with clinical approval to encapsulate mRNA encoding BisCCL2/5i, a novel single-domain antibody that binds and blocks CCL2 and CCL5, two important chemokines that encourage TAM infiltration and cause them to polarize toward the cancer-promoting M2-phenotype. This mRNA nanoplatform reduces immunosuppression in the TME and induces the polarization of M2 macrophages toward the anti-tumoral M1 phenotype in a liver cancer model.^[92] Regulatory B cells (Bregs) are a subset of B lymphocytes that exert immunosuppressive functions primarily through the production of IL-10 and other inhibitory cytokines. They suppress anti-tumor immunity by attenuating the cytotoxic activity of Th1 and CD8⁺ T cells. In addition, Bregs can modulate various immune cell subsets, including CD4⁺ T cells, by generating inhibitory mediators such as TGF- β , which encourage the differentiation of CD4⁺ T cells into Tregs, which promote tumor growth (Fig. 5b).^[93] According to previous studies, Bregs invasion is mediated by CXCL13, which is typically expressed by follicular stromal cells, secondary lymphoid tissues, macrophages, follicular dendritic cells, and follicular T cells.^[94] In order to prevent Bregs infiltration and reduce Bregs activity in the TME, Huang *et al.* used lipid-protamine-DNA (LPD) nanoparticles as a delivery system for the CXCL13 trap protein encoding plasmid. This procedure slowed the growth of tumors and controlled epithelial-mesenchymal transition.^[95]

The profound metabolic reprogramming within the TME acts synergistically with the cytokine/chemokine signaling network to enforce a robust immunosuppressive barrier. However, emerging evidence has revealed that profound metabolic reprogramming within the TME acts synergistically with these signaling networks to enforce a robust immunosuppressive barrier. Malignant cells strategically overexpress nutrient transporters, such as GLUT1, to sequester glucose and essential nutrients, which directly impairs the bioenergetic fitness of effector immune cells and their capacity to secrete pro-inflammatory cytokines. Ren *et al.* demonstrated that a DNA-templated nanoassembly delivering GLUT1 inhibitors could effectively alleviate glucose deprivation, thereby restoring the metabolic vigor and IFN- γ secretion of CD8⁺ T cells (Fig. 5c).^[96] Concurrently, the accumulation of metabolic byproducts, such as lactate, not only acidifies the TME but also triggers a self-reinforcing 'metabolic-chemokine loop.' Li *et al.* developed a bioresponsive nanoreactor to deplete intratumoral lactate, which normalizes the tumor vasculature and inhibits the recruitment of suppressive cell subsets

Furthermore, systemic hypoxia and acidity have been identified as key drivers of the chemokine-mediated recruitment of Tregs and MDSCs. To counter this, Guo *et al.* engineered a dual-alleviated nanoregulator that simultaneously neutralized acidity and mitigated hypoxia, leading to a significant increase in effector T-cell infiltration and a reshaped cytokine profile (Fig. 5d).^[98] In the realm of advanced delivery systems, manganese-based hybrid lipid nanoparticles (Mn-LNPs) have emerged as powerful tools for dual-mode regulation. As reported by Li *et al.*, these catalytic LNPs could potentiate circular RNA-based cytokine immunotherapy by providing the necessary metabolic support while maintaining the high-efficiency expression of IL-12.^[99] Integrating these multifaceted strategies, as summarized in the recent landscape of nanomedicine-mediated metabolic modulation, underscores

Currently, the clinical landscape of mRNA-LNP therapeutics has been significantly advanced by personalized neoantigen vaccines, such as Moderna's mRNA-4157 and BioNTech's BNT122, which have demonstrated potent anti-tumor efficacy in ongoing clinical trials. However, the therapeutic outcome of targeting single chemokine axes such as CXCL12/CXCR4 is often limited by innate compensatory mechanisms. Recent findings have indicated that CXCR4 blockade can trigger a metabolic shift in MDSCs, which upregulates lipid metabolism or alternative pathways to sustain their suppressive fitness.^[101] This "metabolic escape" underscores the urgent need for combination therapies. By integrating CXCR4 antagonists with metabolic modulators into a synergistic

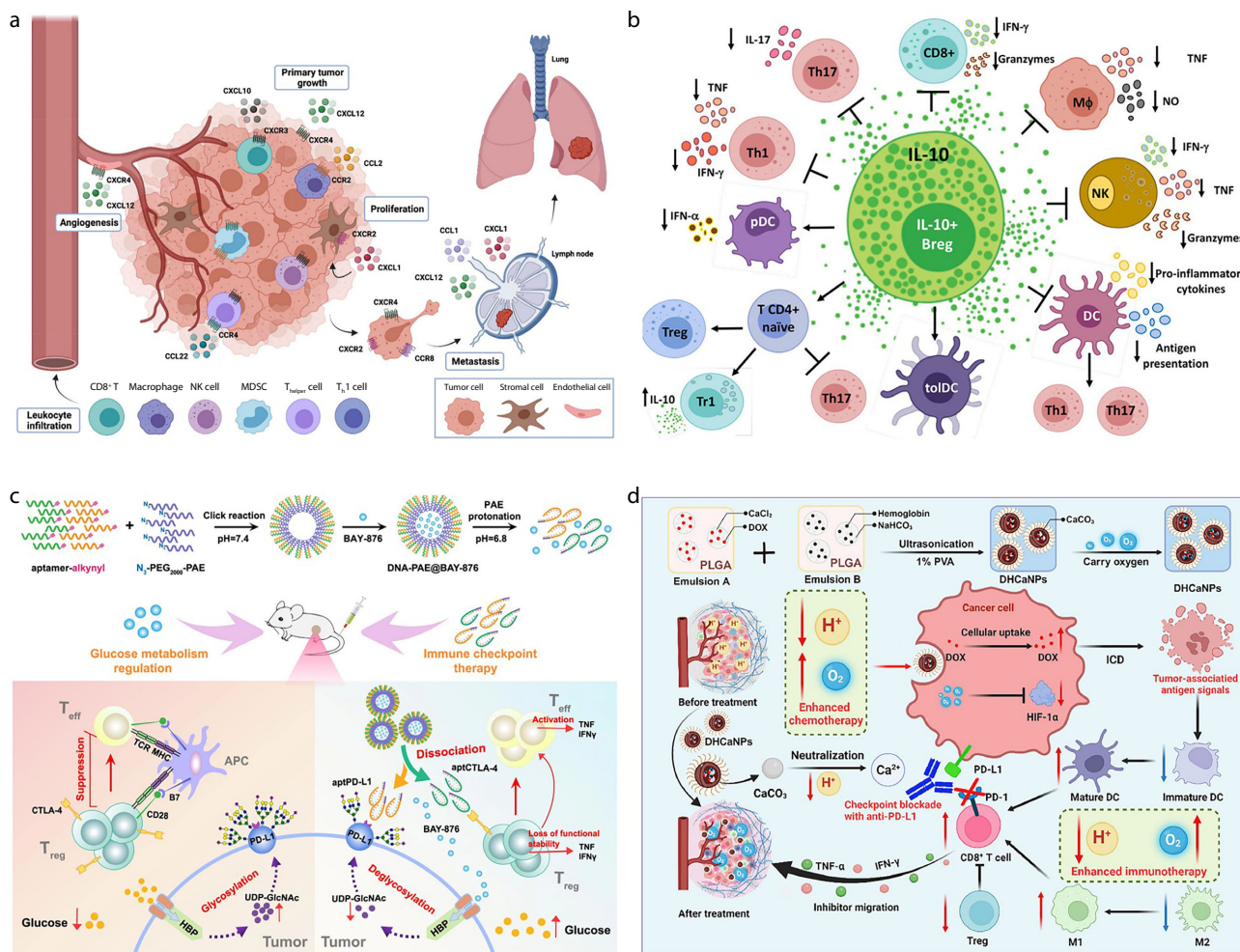


Fig. 5 Interplay between chemokine signaling and metabolic disturbances in shaping a suppressive TME, and nanotherapeutics that remodel the TME and reprogram metabolism to enhance anti-tumor immunity: (a) Multifaceted orchestration of tumor progression by chemokines (Chemokines secreted by tumor, stromal, and immune cells drive four pivotal axes: Immune Remodeling, Tumor Support, Vascular Control.) (Reproduced with permission from Ref. [90]; Copyright (2021), by the authors.); (b) Mechanistic landscape of Bregs-mediated immunosuppression *via* IL-10 (Reproduced with permission from Ref. [93]; Copyright (2021), Catalán, Mansilla, Ferrier, Soto, Oleinika, Aguillón and Aravena.); (c) TME-responsive DNA-PAE@BAY-876 nanoassembly enables pH-triggered release for dual modulation: tumor glycolysis inhibition *via* GLUT1 blockade and restoration of effector T cell metabolic fitness (Reproduced with permission from Ref. [96]; Copyright (2023), The Author(s).); (d) Dual-alleviation nanoregulator neutralizes TME acidity and mitigates hypoxia (Reproduced with permission from Ref. [98]; Copyright (2024), Published by Elsevier B.V. on behalf of Shenyang Pharmaceutical University.).

nanoplatform, these feedback loops can be bypassed and durable immune activation can be achieved.

4.2 Regulation of Chemical and Metabolic Components in the TME

Nanomedicines have been extensively employed to regulate the diverse soluble signaling and metabolic components of the TME. These components, which include ROS,^[102] critical metabolic byproducts such as lactic acid and glucose, abundant glutathione (GSH), and various metal ions, collectively orchestrate a hostile landscape that hampers immune surveillance.^[103] The dysregulation of these factors profoundly affects the pH and redox state of the TME. For instance, the accumulation of lactate owing to the Warburg effect leads to TME acidification. Recent research indicates that as extracellular pH declines, TAMs are prone to polarizing from a pro-inflammatory M1 phenotype into a spindle-shaped, immunosuppressive M2 phenotype. M2 macrophages secrete large amounts of arginase-1, IL-27, and VEGF, creating a permissive niche for tumor evasion while suppressing cytotoxic T lymphocyte (CTL) infiltration.^[104]

To counteract this metabolic immunosuppression, a range of nanoplatforms has been developed. Researchers have designed polymeric platforms to rewrite tumor metabolism by intervening in lactate synthesis. For instance, mitochondria-targeting polymer micelles were developed to deliver dichloroacetate (DCA). Mechanistically, this polymeric nanocarrier specifically accumulates in mitochondria, where DCA inhibits pyruvate dehydrogenase kinase 1 (PDHK1), thereby redirecting pyruvate away from aerobic glycolysis and diminishing lactate generation at the source (Fig. 6a).^[105] The consequent induction of ICD and reduction in the immunosuppressive TME highlighted the potential of polymeric metabolic regulation. However, chemical inhibition alone may not completely reverse the acidic microenvironment. To address this limitation, Sun *et al.* recently constructed a prooxidative lactate-depleting nanoreactor based on semi-permeable polyion complex vesicles (PICsomes). The crosslinked polymeric membrane effectively encapsulated lactate oxidase (LOX) while allowing the influx of the substrate. This polymeric enzymatic system actively consumes intratumoral lactate and converts it to pyruvate and hydrogen peroxide (H₂O₂). This dual-action mechanism not only alleviates the acidic suppression of immune cells but also utilizes the generated ROS to induce ICD, successfully reprogramming M2 macrophages back to the M1 phenotype, and potentiating anti-tumor immunity (Fig. 6b).^[106] Beyond soluble metabolites, the efficacy of immunotherapy is often restricted by dense physical barriers and robust antioxidant defenses. To overcome this physical barrier in desmoplastic tumors such as pancreatic ductal adenocarcinoma, Yang *et al.* engineered polymer-lipid-peptide nanoparticles to deliver lysyl oxidase-like 2 (LOXL2) and discoidin domain receptor 1 (DDR1) inhibitors. By interfering with collagen crosslinking and suppressing MMP1 production, these inhibitors effectively remodeled the aligned stromal fibers, thereby facilitating deep penetration of albumin-bound paclitaxel (nab-paclitaxel) (Fig. 6c).^[107] Once the physical barrier is breached, disrupting the chemical redox balance becomes the next priority. M2 macrophages can sequester endogenous iron, limiting the

generation of pro-inflammatory ROS.^[108] To reverse this and restore redox-mediated immune activation, Zhang *et al.* rationally designed a robust polymeric nanoreactor incorporating a ruthenium (Ru) catalyst within its amphiphilic polymer backbone. This targeted polymeric nanosystem actively catalyzes the oxidation of intracellular GSH to glutathione disulfide (GSSG) in hypoxic tumor cells. The consequent disruption of redox homeostasis initiates a massive buildup of ROS and lipid peroxides, which subsequently activate TRPM2 ion channels to trigger macrophage activation and a systemic immune response (Fig. 6d).^[109] Nevertheless, the therapeutic efficacy of such ROS-based strategies is often compromised by the high concentration of GSH in tumor cells, which scavenges ROS to maintain redox homeostasis. To overcome this, Liu *et al.* developed manganese dioxide (MnO₂)-based sonosensitizers as TME-responsive regulators. Acting as a “redox switch,” the MnO₂ component specifically reacts with excess GSH to generate manganese ions (Mn²⁺), thereby depleting the tumor’s antioxidant defense and sensitizing cancer cells to oxidative stress (Fig. 6e).^[110]

Finally, addressing the twin challenges of tumor hypoxia and acidity remains central to TME regulation. Liu *et al.* rationally synthesized a nanoregulator, PFCE@fCaCO₃-PEG, via the coordination of ferric ions and dopamine-grafted perfluorosulfonic acid. This system integrated a calcium carbonate core with a perfluorocarbon shell. The perfluorocarbon component, which is characterized by high oxygen solubility, functions as an “oxygen nanoshuttle” to alleviate hypoxia-induced radiation resistance. Simultaneously, the nanoparticle acts as a “proton sponge,” neutralizing the acidic TME by reacting with extracellular protons and limiting lactate production (Fig. 6f).^[111] This comprehensive regulation of pH, oxygen, and metabolic factors exemplifies the future direction of nanomedicine in reshaping the immunosuppressive TME.

5 ENGINEERING POLYMERIC THERANOSTIC SYSTEMS FOR ENHANCED CANCER IMMUNOTHERAPY AND IMMUNE STATUS TRACKING

5.1 Polymer Nanocarrier-mediated Synergistic Strategies for Cancer Immunotherapy

Polymer nanomedicines have been widely developed to regulate stromal and immunosuppressive cells in the TME, leading to regression of solid tumors. However, cancer cells can easily evade the immune system rebuilt by nanotherapeutic intervention through various mechanisms such as immunoinhibitory molecule overexpression, antigen recognition restriction, T cell exhaustion, and epigenetic reprogramming. Thus, inadequate nanoplatform-based monotherapy is insufficient for complete tumor regression. Recently, combination nanoplatforms with two or more targets have been extensively investigated for combating tumors while eliminating tumor immune evasion.

In recent years, Tian and his group have been engaged in developing multi-synergistic nanoplatforms through the integration of tumor chemotherapy, gene therapy, immunotherapy, and nanotechnology to overcome multidrug resistance and poor patient response to gene therapy and immunotherapy. For example, an immune cocktail treatment was de-

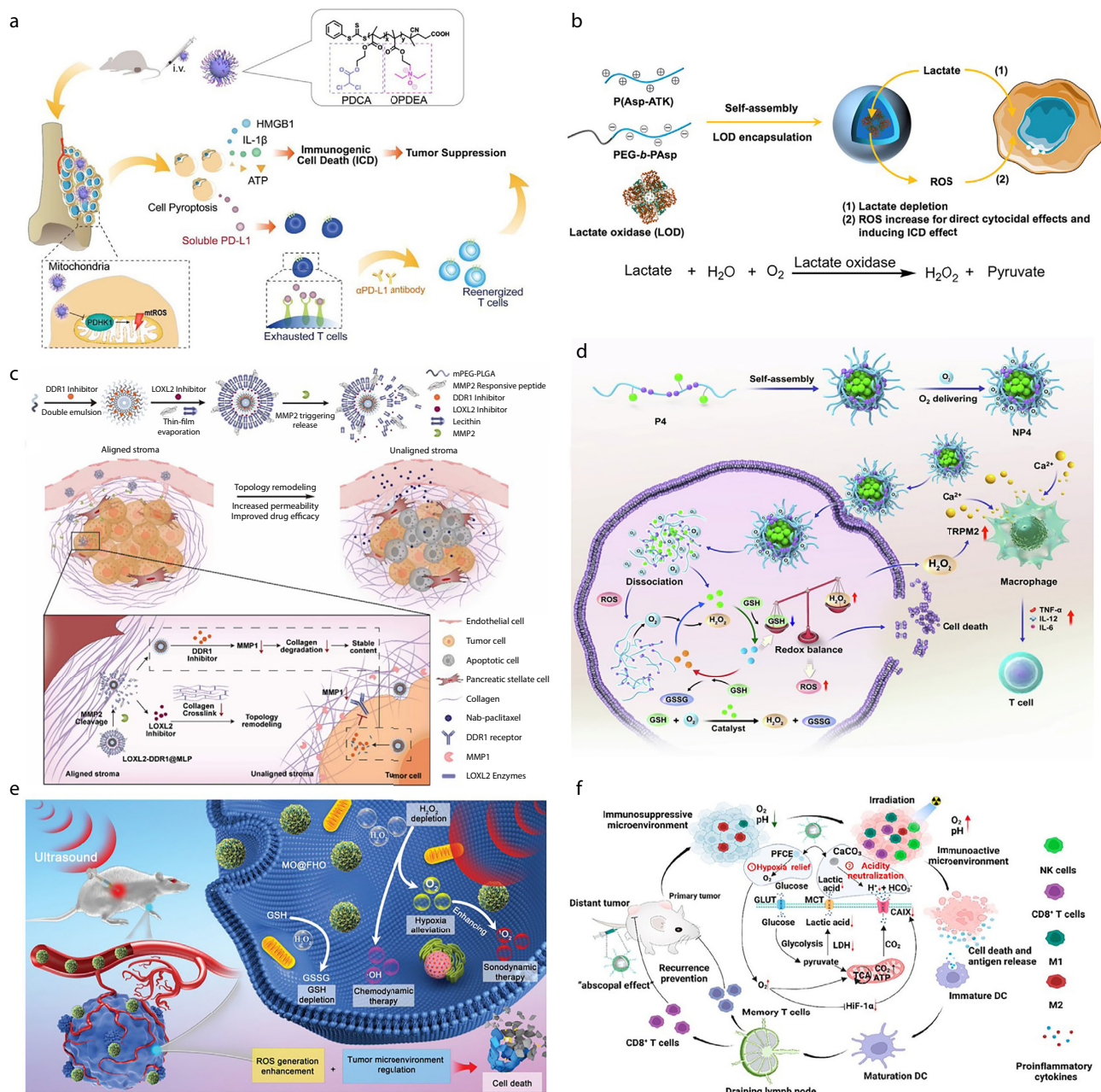


Fig. 6 Nanomedicine-mediated regulation of chemical and metabolic components in the TME: (a) Schematic illustration of mitochondria-targeting polymer micelles (OPDEA-PDCA) for metabolic reprogramming by inhibiting PDHK1 to diminish lactate generation at the source (Reproduced with permission from Ref. [105]; Copyright (2022), American Chemical Society.); (b) Scheme of prooxidative and lactate-depleting nanoreactors based on semi-permeable polyion complex vesicles (PICsomes) for active lactate consumption and biochemical reversal of the acidic TME (Reproduced with permission from Ref. [106]; Copyright (2025), The Authors.); (c) Schematic illustration of stroma-targeted nanoparticles (LOXL2-DDR1@MLP) remodeling stromal alignment to enhance drug delivery and anti-tumor efficacy in pancreatic ductal adenocarcinoma (Reproduced with permission from Ref. [107]; Copyright (2022), Elsevier Ltd.); (d) Schematic illustration of a polymeric nanoreactor incorporating a Ru catalyst for targeted GSH oxidation to disrupt redox homeostasis and trigger macrophage activation (Reproduced with permission from Ref. [109]; Copyright (2024), The Author(s).); (e) Schematic illustration of the preparation and therapeutic mechanism of ultrathin-FeOOH-coated MnO₂ sonosensitizers (MO@FHO) with boosted ROS yield and TME remodeling capabilities (Reproduced with permission from Ref. [110]; Copyright(2022), The Authors.); (f) Schematic illustration of a multifunctional fluorinated CaCO₃ nanoregulator (PFCE@fCaCO₃-PEG) acting as oxygen nanoshuttles and proton sponges to modulate glucose metabolism and potentiate radiotherapy (Reproduced with permission from Ref. [111]; Copyright (2022), American Chemical Society.).

signed to realize high-efficiency tumor immunotherapy for the first time. The combined nanoplatfrom-integrated chemomedicine (doxorubicin, DOX) and two different plas-

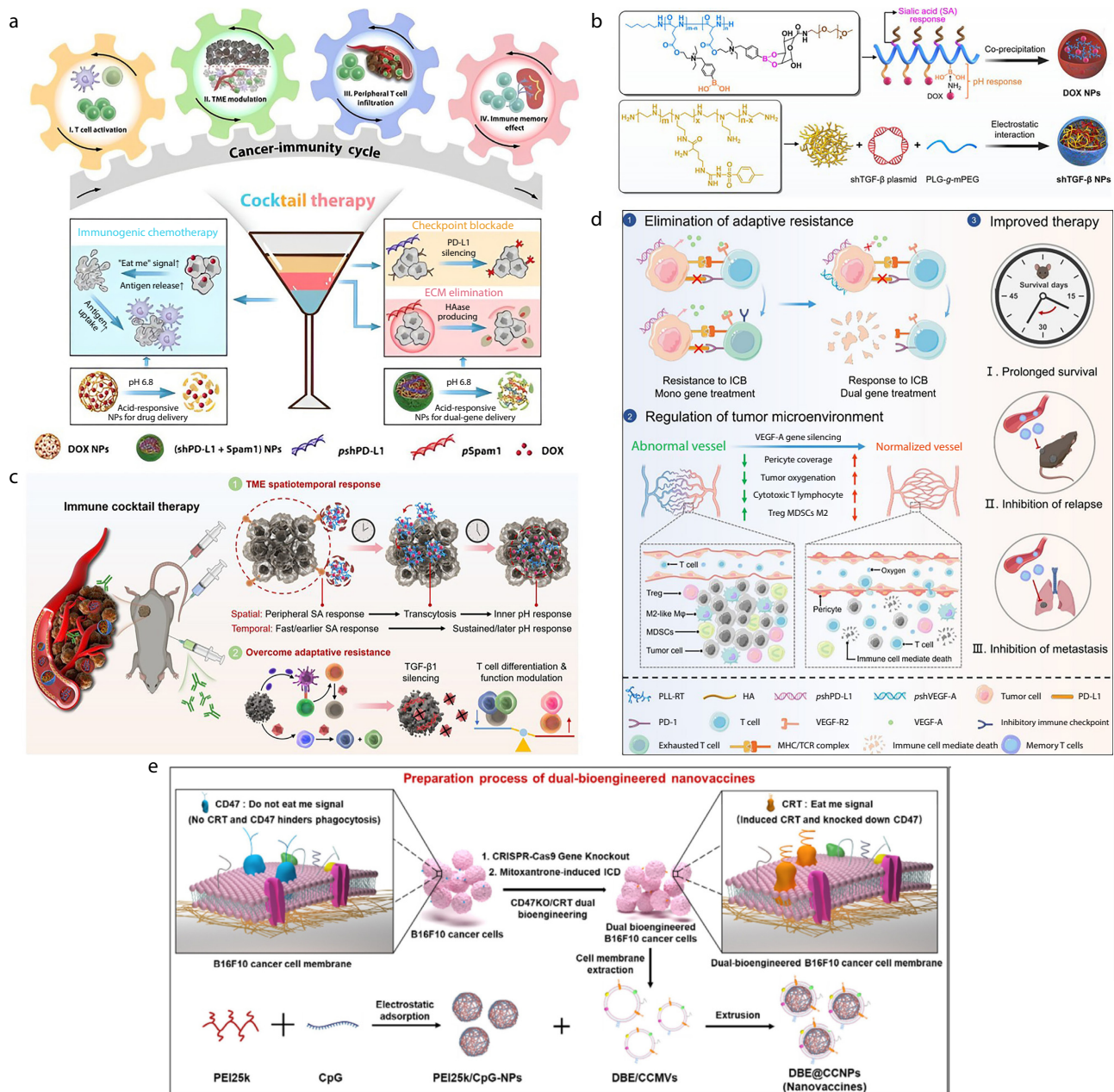
mids expressed the small hairpin RNA of PD-L1 (pshPD-L1) and hyaluronidase (pSpam1) (Fig. 7a). Compared to the simple combination of DOX and the corresponding checkpoint

antibodies, the cocktail nanoplatform exhibited better tumor regression efficiency. Each component in the combined platform mutually interacted with each other and was indispensable for successful anti-tumor outcomes. The cocktail strategy expanded the regulated scope within the TME and paved a new way for multi-synergistic treatment design.^[112]

To target checkpoint blockade receptors and ECM in the TME, another cocktail platform focusing on TGF- β 1 was designed. Briefly, polyethyleneimine modified with p-toluene-sulfonyl arginine (PEI-RT) was synthesized to complex with a plasmid encoding TGF- β 1 small hairpin RNA to form shTGF- β NP (Fig. 7b). By integrating DOX NPs, shTGF- β NPs, and α -PD-L1 into a cocktail nanoplatform, tumor adaptive resistance was successfully overcome, and higher tumor regression efficiency was achieved in comparison to previous monothera-

pies and simple combinations (Fig. 7c).^[113]

Extending this concept to vascular normalization, a dual-gene delivery strategy was subsequently established to simultaneously silence VEGF-A and PD-L1, a dual gene delivery strategy to break down adaptive resistance and reprogram the TME were established. The cationic polymer polylysine grafted with arginine and modified with a tosyl group (PLL-RT) and hyaluronic acid (HA) were selected as co-delivery plasmids pshVEGF-A and pshPD-L1 (Fig. 7d). This system not only reduced immunosuppressive checkpoint expression and overcame PD-L1-induced adaptive drug resistance, but also reprogrammed tumor-associated blood vessels, tumor-infiltrating immune cells, cytokines, and chemokines in the TME.^[114] The same gene delivery system PLL-RT with a shield-



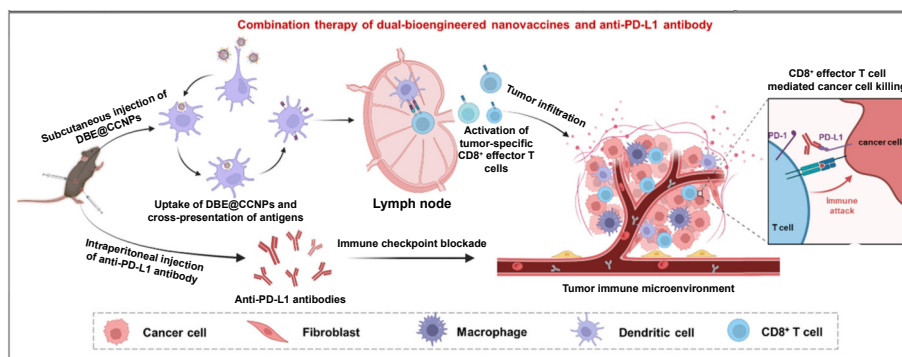


Fig. 7 Overview of emerging nanotechnology-based approaches for cancer immunotherapy that integrate multi-dimensional therapeutic modalities to overcome immune suppression and boost systemic anti-tumor immunity. (a) Schematic diagram of the immune cocktail therapy to realize multiple boosting of the cancer-immunity cycle by the combination of drug/gene delivery nanoparticles (Reproduced with permission from Ref. [112]; Copyright (2020), permission from author.); (b) The preparation of DOX NPs and shTGF- β NPs (Reproduced with permission from Ref. [113]; Copyright (2022), American Chemical Society.); (c) Schematic Diagram of Immune Cocktail Therapy Which Included TME Spatiotemporally Responsive DOX NPs, PD-L1 Antibodies, and shTGF- β NPs (Reproduced with permission from Ref. [113]; Copyright (2022), American Chemical Society.); (d) Schematic illustration of dual gene therapy for improved cancer immunotherapy (Reproduced with permission from Ref. [114]; Copyright (2021), Elsevier Ltd. All rights reserved.); (e) The construction of the CD47KO/CRT dual-bioengineered cell membrane-coated nanovaccine and their anti-tumor therapeutic strategy in combination with an anti-PD-L1 antibody (Reproduced with permission from Ref. [116]; Copyright (2022), The Authors.).

modified dextran (TDPAD), was used to encapsulate pDNA encoding shVEGF to simultaneously achieve triple effects in the TME. First, PLL-RT promoted endocytosis of pDNA encoding shVEGF and greatly reduced the expression of VEGF in the TME, resulting in an amazing anticancer effect. Second, the capability of TDPAD to consume H_2O_2 further modifies the redox balance in the TME, leading to a synergistic tumor regression effect. Third, the small-molecule product mercaptopyruvic acid, produced by the interaction of TDPAD with H_2O_2 was shown to exhibit a substantial anticancer effect for further cancer cell damage.^[115]

Nanomedicines can also be used as tumor vaccines by incorporating potential tumor antigens or by inducing antigenic peptide generation in the TME. Tian *et al.* reported a novel approach for preparing a nano-vaccine package. By exploiting the combination of CRISPR-Cas9 gene editing technology with cell surface translocation calreticulin, CD47KO/CRT double-engineered B16F10 cells were generated, and cell membranes were extracted for *in vivo* vaccination. The nano-vaccine was further prepared by complexing hyperbranched PEI25k with unmethylated cytosine-phosphate-guanine (CpG) and coextrusion with engineered B16F10 cell membranes (Fig. 7e). The nano-vaccine not only promoted the phagocytic capability of DC cells, but also induced the maturation of DCs and the cross-presentation of tumor antigens to T cells. In combination with aPD-L1, cocktail formation achieved a stronger immunization level and induced better tumor inhibition outcomes.^[116]

5.2 Metabolism-modulatory Nanocarriers for TME Reprogramming and Synergistic Immunotherapy

Modulation of tumor metabolism represents a pivotal paradigm for reprogramming the immunosuppressive landscape of the TME. Tian *et al.* further proposed a biomineralization-like method to encapsulate hybridized nanozymes and glucose oxidase (GOx), which could self-amplify the regulation of glycometabolism inside tumor cells (Fig. 8a). To prevent the immune evasion of tumor cells, checkpoint blockade inhibitors

were incorporated into this nanoplatform, realizing the sustained reduction of MDSCs, Tregs, and M2 macrophages. These integrated approaches provide robust platforms for clinical translation of multifaceted cancer management.^[117]

In addition to metabolic interventions, several sophisticated nanoplatforms have been developed to achieve comprehensive TME modulation. Li *et al.* designed a cocktail therapeutic strategy to co-deliver the EGFR-TKI gefitinib (Gef) and YAP-siRNA for non-small-cell lung cancer therapy with an amphiphilic block dendrimer, realizing multi-synergistic tumor inhibition (Fig. 8b). In addition to inducing ICD by the photodynamic effect of the nanoformulation, Gef effectively blocked the EGFR signaling pathway, and YAP-siRNA inhibited the EGFR bypass signal, thus alleviating the suppression of the TME and impairing the glycolysis pathway in cancer cells by downregulating the expression of hypoxia-inducible factor 1- α (HIF-1 α) (Figs. 8c and 8d).^[118] Zhuang Liu *et al.* integrated ICD-inducing chemotherapeutics, immune adjuvants, and alginate (ALG) into a cocktail nanoplatform for localized chemoimmunotherapy. With the retention of ALG, chemotherapy and immune adjuvants induce persistent tumor-specific immune responses and reprogram the suppressive TME. Collectively, this nanoformulation, based on clinically approved agents for tumor-localized cocktail chemoimmunotherapy, has great potential for clinical translation.^[119]

The versatility of metabolism-modulatory polymeric nanocarriers is exemplified by three recent strategies that target distinct metabolic nodes within the TME. In one approach, Wang *et al.* engineered a GSH-responsive polymeric nanocarrier that underwent mitochondria-localized *in situ* self-assembly, disrupting metabolic homeostasis via pro-death mitophagy while concurrently remodeling the immune landscape through ICD induction and TAM repolarization (Fig. 8e).^[120] Expanding on the concept of TME-responsive design, Zhang *et al.* constructed redox-responsive supramolecular polyrotaxane-based nanoparticles (RDPNs@diABZIs) capable of co-delivering a STING agonist

and methyl- β -cyclodextrin. This platform metabolically reprograms the TME by depleting membrane cholesterol to counteract the mechanical softness of cancer cells, thereby enhancing CTL-mediated killing while initiating de novo T cell responses *via* STING activation (Fig. 8f).^[121]

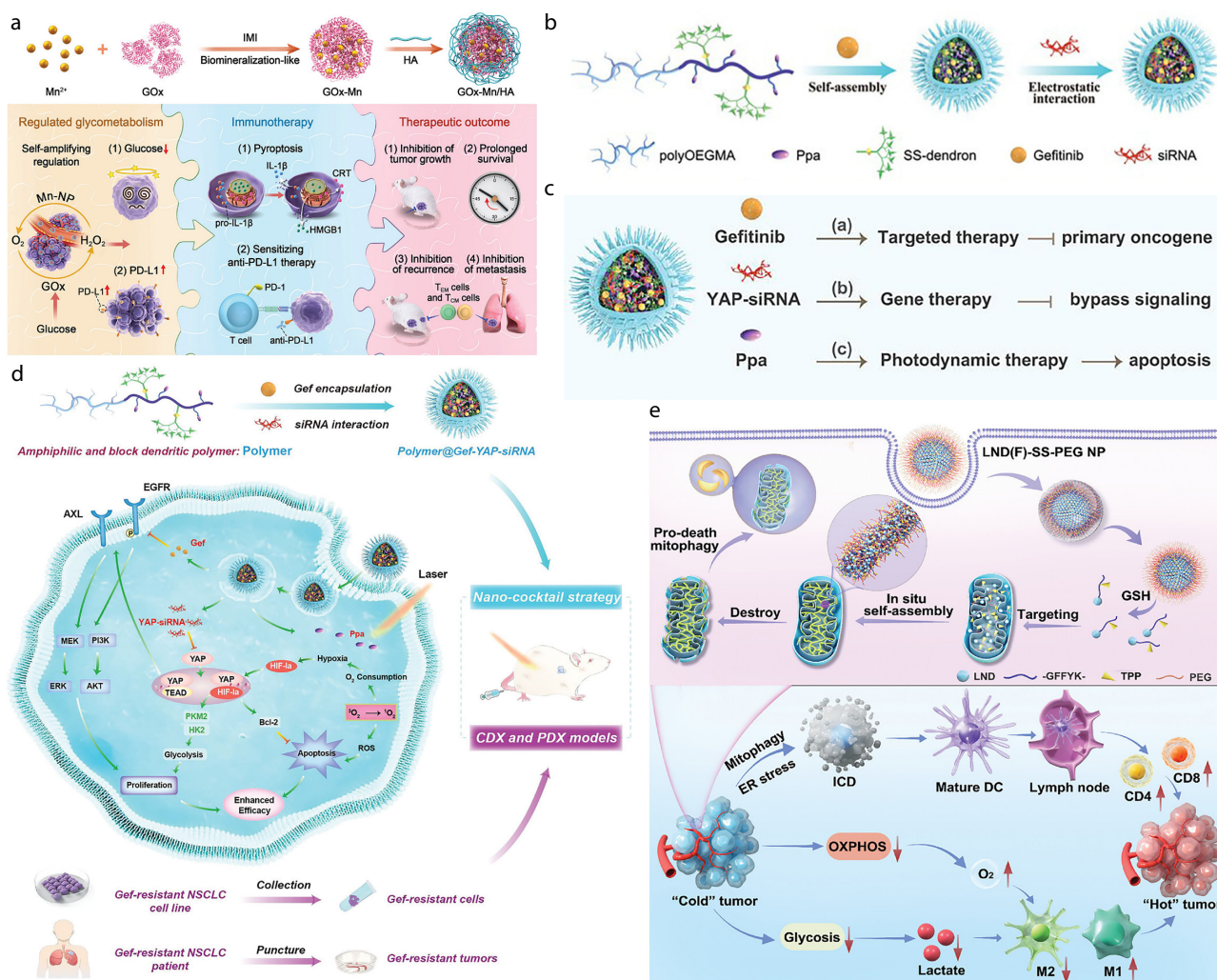
Using a distinct immunometabolic engineering approach, An *et al.* designed an L-arginine-based polymeric nanomicelle system that integrates with adoptive macrophages to provide a sustained metabolite supply within the nutrient-deprived TME, demonstrating that polymer-mediated metabolic support can potentiate adoptive cell therapy against solid tumors (Fig. 8g).^[122] In a complementary manner, Wang *et al.* recently developed a peptide-based nanorobot that recognizes PD-L1 and disrupts cancer cell membranes *via* pH-responsive fibril formation, thereby inducing ICD and enhancing T-cell infiltration within the TME.^[123] Collectively, these emerging strategies underscore the capacity of polymeric nanocarriers to orchestrate the multifaceted metabolic reprogramming of the TME, thereby advancing the efficacy of cancer immunotherapy.

5.3 Non-invasive Monitoring of Immune Responses and Image-guided Therapy

Although nanomedicine-based cocktail strategies have elicited

robust immune responses in preclinical and clinical settings, evaluating these therapeutic outcomes remains a challenge. Conventional methods, such as histological staining, flow cytometry, and serum cytokine analysis, are inherently invasive and provide only static snapshots of immune status. They fail to capture the dynamic, real-time evolution of the TME, limiting their ability to guide regimen optimization. Consequently, there is an urgent need to develop non-invasive, image-guided nanoplatforms that allow for *in situ* visualization of immune activation and early diagnosis of therapeutic responsiveness.

The immune microenvironment is characterized by acidity, various cytokines, and many immunosuppressive cells, which have been used not only as tumor-specific targets to realize the targeted release of cargo but also as biomarkers for tracking immune responses. Recently, metabolic acidosis, immune cell-secreted specific enzyme-based imaging formulations, and micro ribonucleic acid (miRNA) probes have been developed.^[124] Kang & Chang *et al.* reported a fluorescent probe, CDr17, which specifically targeted M1 macrophages instead of M2 or M0 macrophages. The strategy for probe design is based on libraries of fluorescently labeled carbohydrates that can serve as substrates for glucose transporters (GLUTs). M2 macrophages prefer to accept fatty acids using



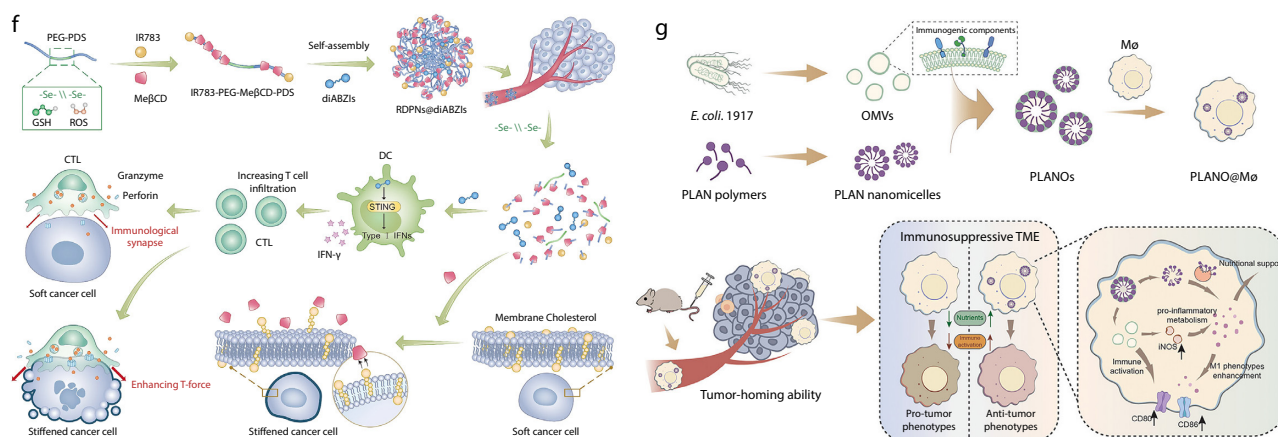


Fig. 8 Overview of emerging nanotechnology-based approaches for cancer immunotherapy that integrate multi-dimensional therapeutic modalities to overcome immune suppression and boost systemic anti-tumor immunity: (a) Scheme of GOx-Mn/HA synthesis and biomimetic mineralized two-enzyme nanoparticles that regulate tumor glycol-metabolism inducing tumor cell pyroptosis and robust anti-tumor immunotherapy (Reproduced with permission from Ref. [117]; Copyright (2022), Wiley-VCH GmbH.); (b) Schematic illustration of formation of multifunctional core-shell Polymer@Gef-siRNA NPs through self-assembly and complexation (Reproduced with permission from Ref. [118]; Copyright (2022), Wiley-VCH GmbH.); (c) Schematic illustration of a cocktail therapy via using Polymer@Gef-YAP-siRNA NPs for treating Gef-resistant tumor cells (Reproduced with permission from Ref. [118]; Copyright (2022), Wiley-VCH GmbH.); (d) Diagrammatic representation of the anti-tumor pathways elicited by a multifunctional core-shell nanoplateform (Polymer@Gef-YAP-siRNA NPs) for combinatorial therapy (Reproduced with permission from Ref. [118]; Copyright (2022), Wiley-VCH GmbH.); (e) Schematic illustration of GSH-triggered peptide release and mitochondria-localized *in situ* self-assembly, inducing mitochondrial dysfunction and pro-death mitophagy (Reproduced with permission from Ref. [120]; Copyright (2024), Wiley-VCH GmbH.); (f) Schematic of cancer-cell stiffening using RDPNs@diABZIs boosts T-force-mediated killing for anticancer STING immunotherapy (Reproduced with permission from Ref. [121]; Copyright (2025), The Author(s).); (g) Schematic illustration of the integration of PLANOs with Mφ (PLANO@Mφ) and their immunometabolic engineering mechanism (Reproduced with permission from Ref. [122]; Copyright (2025), Wiley-VCH GmbH.).

CD36 to feed on the TCA cycle and oxidative phosphorylation, as opposed to M1 macrophages, which primarily employ glucose transporters (GLUTs) to promote carbohydrate absorption to sustain aerobic glycolysis (OXPHOS). Moreover, Studies have shown that M1 macrophages prefer cyanine dyes and various glucose analogs. Thus, CDr17 facilitates the detection of M1 macrophages over M2 or M0 macrophages.^[125] With the assistance of the Nanoprobe CDr17, dynamic monitoring of the immune activation environment to guide clinical drug delivery strategies was realized. Ultrasound offers deeper tissue penetration in addition to optical imaging. Sun *et al.* engineered a multifunctional theranostic nanoplateform (Pt/CQ/PFH-NPs) designed to target the metabolic hallmarks (high lactate and ROS levels) of triple-negative breast cancer (Fig. 9a). Crucially, the encapsulation of perfluorohexane (PFH) endowed the nanoparticles with ultrasound-imaging capabilities. Upon stimulation, liquid PFH undergoes a phase transition into echogenic gas microbubbles, significantly enhancing ultrasound contrast for precise tumor localization. Therapeutically, the prodrug platinum (IV) is reduced to cisplatin, which elevates intracellular ROS levels and promotes dendritic cell (DC) maturation. Concurrently, the co-delivered chloroquine blocks cisplatin-induced protective autophagy, whereas PD-L1 antibody reverses immune exhaustion. The integration of acoustic imaging with metabolic modulation and checkpoint blockade exemplifies a potent image-guided immunotherapeutic strategy.^[126] In addition, NIR-II imaging can minimize self-luminescence and photon scattering, increase the tumor penetration depth, and achieve more accurate tumor diagnosis and treatment.^[127] Stang *et al.* constructed a supramolecular nanoprobe by incorporating a Pt(II) metallacycle and organic

dye into PEGylated lipids (Fig. 9b). This system not only facilitated high-resolution NIR-II diagnosis of tumor margins, but also ensured the specific delivery of the therapeutic Pt(II) metallacycle, realizing precise “see-and-treat” capabilities (Fig. 9b).^[128]

Furthermore, functional biomarkers such as miRNAs and effector enzymes offer direct evidence of their therapeutic efficacy. Cai *et al.* developed a thermoactivatable DNA nanothermometer based on mesoporous polydopamine. Under NIR irradiation, the photothermal effect triggers the exposure of DNA strands, which then undergo a strand displacement reaction (SDR) with the target miRNAs. This design allows for simultaneous photothermal ablation of tumors and *in situ* quantification of miRNA markers.^[129] Similarly, to monitor the execution phase of immunity, Pu *et al.* synthesized a macromolecular renal-clearable reporter specific for Granzyme B, a cytolytic enzyme released by activated T cells and NK cells. Upon cleavage by Granzyme B in the TME, fluorescent fragments are excreted *via* the kidneys. This allows researchers to evaluate the systemic immune activation status simply by performing an optical analysis of the urine, offering a novel, noninvasive paradigm for tracking immunotherapy responses (Fig. 9c).^[130] Building on the paradigm of urine-based monitoring of immune activity, research efforts have further extended this noninvasive strategy to target a broader spectrum of immune cells. A library of activatable molecular probes was developed for the real-time *in vivo* near-infrared fluorescence imaging of specific TILs, including M1 macrophages, cytotoxic T lymphocytes, and neutrophils. Owing to renal clearance, these probes also enable noninvasive monitoring *via* urine analysis (Fig. 9d).^[131]

Complementing optical and ultrasound modalities, Mag-

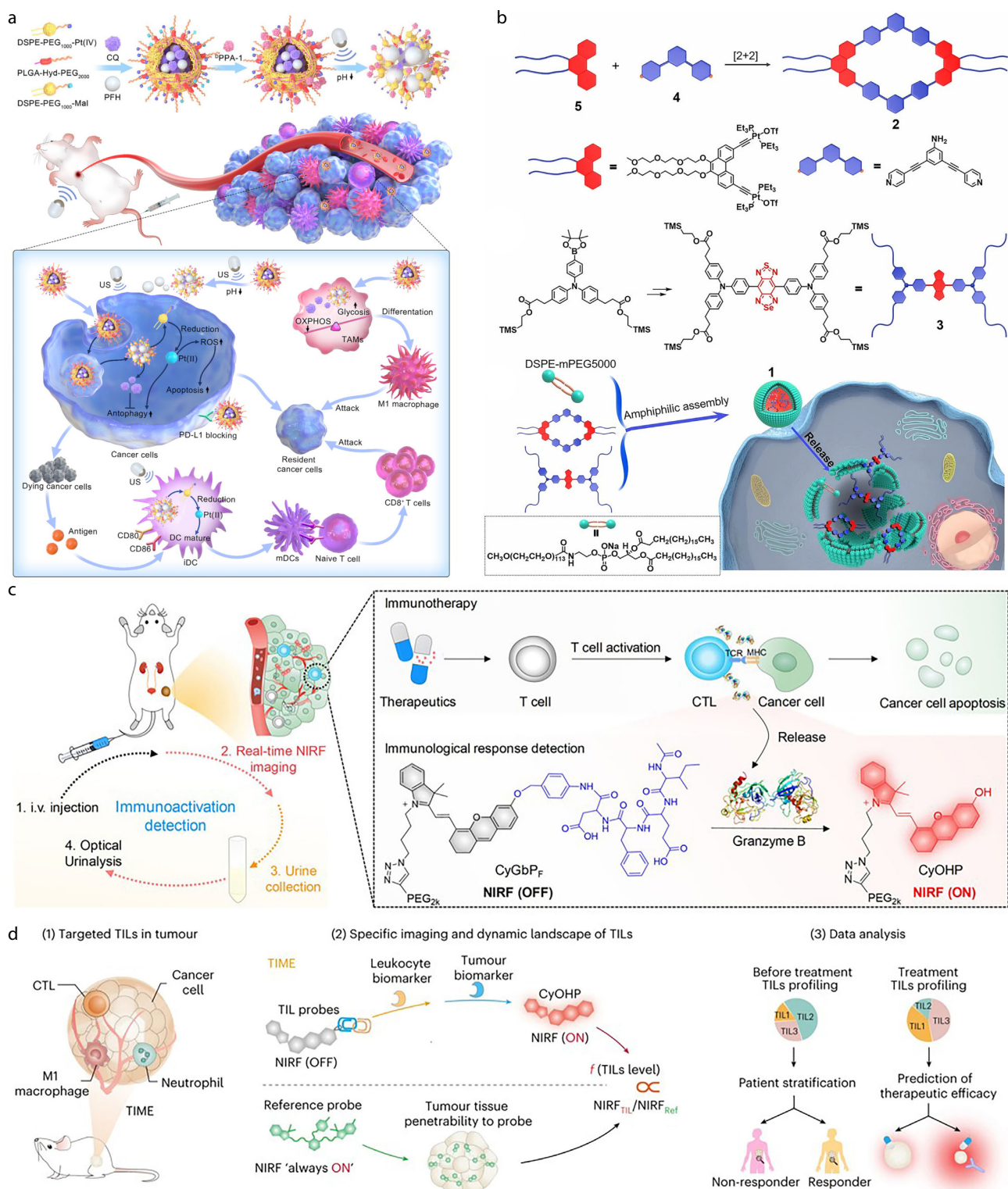


Fig. 9 Overview of representative nanoprobe for tumor theranostics: (a) Synthesis process used to prepare NPs and schematic illustration of Pt(IV)/CQ/PFH NPs-DPPA-1 assisted by ultrasound for augmenting chemoimmunotherapy of breast cancer (Reproduced with permission from Ref. [126]; Copyright (2022), American Chemical Society.); (b) The rhomboid structure 2 was first self-assembled from dipyrindyl donor 4 and diplatinum (II) acceptor 5, then functionalized with the NIR-II molecular dye 3, and finally formulated into the nanoprobe 1 for cellular uptake (Reproduced with permission from Ref. [128]; Copyright (2019), The Authors.); (c) Optical Urinalysis and Fluorescence Imaging Mechanism of CyGbP₇ (Reproduced with permission from Ref. [130]; Copyright (2020), American Chemical Society.); (d) TAMPs enables real-time and specific imaging of targeted Tumor-Infiltrating Lymphocytes (TILs) in cancer immunotherapy (Reproduced with permission from Ref. [131]; Copyright (2023), The Authors, under exclusive licence to Springer Nature Limited.).

netic Resonance Imaging (MRI) has also been used for non-invasive tracking of immune cells, offering high spatial resolution and deep tissue penetration.^[132] For example, Zhou *et al.* engineered T cell-targeting fusogenic liposomes (T-Fulips) functionalized with anti-CD3 F(ab')₂ fragments and decorated them with 2,2,6,6-tetramethylpiperidine (TEMP). This design cleverly exploits the oxidative TME; excess ROS neutralizes TEMP, thereby protecting T cells from oxidative damage. Crucially, this reaction converts diamagnetic TEMP into a paramagnetic TEMPO radical, effectively “switching the MRI signal on.” This mechanism enables the simultaneous protection and real-time MRI tracking of T cells within the tumor site.^[133]

Collectively, the integration of these advanced imaging modalities provides critical insights into optimizing cancer immunotherapy. Real-time monitoring allows for precise evaluation of the immune status within the TME, facilitating the dynamic tuning of therapeutic dosages to maximize efficacy while mitigating the risks of immune overactivation (e.g., cytokine storms). Furthermore, these imaging techniques serve as valuable tools for assessing the inherent immunogenicity of nanocarrier materials and guiding the selection of biocompatible polymers.

However, several challenges remain. Many current strategies rely on decoupled imaging and therapeutic modules, which introduce temporal lags in assessment and increase the complexity of clinical regimens. Consequently, the future frontier lies in the development of streamlined “All-in-One” theranostic nanoplateforms. Key priorities include (1) ensuring functional independence, yet the synergistic operation of imaging and therapeutic segments; (2) achieving high spatiotemporal synchronization between diagnosis and treatment; and (3) enabling remote-controlled modulation of therapeutic activity based on *in situ* imaging feedback. These efforts will pave the way for intelligent adaptive nanomedicines capable of precisely modulating host immunity.

6 CHALLENGES IN CLINICAL TRANSLATION OF TME-TARGETED POLYMERIC NANOMEDICINES

Despite the remarkable efficacy of TME-targeted polymeric nanomedicines summarized in this review, their clinical translation still faces multiple non-negligible bottlenecks that restrict the transition from laboratory research to clinical applications.

6.1 The Immunogenicity and Long-term Toxicity of Polymeric Carriers

Many polymeric carriers naturally stimulate the immune system because of their structural heterogeneity. This property can be advantageous in cancer vaccines, where the carrier acts as both a delivery vehicle and immune adjuvant. However, there is a significant risk of severe immune toxicity. For example, cationic polymers can trigger the release of excessive pro-inflammatory cytokines or hypersensitivity reactions. This can result in severe secondary damage to the immune system. Furthermore, widely used polymers such as PEG are not completely biologically inert. Repeated administration often elicits the production of anti-PEG antibodies. This triggers the accelerated blood clearance (ABC) phenomenon, which severely reduces the therapeutic efficacy. In addition to immunogenicity, long-term *in vivo* safety is also a

major translational hurdle. Non-biodegradable polymers tend to accumulate in vital organs and potentially cause chronic inflammation and metabolic disorders. Although biodegradable polymers are preferred, their degradation kinetics and the toxicity of their byproducts are often unclear.

To overcome these clinical bottlenecks, researchers must rigorously characterize polymer structures and molecular weights, ensuring thorough purification. Most importantly, polymeric carriers should be designed to degrade highly biocompatible, small molecules. This is essential for minimizing systemic accumulation and adverse immune responses.

6.2 Batch-to-batch Stability and Quality Control in Large-scale Manufacturing

The transition from precise small-scale laboratory preparation to large-scale production presents profound challenges for polymeric nanomedicines. Most preclinical studies rely on small batches in which preparation parameters are strictly controlled; however, scaling up this process while maintaining batch-to-batch consistency is notoriously difficult. This bottleneck is particularly pronounced for multifunctional polymeric nanomedicines (e.g., TME-targeted or co-delivery systems integrated with responsive structures), which typically require complex multi-step processes involving polymer synthesis, self-assembly, surface modification, and payload encapsulation. During large-scale batch synthesis, these thermodynamically driven processes become highly sensitive to minor fluctuations in operational parameters, such as temperature, pH, stirring rate, and reactant ratios. Consequently, scaling up often introduces inevitable variations in critical quality attributes (CQAs), including the particle size distribution, polydispersity index (PDI), surface zeta potential, and drug encapsulation efficiency. Overcoming these batch-to-batch inconsistencies in large-scale synthesis remains a formidable hurdle for successful clinical translation of next-generation polymeric therapeutics.

7 CONCLUSIONS

The limited and variable efficacy of current cancer immunotherapies underscores the central challenge that solid tumors are not merely a collection of malignant cells, but a fortified immunosuppressive ecosystem. This review explored how polymeric nanomedicines fundamentally shift the therapeutic paradigm from a narrow attack on cancer cells to a multifaceted campaign of immune microenvironment reprogramming. The versatility of polymer design allows the creation of integrated platforms that concurrently address the cellular, physical, and biochemical barriers of the TME. By depleting or reprogramming suppressive stromal cells, normalizing vasculature, degrading dense ECM, and scavenging immunosuppressive signals, these advanced systems work synergistically to dismantle the tumor's defenses and convert an immunologically “cold” TME into a “hot,” lymphocyte-inflamed state conducive to treatment efficacy.

This capacity for coordinated TME remodeling transforms polymeric nanoparticles into potent vectors for delivering a synergistic immunotherapeutic “cocktail”, thereby maximizing anti-tumor immune activation. The field is evolving beyond mere combinatorial delivery toward intelligent theranostic systems. The true promise lies in endowing these multifunctional platforms with real-time, *in situ* sensing capability

ties, such as tracking immune cell infiltration or activity, enabling them to provide dynamic feedback on the treatment response. Thus, the future of cancer immunotherapy may be guided by closed-loop, adaptive nanoplateforms that not only deliver complex regimens to reprogram the TME, but also monitor the resulting immune status, paving the way for truly personalized and predictably effective cancer immunotherapies.

BIOGRAPHIES

Kai Hao received his Ph.D. in Polymer Chemistry and Physics from the University of Science and Technology of China in 2021. Currently, he serves as an Assistant Professor at the Institute of Flexible Electronics (IFE, Future Technologies), Xiamen University. His research primarily focuses on the design of novel non-viral nucleic acid delivery vectors and their application in tumor immunotherapy.

Hua-Yu Tian obtained his Ph.D. degree from the Changchun Institute of Applied Chemistry, Chinese Academy of Sciences in 2005. From 2006 to 2022, he conducted research at institutions including the Changchun Institute of Applied Chemistry, the Chinese Academy of Sciences, the Korea Advanced Institute of Science and Technology, Kyushu University, and the University of Utah. In 2022, he joined the College of Chemistry and Chemical Engineering at Xiamen University. His research topics include biomedical polymers, nanogene/drug carriers, biotherapy, nucleic acid vaccines, immunotherapy, and energy polymers.

Conflict of Interests

The authors declare no interest conflict.

ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (Nos. 52433006, 52495010, 52495015 and 52503178), Fundamental Research Funds for the Central Universities (No. 20720230008), and Talent Cultivation Project Funds for the Innovation Laboratory for Sciences and Technologies of Energy Materials of Fujian Province (HTRP-[2022] 52).

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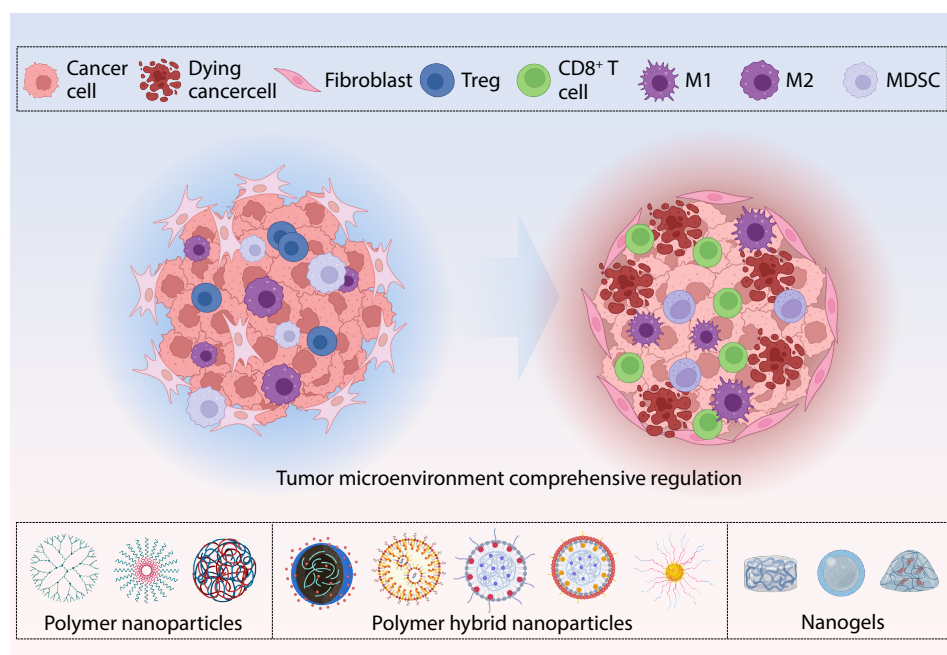
Graphical Abstract

Polymeric Nanomedicines for Comprehensive Regulation of Tumor Microenvironment

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Polymeric nanomedicines provide versatile platforms for comprehensive tumor microenvironment (TME) regulation. By coordinating immune cell modulation and stromal remodeling, these systems dismantle biological barriers and transform “cold” tumors into a “hot” state to maximize synergistic anti-tumor immune activation.



Chinese J. Polym. Sci. 2026, 44, 2427–2452

<https://doi.org/10.1007/s10118-026-3678-6>

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