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REVIEW

Nanomedicines Reshape the Tumor Microenvironment: Multidimensional Strategies from Modulating "Barriers" to Metabolic Intervention

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Abstract: Nanoparticle-driven remodeling of the Tumor Microenvironment (TME) represents a transformative strategy in cancer therapy, shifting from traditional approaches to multidimensional modulation. This review explores how engineered nanoparticles precisely target and alter key TME components—including immune cells (eg, NK cells, dendritic cells, T cells), cancer-associated fibroblasts, and the extracellular matrix—to overcome "Chemical barriers" and "physical barriers". Furthermore, we highlight the pivotal role of nanoparticles in reprogramming TME metabolism, such as alleviating hypoxia, disrupting the Warburg effect, and modulating lipid and adenosine metabolism. By integrating immune activation with metabolic intervention, nanomedicines not only enhance anti-tumor immunity but also restore metabolic balance, offering a synergistic and potent therapeutic avenue for overcoming treatment resistance and inhibiting tumor progression.

Keywords: tumor microenvironment, nanomedicine, metabolic reprogramming, drug delivery

Introduction

Cancer poses a significant threat to human health,[1] and treatment approaches have matured over time, including surgery, drug therapy, chemotherapy, targeted therapy, and immunotherapy.[2–5] However, surgical efficacy for advanced or metastatic cancers remains uncertain,[6] while other treatments face challenges such as inefficient drug delivery, high recurrence rates, and drug resistance development.[7] Therefore, developing novel drug delivery systems represents a promising new approach to overcoming the challenges in cancer treatment.

The Tumor Microenvironment (TME) is a complex ecosystem essential for the survival and growth of tumor cells.[8] It encompasses not only the tumor cells themselves but also diverse non-cancerous cell types and non-cellular components. These non-cancerous cells primarily include cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), endothelial cells, immune cells (such as T cells, B cells, and regulatory T cells), as well as adipocytes and mesenchymal stem cells; Non-cellular components include the extracellular matrix (ECM), soluble factors (eg, cytokines, chemokines, growth factors).[9,10] These components exhibit distinct phenotypes through the co-expression of multiple proteins and form spatially structured arrangements, creating microenvironment niches, nutrient gradients, and intercellular interactions.[11] Each may represent a novel therapeutic target[12,13](Figure 1). TME plays a crucial role throughout all stages of tumor development, from initiation and progression to metastasis and response to treatment.[11,14] Currently, numerous approaches target the TME, including the immune microenvironment, metabolic microenvironment, hypoxic niche microenvironment, mechanical niche microenvironment, and innervated niche microenvironment.[15–18] However, these strategies still rely on conventional drugs, which cannot overcome treatment-related limitations. Consequently, the emergence of nanoparticles offers a solution to these challenges.

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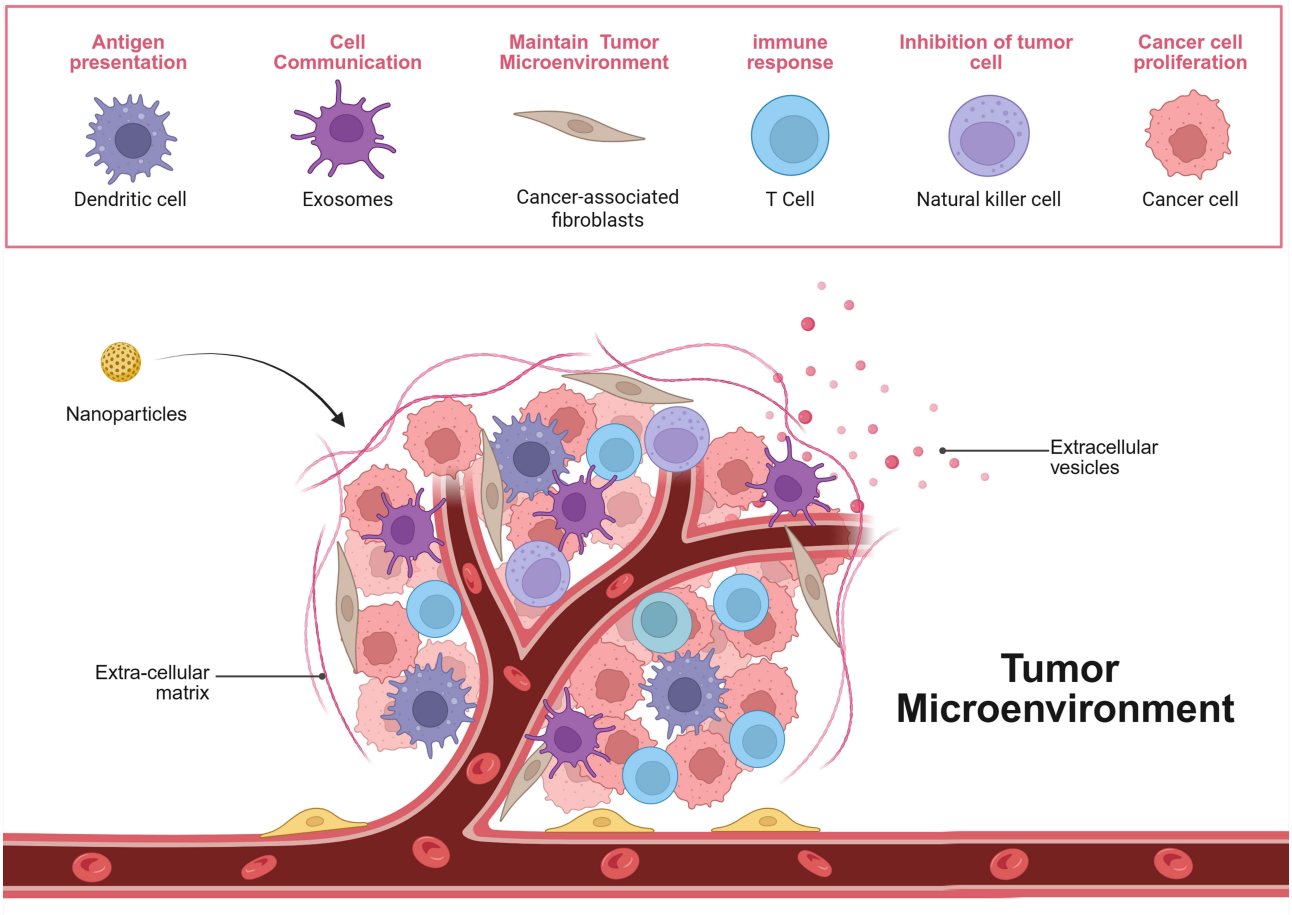

Figure 1 Tumor Microenvironment The tumor microenvironment consists of complex cellular and non-cellular components, serving as an essential factor for tumor survival and invasion.

Nanomedicine refers to the application of nanotechnology in medicine,[19] with drug delivery systems composed of nanoparticles(NPs) ranging from 1 to 100 nm in diameter serving as its primary tools. NPs, measuring between 1 and 100 nanometers in diameter, exhibit exceptional hardness, stability, porosity, and specific surface area, making them the preferred choice for drug delivery systems.[20,21] As an emerging drug delivery system, nanoparticles demonstrate significant advantages over traditional drug therapies. They enhance therapeutic efficacy by increasing bioavailability, improving permeability and retention (EPR) effects, and enabling more precise targeted delivery,[22,23] these advantages also provide benefits for the clinical translation of nanoparticles. Despite significant advances in nanotechnology for drug delivery, the EPR effect remains inconsistent due to variations in tumor tissue regions and tumor types.[24] Furthermore, achieving targeted delivery of NPs to diseased tissues remains a critical objective.[25]

Despite the noteworthy advancements in nanomedicine, particularly in the domains of cancer diagnosis and treatment, these therapeutic agents continue to confront substantial physiological barriers within the TME before achieving effective delivery to their intended targets within tumors. The intricate nature of the TME stems from the dynamic interplay between cellular and non-cellular components, which collectively exert a substantial influence on critical processes such as tumor proliferation and metastasis. To effectively treat cancer, it is essential to deeply understand the dynamic interactions among TME components and their mechanisms of action in tumor progression. In recent years, nanotechnology has been developed for the purpose of targeting the TME and circumventing its inherent barriers, leading to innovative imaging approaches and improved therapeutic outcomes.[26] NPs can be engineered to achieve spatiotemporal controlled release of their contents in response to internal stimuli within the TME (eg, pH, redox conditions, and enzymes) or external stimuli (eg, light, magnetic fields, electric fields, and ultrasound). Furthermore, nanotechnology has facilitated advancements in gene and immune modulation, offering novel

alternative therapies for emerging diseases such as cancer.[27] Nevertheless, the development of nanotechnology-based strategies to modulate the TME and support anticancer therapies still faces numerous challenges, including the reproducible synthesis of nanomaterials, the evaluation of optimal physicochemical properties, and obstacles to clinical translation.

The TMEis highly heterogeneous across different tumors, and the efficacy of cancer immunotherapies targeting the immune TME differs among tumor types.[12] At present, much of the literature focuses on investigating the regulatory mechanisms of nanoparticle knives on individual components within the TME, with few studies categorizing the TME into "physical barriers" and "chemical barriers." To address this gap, we analyze how nanoparticles regulate different components within the TME by examining their regulatory mechanisms on distinct barriers. We further examine nanoparticle regulation of TME-related metabolic processes, particularly hypoxic microenvironments. Finally, we discuss challenges in the clinical translation of nanoparticle-mediated TME regulation and highlights how novel nanoparticle platforms—specifically exosomes—are emerging as a new direction for TME modulation due to their superior performance.

Nano-Particles Modulate the "Chemical Barriers" in the Tumor Microenvironment

The tumor immune microenvironment is a crucial component of the TME. Tumor cells employ multiple mechanisms to reduce antigen presentation efficiency, achieve immune escape by suppressing immune cell function and modulating immune cell recognition mechanisms, alter antigen processing and presentation pathways, and decrease antigen expression through epigenetic or transcriptional regulation. These mechanisms collectively pose significant barriers to immunotherapy and related treatments.[28] Recent studies on specific NPs have indicated a promising new approach to addressing these challenges: the utilization of NPs as drug delivery systems to regulate immune cells and the immune microenvironment, thereby achieving therapeutic effects against tumors (Table 1).

Table 1 Nanoparticles Modulate Immune Cells in the Tumor Microenvironment

Cells	Nanoparticles	Drugs	Target	Strategies	References
NK cells	Lipid-based non-viral vector	siRNA	SHP–1, Cbl–b, c-Cbl	Immune activation	[29]
NK cells, T cells	Tri-specific nanobody	Nanobody	PD–L1, 4–1BB, NKG2A, TIGIT	Immune activation	[30]
NK cells	R-NKm@NPs	Temozolomidez, IL–15	–	Induces an immune-stimulatory response	[31]
DCs	Ce6/BMS-202 nano-assemblies	BMS-202	PD–1/PD–L1	Enhances the maturation of DCs Enhances the infiltration of antigen-specific T cells	[32]
DCs	DC membrane-coated nanovaccines	PD–1 blockade	PD–1	Upregulate cytotoxic T cells, Reduce Tregs, Promote M1 macrophage polarization	[33]
DCs, T cells	TAA-DCm@ PTX nanoparticles	Paclitaxel	Blood–brain barrier	Promote DCs maturation, T cell activation	[34]
T cells	MLP-aTIM-3 nanovaccines	TIM–3-targeted lipid nanoparticles	TIM–3	Reversing T cell exhaustion Restoring T cells proliferative capacity	[35]
DCs, T cells, NK cells	M-CHNP/D	PD–L1-blocking peptide DPPA-1	PD–L1	Immune activation	[36]

(*Continued*)

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Table 1 (Continued).

Cells	Nanoparticles	Drugs	Target	Strategies	References
T cells	EMVs	CD73 inhibitor, PD-L1 inhibitor	CD73, PD–L1	Immune activation	[37]
T cells	Magnesium hydride nanoparticles	Nano-MgH_2	–	Immune activation, Immune Cell Differentiation	[38]

Nanoparticles Regulate Natural Killer Cells

Natural killer (NK) cells, as innate cytotoxic lymphocytes, exhibit broad antitumor effects by directly recognizing and killing cancer cells.[39] The TME is a complex network composed of diverse cellular and noncellular components, whose constituents can significantly influence NK cell function, including their infiltration, activation, cytotoxicity, and metabolic state.[40] Within the TME, NK cells interact with multiple immune cells and dynamically regulate the TME.[41] For example, NK cells can interact with T cells, dendritic cells (DCs), neutrophils, and macrophages to modulate antitumor immune responses.[42–45] NK cells can directly kill cancer cells by releasing cytotoxic granules such as perforin and granzyme B, and can also induce cancer cell apoptosis by expressing death receptors like Fas ligand and TNF-associated apoptosis-inducing ligand.[46] Additionally, NK cells can modulate the function of other immune cells by secreting cytokines such as IFN-γ and TNF-α, thereby enhancing the overall antitumor immune response.[47] Nevertheless, immunosuppressive components within the TME, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and certain cytokines (eg, TGF-β and IL-10), can significantly suppress NK cells activity.[48,49]

To overcome the suppression of NK cells function by the TME, researchers are exploring multiple therapeutic strategies, including the use of nanoparticles. These approaches aim to enhance NK cell-mediated antitumor immune responses by modulating NK cells function and TME characteristics. For instance, nanoscale liposomes and nanoemulsion systems can be employed to deliver TGF-β inhibitors and modify the TME.[50,51] NPs are also employed to enhance NK cell activity, thereby improving their antitumor capacity within the TME. A lipid-based non-viral vector encapsulates and delivers small interfering RNA (siRNA) to target and silence key intrinsic inhibitory checkpoint molecules (SHP-1, Cbl-b, and c-Cbl). This strategy not only enhances NK cell cytotoxicity within the tumor microenvironment but also demonstrates favorable safety and antitumor efficacy in in vivo experiments.[29] By immobilizing three monoclonal antibodies (PD-L1, 4–1BB, and NKG2A/TIGIT expressed on NK and T cell surfaces) onto optimized albumin/polyester composite nanoparticles, a tri-specific nanobody (Tri-Nab) was assembled. This Tri-Nab simultaneously activates NK cells and T cells, stimulating their immune responses to achieve synergistic tumor killing effects. It demonstrated potent antitumor activity in multiple tumor models, including colorectal cancer and melanoma models.[30] The nanomedicine system (R-NKm@NPs) consists of NK cell membranes modified to encapsulate temozolomide (TMZ) and interleukin-15 (IL-15). This system enables efficient drug release within the TME, enhances the cytotoxic function of NK cells, and induces an immune-stimulatory response. It has demonstrated excellent antitumor efficacy against glioblastoma in both in vitro and in vivo studies.[31]

Nanoparticles Modulate Dendritic Cells and T Cells

Dendritic cells (DCs) are bone marrow-derived cells distributed throughout all tissues,[52] DCs exhibit distinct antigen-presenting capabilities, recognizing antigens released by tumor cells, expressing co-stimulatory molecules,[53] and presenting these molecules to T cells to initiate immune responses.[54] As downstream effector cells of DCs, T cells also undergo corresponding regulatory effects when nanoparticles modulate DCs.[55] BMS-202 is a small-molecule PD-1 inhibitor that binds to PD-L1 and induces its dimerization, thereby preventing the formation of the PD-1/PD-L1 complex.[56] The photosensitizer (Ce6) can bind to it to form Ce6/BMS-202 nano-assemblies. This nano-platform enhances the maturation of dendritic cells (DCs) and the infiltration of antigen-specific T cells, thereby boosting the efficacy of immunotherapy.[32] Although photothermal therapy (PTT) can induce immunogenic cell death (ICD), its

immune protective effect is often transient and insufficient. This may be due to inadequate uptake and processing of tumor-associated antigens (TAAs) generated by PTT by antigen-presenting cells (APCs) in the TME.[57] A novel nanogold-adjuvanted polymeric vesicle (nGAP) modulates the tumor microenvironment by integrating PTT with immunotherapy, achieving effective treatment across multiple tumor models. nGAP not only efficiently kills tumor cells but also activates DCs, enhances antigen presentation and T-cell responses, while reducing the number of immunosuppressive cells such as Tregs and MDSCs, thereby reshaping the tumor immune microenvironment.[57]

Cell membrane coating technology provides a multifunctional "biosimilar cloak" for nanomedicine delivery systems by integrating natural cell membranes onto nanoparticle surfaces. This technology enables nanocarriers to inherit intrinsic biological properties of source cells, such as immune evasion, prolonged circulation time, dynamic targeting capabilities, biocompatibility, and biodegradability. Simultaneously, surface functionalization modifications can further enhance the programmability, multifunctionality, and biointerface compatibility of nanocarriers, thereby improving targeted delivery efficiency and extending their circulation time in vivo.[58] Dendritic cell membrane-coated nanoparticles (DCM-CN), which utilize this technology to combine DCs with nanoparticles, have been applied for tumor therapy. For instance, the DC membrane-coated nanoparticles (DC@AIEdots) developed by Xu et al can deliver drugs to breast cancer regions through interaction with T cells. Under light irradiation, they generate reactive oxygen species (ROS) to kill tumor cells while simultaneously activating immune responses.[59] DC membrane-coated nanovaccines (Si9GM) can upregulate cytotoxic T cells, reduce Tregs, and promote M1 macrophage polarization. When combined with PD-1 blockade therapy, they significantly enhance antitumor efficacy.[33] Similarly synthesized using this technology, the dendritic cell membrane-coated nanoparticles—Tumor-associated antigen-loaded dendritic cell membrane-coated paclitaxel nanoparticles (TAA-DCm@ PTX NPs)—effectively overcame challenges in Glioblastoma multiforme(GBM) immunotherapy, including blood-brain barrier (BBB) limitations and the immunosuppressive GBM microenvironment, through a dual strategy of "igniting the engine" and "releasing the brakes." These nanoparticles not only successfully penetrate the BBB and target GBM but also promote dendritic cell (DC) maturation and T cell activation through PTX-induced immunogenic cell death (ICD), while alleviating T cell exhaustion and dysfunction.[34] In GBM mouse models, this nanoplatform demonstrated significant antitumor efficacy with prolonged survival. Immunological cell analysis revealed that treatment markedly increased $CD45^+$ immune cell infiltration, reduced the proportion of MDSCs, elevated $CD8^+$ and $CD4^+$ T cell counts, and enhanced T cell-DC interactions. Immunohistochemical analysis also revealed a marked reduction in Ki67-positive cells within tumor tissues of the treated group, indicating significantly suppressed tumor cell proliferation activity and demonstrating the nanoparticle's capacity to remodel the immune microenvironment.[34] NPs prepared using cell membrane coating technology can also be applied to modulate different immune cells. For example, antigen-sensitized DC membranes were fused with TIM-3-targeted lipid NPs to prepare MLP-aTIM-3 nanovaccines; however, the primary focus of this nanovaccine's modulation was on T cells.[35] This nanovaccine targets the TIM-3 (inhibitory receptor) molecules on T cell surfaces to exert multifaceted regulation. It not only directly presents tumor antigens to exhausted T cells but also provides co-stimulatory signals, thereby reversing T cell exhaustion and restoring their proliferative capacity and effector molecule production. In vitro experiments demonstrated significantly enhanced proliferative capacity in exhausted T cells treated with MLP-aTIM-3, accompanied by markedly reduced CFSE fluorescence intensity, indicating extensive cell division. MLP-aTIM-3 markedly elevated CD107a and IFN-γ expression levels in exhausted T cells, promoting degranulation and cytokine secretion. This nanovaccine demonstrated potent antitumor efficacy in mouse models, significantly prolonging survival and enhancing immune memory responses.[35] Tissue-resident macrophages (TRMs) coated nanoparticles exert significant regulatory effects on T cells. TRMs present antigens to T cells via MHC molecules expressed on their surfaces, thereby activating T cells. For example, brain-resident macrophages (such as microglia) can present antigens to $CD4^+$ T cells via MHC-II, activating their anti-tumor function to secrete IFN-γ. These activated T cells, in turn, enhance macrophage phagocytic activity through AXL and MER signaling pathways, establishing a positive feedback loop that further amplifies the antitumor immune response. In cancer therapy, TRM-coated nanoplatforms can carry drugs and deliver them precisely to tumor sites, increasing local drug concentrations. They can also modulate immune cell functions within the tumor microenvironment, particularly enhancing T cell activity and function, thereby achieving tumor suppression.[60]

A photosensitizer-protein complex-based photodynamic therapy nanosystem induces ICD in tumor cells through photodynamic therapy (PDT), thereby releasing large amounts of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs). This process includes increased exposure of calreticulin (CRT) on the cell membrane, release of high mobility group box 1 (HMGB1), and enhanced ATP secretion. These substances attract and activate APCs, such as dendritic cells (DCs), promoting their maturation and efficient presentation of tumor antigens to T cells, thereby activating T cell-mediated immune responses. Furthermore, DAMPs released during PDT-induced ICD also promote APC maturation and activation, enhancing their antigen presentation capacity and thereby more effectively activating T cells. Nanoparticles can also modulate T cell subsets within the tumor microenvironment by reshaping it, reducing the number of Tregs or suppressing their function, breaking immune suppression, and enabling $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells to exert more effective antitumor effects.[61] A novel nanoparticle delivery system based on Cistanche deserticola polysaccharide (CDP)-functionalized dendritic fibrous nano-silica (DFNS) (CDP-DFNS) significantly enhances antigen cellular uptake and transmembrane transport, effectively activates DCs, and simultaneously promotes antigen-specific systemic and mucosal immune responses in in vivo experiments.[62] Although this nanoplatform was not applied to cancer treatment in this study, its capacity to activate immune system functions provides a starting point for cancer research. Another nanovesicle-based nanovaccine (termed NICER) encapsulates an epigenetic nanoregulator (ENR) that suppresses lysosomal protease activity in DCs, thereby reducing antigen degradation and enhancing cross-presentation. This enables DCs to more effectively activate $CD8^+$ T cells, increasing their ability to recognize and kill tumor cells. Furthermore, activated $CD8^+$ T cells can further infiltrate the tumor microenvironment to attack and eliminate tumor cells, including cancer stem-like cells, thereby improving the TME and enhancing therapeutic efficacy.[63] Immuno-initiator is a bioinspired nanoplatform specifically engineered to overcome immune suppression in IDH-mutant glioma (IDH-mt glioma). This nanoplatform efficiently activates DC maturation by inducing ROS-driven ICD in tumor cells, leading to the extracellular release of DAMPs such as CRT, HMGB1, and ATP. Mature DCs further cross-present tumor antigens, driving $CD8^+$ T cell proliferation and activation. Concurrently, the naturally occurring compound α-Mangostin carried by the nanoplatform reverses glioma-induced thymic and splenic atrophy at the systemic level, restoring the systemic T cell pool and promoting tumor-specific T cell infiltration within the brain, thereby inhibiting glioma growth.[64]

The intelligent delivery system M-CHNP/D, formed by fusing bacteria with acid-responsive calcium carbonate NPs, simultaneously achieves microenvironment regulation, targeted retention, and immune modulation deep within tumors tissues. By harnessing bacterial chemotaxis and hyaluronic acid-CD44 binding affinity, this nanoparticle precisely releases the loaded PD-L1-blocking peptide DPPA-1. It further releases calcium ions and buffers lactic acid, lifting acid-induced inhibition of DCs. Meanwhile, bacterial components like lipopolysaccharides induce massive CCL3 secretion via TLR pathways, recruiting DCs to the tumor site. This process stimulates rapid DCs maturation and efficient antigen presentation, directly activating $CD8^+$ T cells and NK cells to create a "hot" microenvironment coupling innate and adaptive immunity. In both colorectal and breast cancer models, M-CHNP/D not only significantly suppressed primary tumors but also established durable immune memory in vivo, resulting in long-term recurrence-free survival.[36] Bacterial outer membrane vesicles (OMVs) hold significant potential for immunotherapy.[65] The nano-platform Hf-OMVs, formed by combining bacterial OMVs with metal-phenolic networks, continuously catalyzes H_2O_2 to O_2 within the TME due to its innate immune-stimulating properties and surface-enriched catalase. This rapidly reduces HIF-1α expression and alleviates hypoxia. Meanwhile, the high Z-effect of Hf^{4+} significantly enhances local X-ray energy deposition, inducing DNA double-strand breaks (with peak γ-H2AX expression) that trigger massive tumor cell apoptosis and release tumor-associated antigens. These antigens, along with pathogen-associated molecular patterns (PAMPs) carried by OMVs, are jointly taken up by DCs, significantly promoting DC maturation (increased $CD80^+CD86^+$ ratio). Mature DCs efficiently present antigens in draining lymph nodes, activating $CD8^+$ T cells and inducing their massive infiltration into tumors. This process upregulates the cytotoxic molecule Granzyme B and stimulates a significant increase in local pro-inflammatory cytokines TNF-α, IFN-γ, and IL-6, forming a positive feedback loop. In a bilateral 4T1 breast cancer model, Hf-OMVs combined with radiotherapy achieved a primary tumor weight suppression rate of 78.2% and significantly inhibited distant tumor growth, demonstrating potent tumor suppression effects.[66]

Combining strategies that utilize nanoparticles to target DCs and T cells with conventional therapies such as PD-1/PD-L1 immune checkpoint inhibitors may yield highly synergistic effects.[21] PD-L1 is a transmembrane protein expressed on tumor cell surfaces. Binding of the programmed death-1 (PD-1) receptor on T cells to PD-L1 generates an inhibitory signal that suppresses T cell function, preventing effective tumor cell killing.[67]

In a mouse bladder cancer model, researchers utilized macrophage-derived exosome-mimetic nanovesicles (EMVs) as a nanocarrier to co-deliver the CD73 inhibitor AB680 and the PD-L1 inhibitor; The resulting nanocomplex (AB680@EMVs-aPDL1) demonstrated superior tumor targeting efficacy,[68] and the combination treatment markedly enhanced cytotoxic T lymphocyte activation and infiltration.[37] TP-SL@PB is a pH-responsive nanoplatform composed of tumor-penetrating polymer (TP) and solid lipid (SL) co-encapsulating Prussian blue (PB), designed to deliver PD-L1 siRNA to avascular lung metastases while capturing tumor antigens. Following intravenous injection, its cationic lipid shell interacts with the negatively charged lung tissue, enabling NPs to accumulate in the lungs. Subsequently, the transmembrane polymer undergoes charge reversal in the acidic tumor microenvironment, synergizing with Prussian blue-induced endothelial leakage to facilitate particle penetration into hypovascular metastases. Prussian blue catalyzes intranuclear hydrogen peroxide to generate hydroxyl radicals, inducing immunogenic tumor cell death and releasing tumor-associated antigens and damage-associated molecular patterns (DAMPs). These antigens are captured by positively charged lipids and polymer chains on the particle surface, delivered to DCs, and promote their maturation and migration to draining lymph nodes, activating $CD4^+$ and $CD8^+$ T cells. Concurrently, co-delivered PD-L1 siRNA downregulates PD-L1 expression on tumor cells, relieving T cell suppression and enhancing their infiltration and killing functions.[69] Magnesium hydride nanoparticles represent a highly promising novel nanomaterial offering significant advantages in optimizing the efficacy of transarterial chemoembolization for in situ liver tumors. Reacting with water, nano-MgH_2 releases Mg^{2+} ions that act as immunomodulators to activate T cells. This increases the ratio of cytotoxic T lymphocytes ($CD3^+CD8^+$) to helper T cells ($CD3^+CD4^+$) and promotes interferon-γ (IFN-γ) secretion. The resulting H_2 bubbles facilitate tirapazamine diffusion, enhancing chemotherapy efficacy while neutralizing the acidic TME to improve immunosuppression. Furthermore, combination with immune checkpoint inhibitors (eg, αPD-L1) can further activate antitumor immunity. In mouse models, tumors completely disappeared in the treatment group with significantly prolonged survival; in rat models, tumors were cleared within 3 weeks.[38]

Nano-Particles Modulate "Physical Barriers" in the Tumor Microenvironment

Nanoparticle Modulation of Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) are the most abundant cells in the TME matrix. They secrete large amounts of growth factors, cytokines, chemokines, and extracellular matrix (ECM) proteins,[70,71] these molecules may promote tumor cell growth, angiogenesis, invasion, and metastasis by influencing the TME.[72] Normal fibroblasts suppress tumor formation, whereas CAFs promote tumor cell proliferation, angiogenesis, and inflammation, regulate immune cells, and remodel the extracellular matrix (ECM). They further drive tumor progression by maintaining tumor stem cell properties and enhancing drug resistance.[73] CAFs also interact with various immune cells—including T cells, dendritic cells, tumor-associated macrophages, and regulatory T cells—to establish an immunosuppressive microenvironment that significantly weakens the body's antitumor immune response[74,75](Figure 2). However, CAFs are not solely "malignant components"; some studies reveal their tumor-suppressive roles. In pancreatic ductal adenocarcinoma, depletion of αSMA^+ myofibroblasts resulted in invasive, undifferentiated tumors with increased $CD4^+Foxp3^+$ Tregs, suggesting their role in promoting anti-tumor immunity.[76] Certain CAF subpopulations can indirectly inhibit tumor progression by inducing tertiary lymphoid structures (TLS) formation, thereby enhancing local anti-tumor immune responses.[75] Despite CAFs' dual role in tumor growth, current nanoparticle-based therapeutic strategies primarily target the suppression of their tumor-promoting effects. Nanomedicine delivery systems primarily treat cancer through several mechanisms: depleting CAFs, inhibiting CAF activation, normalizing CAFs, and modulating CAF effects on tumor cells and the ECM.[77]

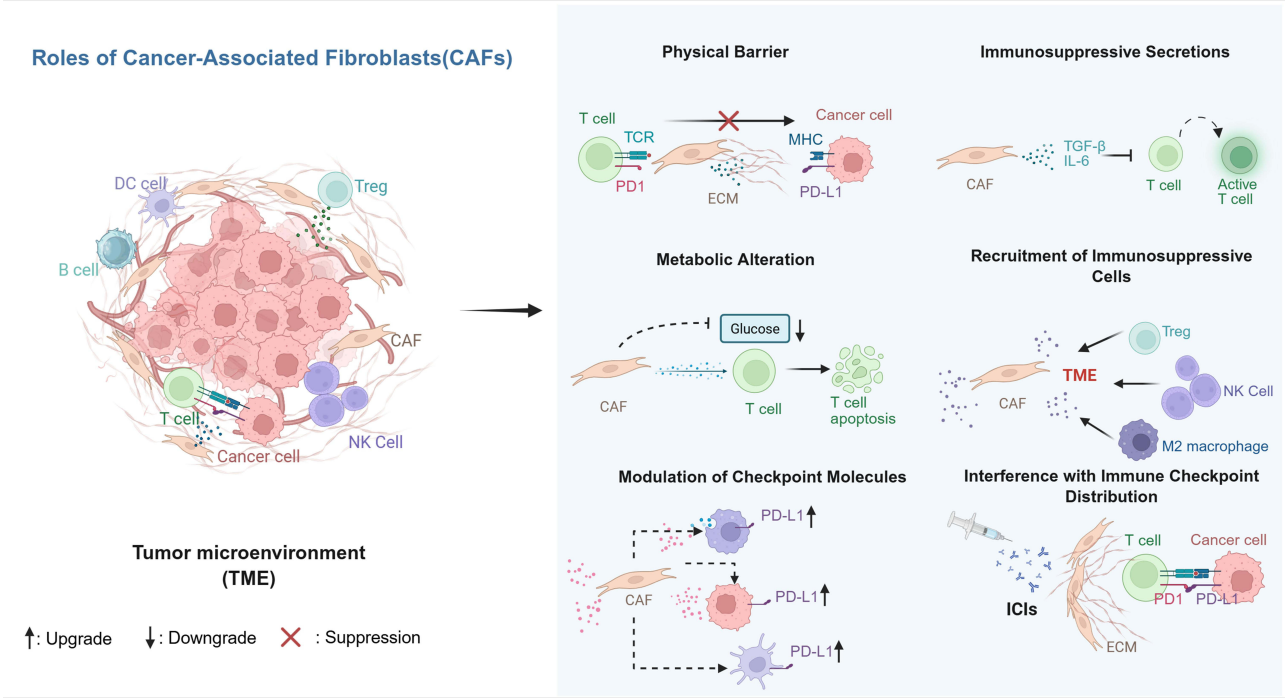

Figure 2 Roles of Cancer-Associated Fibroblasts (CAFs) Cancer-associated fibroblasts (CAFs) not only shape the tumor microenvironment by secreting cytokines, but also exert their effects through their own expression of PD-L1. CAFs not only function as a "physical barrier" within the tumor microenvironment (TME), but also regulate the "chemical barrier" through metabolic modulation and immunoregulation. This includes secreting cytokines, regulating immune cells, and modulating immune checkpoints.

Nanoparticle-Mediated CAF Consumption

Recent studies have identified several biomarkers that can be used to target CAFs within the TME of breast cancer. These include alpha-smooth muscle actin (α-SMA), fibroblast activation protein (FAP), fibroblast-specific protein, vimentin, and proline 4-hydroxylase. Nanoparticles can precisely deliver these biomarkers into the TME.[78,79] Among these markers, FAP has become the most frequently used CAF antigen for tumor targeting due to its overexpression on CAF surfaces. A nanoparticle-based photoimmunotherapy (nano-PIT) utilizes ferritin as a photosensitizer carrier, conjugating single-chain variable fragments of anti-FAP antibodies to ferritin. Through this approach, nano-PIT modulates and eliminates CAFs within the tumor microenvironment, thereby suppressing the secretion of CXC motif chemokine ligand 12 (CCL12) by CAFs while disrupting the ECM. This process enhances T-cell infiltration and effectively inhibits tumor growth.[80] Similarly, carboxymethylcellulose-docetaxel nanoparticle (Cellax-DTX) has shown enhanced therapeutic efficacy against pancreatic cancer by depleting CAFs. Serum albumin adsorbed onto the Cellax-DTX nanoparticle surface binds to the SPARC protein produced by CAFs, trapping the nanoparticles within the tumor microenvironment and triggering cellular internalization. This targeted action enables Cellax-DTX to sustainably deplete CAFs, reduce matrix density, increase tumor perfusion, and inhibit tumor growth and metastasis. Across multiple pancreatic cancer models, Cellax-DTX demonstrated superior antitumor activity and metastasis suppression compared to gemcitabine, significantly improving mouse survival rates.[81] To target CAFs, a telmisartan (Tel)-loaded liposome carrying doxorubicin (DOX) was engineered. This nanoparticle exerts highly efficient tumor treatment by sequentially targeting the angiotensin II type 1 receptor (AT1R) overexpressed on both CAFs and tumor cells. The mechanism involves: Subsequently, the nanoparticles penetrate deeper and more uniformly into the tumor interior to target tumor cells. Concurrently, CAFs apoptosis reduces pro-tumor cytokine secretion, enhancing tumor cell sensitivity to chemotherapeutic agents and reversing tumor microenvironment-mediated drug resistance.[82] Regarding therapeutic efficacy, this nanoparticle significantly inhibited tumor growth in a breast cancer nude mouse model without causing noticeable weight loss or other organ toxicity, indicating favorable safety and antitumor effects.[82]

Nanoparticles Suppress CAF Activation and Normalize CAFs

TGF-β is a multifunctional cytokine in tumorigenesis that participates in CAF activation, proliferation, and related activities.[77,83] It is also a key cytokine maintaining the CAF phenotype; inhibiting TGF-β in the TME can reverse the state of CAFs.[84] The mechanism by which anisamide-modified red blood cell membrane-coated silybin nanoparticles (ARm@SNP) inhibit tumor invasion and metastasis by regulating the TGF-β/Twist/EMT signaling pathway is as follows: CAFs secrete TGF-β, which activates transcription factors such as Twist and promotes epithelial-mesenchymal transition (EMT). This causes epithelial cells to lose their characteristics and acquire mesenchymal cell properties, weakening intercellular junctions while enhancing motility and invasive capacity, thereby facilitating tumor metastasis. ARm@SNP/Cis targets CAFs to reduce TGF-β secretion. Experimental data show significantly lower TGF-β expression in tumor tissues of the treatment group compared to other groups. It also markedly decreases Twist expression and inhibits EMT-related gene expression. Results indicate reduced expression of tumor stroma markers (Vimentin, CD44, MMP2) and increased expression of epithelial markers (E-cadherin) in the treatment group's tumor tissues. In summary, ARm@SNP/Cis effectively suppresses EMT and inhibits tumor cell invasion and metastasis by regulating this signaling pathway.[85] Bioactive Black Phosphorus Nanomaterials suppressed CAF activation by reducing TGF-β expression, thereby decreasing the number of inflammatory CAFs and myofibroblast. Following nanoparticle treatment, CAF activation markers such as ACTA2, COL1A1, COL1A2, and FAP were downregulated at both the RNA and protein levels. In animal studies, survival time was significantly prolonged in the treatment group. Furthermore, in an orthotopic tumor-stromal xenograft model, bioactive BP therapy suppressed the liver metastasis potential of pancreatic ductal adenocarcinoma, with downregulated expression of CAF activation markers in metastatic tumor tissues.[86] The lipid-polymer hybrid drug delivery system (PI/JGC/L-A) loaded with the bromodomain-containing protein 4 inhibitor JQ1 normalizes CAFs, reduces ECM deposition, and promotes immune cell infiltration. Furthermore, through gene transfer, it induces CAFs to express and secrete IL-12, thereby activating immune cells at the tumor site and enhancing the antitumor immune response.[87]

Concurrently, nanomedicine delivery systems can influence CAF activity through alternative pathways. One such LDL-based nanoplatform—the "Artesunate Nanoplatform"—specifically targets CAFs via aminoethyl anisamide modification while simultaneously carrying a photothermal agent and artesunate (ARS). This nanoplatform disrupts serine metabolism within CAFs, thereby inhibiting GTPase activity in the MAPK pathway and weakening the tissue resistance barrier formed by CAFs. Experimental data demonstrate that in multiple triple-negative breast cancer mouse models, compared to PTT monotherapy, the nanoplatform-combined treatment group exhibited significantly reduced tumor weight (approximately 100 mg decrease) by day 6 post-treatment and slower tumor volume growth within 12 days, indicating effective overcoming of PTT tolerance.[88]

Nanoparticles Modulate the Effects of CAFs on Tumor Cells and the Extracellular Matrix

FAP Peptide-Displaying Small Lipid Nanoparticles Surface-displayed Fibroblast Activation Protein (FAP) epitope peptides can be recognized by APCs, which in turn activate FAP-specific $CD8^+$ and $CD4^+$ T cells. These activated T cells subsequently attack FAP^+ CAFs within the TME, reducing CAF proliferation and function. The diminished CAF activity leads to decreased ECM production, which disrupts the tumor's fibrotic barrier, improving drug penetration, and enhancing chemotherapy efficacy.[89] A nanoplatform composed of Ca^{2+}-doped polydopamine loaded with GLS1 inhibitor CB-839 and modified with glutamine utilizes photothermal effects to reduce CAF numbers and degrade the ECM, effectively remodeling the tumor microenvironment to enhance drug delivery efficiency and immune cell infiltration. 839/CG generates localized hyperthermia under near-infrared (NIR) irradiation, disrupting CAF structure and function while decreasing ECM secretion. Experimental data revealed significantly reduced expression of the CAFs marker α-SMA following NIR treatment, indicating diminished CAFsnumbers. Such microenvironmental remodeling not only facilitates nanoparticle penetration into tumor tissues but also promotes immune cell infiltration, enhancing immunotherapy efficacy. Furthermore, the 839/CG-based nanomaterial combined with photothermal therapy demonstrated significant tumor growth inhibition and reduced lung metastasis foci in in vivo experiments.[90] Photodynamic therapy nanoparticles M1@PAP composed of a type I photosensitizer and anti-PD-L1 siRNA (siPD-L1) composed of photosensitizer I and anti-PD-L1 siRNA (siPD-L1). Poly-L-arginine (Arg9) within the M1@PAP nanoparticles releases NO upon ROS stimulation during PDT. This NO inhibits CAF activation, reduces expression of α-smooth muscle actin (α-SMA) and

collagen I in CAFs, thereby attenuating CAF-mediated ECM deposition. Furthermore, NO and its derivatives directly degrade ECM components such as collagen and fibronectin, decreasing tumor tissue density and enhancing nanoparticle and immune cell infiltration. Experimental results demonstrate that M1@PAP combined with laser irradiation significantly reduced the expression levels of α-SMA, Collagen I, and Fibronectin in CAF cells (NIH3T3 cells) and tumor tissues. These findings conclusively validate the pivotal role of NO in regulating CAFs and ECM degradation. Through this mechanism, M1@PAP not only effectively inhibits tumor growth by modulating CAFs and the ECM but also significantly enhances the synergistic effects of photodynamic therapy and immunotherapy.[91] A nanoscale platform composed of hyaluronic acid-modified pH-sensitive liposomes (CTHLs) and glycyrrheic acid-modified nanomicelles (DGNs) targets CAFs via CTHLs. By co-loading CAP and TEL, it blocks CAFs activation and ECM deposition, thereby modulating the TME. Concurrently, DGNs achieve deep penetration due to their small particle size, enabling precisely targeted tumor cell killing by the loaded DOX, thereby exerting anticancer effects.[92] A thermosensitive hydrogel-based nanoplatform loaded with disulfiram derivative CPD12C15 (SCC15) and tumor-targeted Cu^{2+} (PLHCu) ($SCC15^{+}$PLHCu@Gel) was applied to treat pancreatic cancer. SCC15 nanoparticles passively accumulated in the tumor stroma via size effect (approximately 107 nm) and surface charge, then were efficiently taken up by activated CAFs; Within CAFs, the encapsulated CPD12C15 selectively inhibits TGF-β1-induced Smad3 phosphorylation, directly downregulating α-SMA and Collagen I gene transcription and protein secretion, thereby reversing CAFs from a pro-fibrotic phenotype to a quiescent state. The consequent deactivation deactivation of CAFs dismantles the physical barrier of the ECM, removing spatial obstacles to chemotherapy drugs and immune cells. Following ECM degradation, pro-inflammatory cytokines such as IFN-γ, TNF-α, and IL-12 significantly increase within the tumor. These cytokines then continuously suppress CAF activity via paracrine pathways, establishing a "matrix-immune" positive feedback loop.[93] Nano-NIC, which encapsulates nicosamide (NIC) within nanoparticles through nanoengineering, inhibits key signaling pathways including STAT3, NF-κB, Wnt/β-catenin, and other key signaling pathways. This platform blocks the EMT process and CAF-mediated ECM remodeling, reverses M2 tumor-associated macrophage polarization, and reduces levels of pro-inflammatory factors such as IL-1β, IL-6, and TNF-α. This significantly inhibits the growth of primary prostate cancer lesions and bone metastasis.[94]

Nanoparticles Modulate the Extracellular Matrix

The extracellular matrix (ECM) is a non-cellular three-dimensional macromolecular network composed of collagen, proteoglycans, laminin, and fibronectin. This network regulates multiple cellular functions such as survival, growth, migration, and differentiation, and is crucial for maintaining normal homeostasis.[95,96] The ECM constitutes a vital component of the TME, providing structural support and transmitting mechanical signals that influence carcinogenic processes.[97] It plays an exceedingly complex role in cancer initiation, progression, and treatment. Increased ECM rigidity can activate signaling pathways within cancer cells, promoting their proliferation and invasive capabilities. Concurrently, ECM remodeling alters cell-cell interactions and releases growth factors and cytokines that support tumor growth.[98] ECM stiffening induced by increased collagen deposition and cross-linking disrupts tissue morphogenesis and drives malignant progression.[99] Collagen cross-linking is primarily mediated by LOX and LOX-like enzymes, which are frequently overexpressed in many cancers and metastatic sites.[100] In breast cancer, LOX-induced collagen cross-linking increases stiffness, β1 integrin aggregation, PI3K signaling, and focal adhesion formation, thereby driving invasion and tumor progression.[101] Current research frequently targets the interactions between heparin and various proteins closely associated with the ECM—such as proteases, apolipoproteins, and fibroblast growth factors—to modulate key biological signaling pathways involved in tumor progression, thereby progressively inhibiting tumor metastasis.[102–104] For instance, nanoheparin modulates the transcription of specific genes and the expression levels of ECM macromolecules.[105] Hyaluronic acid-chlorhexidine co-delivered albumin nanoscale systems containing cyclopentadiene and diselenide demonstrated potent antitumor effects and consistently suppressed distant tumor metastasis.[106] Overexpression and remodeling of the ECM may significantly impair the ability of NPs to reach target sites, compromising the effective delivery of therapeutic payloads.[107] Therapeutic targets within the ECM extend beyond heparin; collagen, as a major structural component of the ECM, exhibits abnormal accumulation in the TME. This accumulation not only increases tissue stiffness but also restricts the penetration of drugs and nanomedicines, ultimately undermining

therapeutic efficacy.[108] Fibrosis can be reduced, tissue stiffness lowered, and drug penetration improved by inhibiting collagen synthesis, degrading matrix collagen, suppressing collagen cross-linking, and blocking collagen-integrin signaling.[109–112]

Type I collagen is the primary component of the ECM and a key research target for numerous nanoparticles.[113] Adjusting the ECM without disrupting its structure remains a current research focus. Bioinspired lipoprotein (BLP) prepared using phosphatidylcholine as a scaffold, specifically BLP-M, was found to precisely control the thermodynamics of binding and diffusion kinetics between nanoparticles and type I collagen (COL1) by regulating the chain length of phosphatidylcholine. In an in situ pancreatic cancer mouse model, BLP-M employs a "weak binding-high diffusion" mechanism to penetrate the collagen network and extravasate into tumor parenchymal regions distant from blood vessels, enabling deep drug delivery. This approach significantly extended median survival without histological evidence of ECM chemical composition or structural damage, preserving TME integrity.[114] Superparamagnetic nanoparticles (MagNPs) with Fe_3O_4 cores and PO-PEG-NH_2 surface coatings also target COL1. Through photothermal therapy, when temperatures rise to 46 °C, COL1 undergoes irreversible thermal denaturation: The originally dense, ordered fibrous network rapidly disintegrates. This physical disruption directly weakens the ECM's mechanical barrier function and reduces interstitial hydraulic pressure, potentially enhancing the permeability of subsequent therapeutic drugs. Moreover, it simultaneously weakens the ECM and kills/tames cancer cells without compromising the chip's overall structure, creating conditions for subsequent combination therapies.[115]

Hyaluronic acid (HA), as one of the primary components of the ECM, plays a pivotal role in the TME. Its abnormal accumulation leads to reduced elasticity and increased gel pressure in tumor tissues, limiting the penetration of drugs and nanomedicines while promoting tumor progression and metastasis.[116,117] Consequently, HA has emerged as a critical therapeutic target for remodeling the ECM. By degrading hyaluronic acid, inhibiting its synthesis, and blocking its signaling pathways, drug penetration and distribution can be significantly enhanced, thereby modulating the TME and improving therapeutic outcomes.[118,119] A recent study confirmed that ECM topological features significantly influence NB invasiveness and therapeutic resistance by inducing adrenergic (ADRN) to mesenchymal transition. This research employed nano-grooved collagen type III-coated arrays (NGCA), a nanoparticle-based biomaterial capable of mimicking the ECM arrangement observed in high-risk and recurrent neuroblastoma tumors. By culturing NB cells on NGCA, the study revealed that this nanoparticle-induced ECM topology promotes adrenergic-to-mesenchymal transition (AMT) through activation of ROCK and YAP signaling pathways, enhancing MES phenotypic traits including increased invasiveness and resistance to chemotherapeutic drugs. Furthermore, the study demonstrated that treatment with ROCK inhibitors or YAP inhibitors reverses these effects, restores the ADRN phenotype, and increases NB cell sensitivity to chemotherapy.[97]

Disrupting the ECM structure is another method of modulating the ECM. The Thiodiacetic acid-coordinated Europium-Ferric nanowire (TFE) nanoplatform rapidly crosslinks into a gel at the tumor site. Leveraging its nanowire scale to match ECM fibers, it mechanically tears apart the dense collagen and fibronectin network, loosening the overall ECM structure. Subsequently, Eu^{3+} undergoes high-affinity competitive chelation with sialic acid highly expressed on the surfaces of the ECM and tumor cells, causing the nanowires to disintegrate and simultaneously release Fe^{3+} and DOX. Fe^{3+} catalyzes ROS bursts, depleting glutathione (GSH), triggering lipid peroxidation and inducing ferroptosis; Concurrently, sialic acid chelation blocks the "don't eat me" signal and releases High Mobility Group Box 1 (HMGB1), inducing immunogenic cell death. This polarizes macrophages toward the M1 phenotype and recruits $CD8^+$ T cells, establishing sustained immune attack. Animal studies demonstrate that the nanoparticle-based treatment group exhibits significantly superior breast cancer suppression compared to free drug administration, with lower systemic toxicity.[120]

Extracellular vesicles (EVs) are nano- to micrometer-sized particles bounded by a lipid bilayer membrane.[121] EVs are also recognized as key mediators of cellular communication within the TME.[122,123] Although studies have demonstrated the role of EVs in metabolic regulation,[124,125] few publications have summarized the mechanisms by which EVs contribute to metabolic reprogramming within the TME. EVs influence cellular functions by carrying proteins, RNA, DNA, lipids, metabolites, and other bioactive substances.[126] As transmembrane proteins, integrins are widely expressed on various types of EVs,[127] and play a crucial role in cell communication.[128] Integrins exert dual regulation of the ECM through distinct mechanisms. Integrins (such as αvβ3, α6β4, and αvβ5) expressed on tumor cell surfaces or carried by exosomes bind with high affinity to fibronectin, collagen, and laminin, rapidly forming focal adhesions.[129] Simultaneously, exosomal integrins

stimulate recipient cells (eg, CAFs) to release matrix metalloproteinases (MMPs), thereby degrading the ECM barrier. This bidirectional regulatory mechanism is also the key approach we utilize to modulate the TME via EVs.

Nanoparticles Modulate Metabolic Processes in Immune Cells Within the Tumor Microenvironment

TME plays a pivotal role in promoting the proliferation and dissemination of malignant cells,[130] while its physicochemical environment is characterized by elevated H_2O_2 levels, GSH overexpression, low pH, hypoxia, hypermetabolism, and high ATP levels.[131–134] Therefore, modulating TME metabolic reprogramming to alter its physicochemical environment has emerged as a novel approach to improving tumor treatment efficacy. However, immune cells, as a vital component of the TME, exhibit metabolic mechanisms that profoundly influence the surrounding tissue environment through their utilization of nutrients, environmental factors, and cellular metabolic byproducts.[135,136] Consequently, the metabolic processes of immune cells are crucial for TME regulation[137,138](Figure 3). This section discusses not only nanoparticle-mediated modulation of the physicochemical environment of the TME but also summarizes nanoparticle effects on immune cells and TME-related cellular metabolic regulation mechanisms.

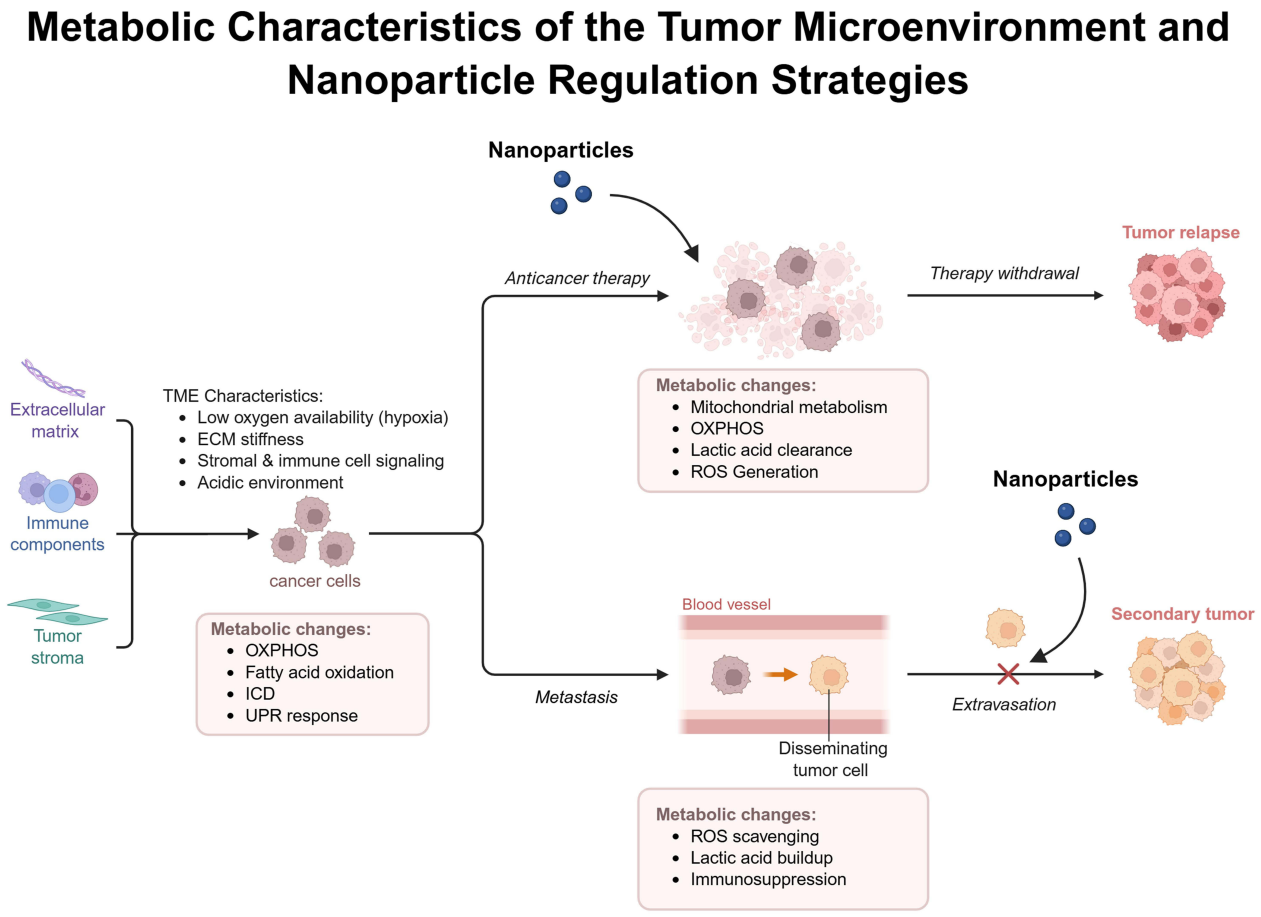

Figure 3 Metabolic Characteristics of the Tumor Microenvironment and Nanoparticle Regulation Strategies The metabolic landscape of the tumor microenvironment (TME) can be summarized as a systemic reprogramming characterized by "cancer cell dominance, stromal cell collaboration, and immune cell suppression." In essence, malignant cells undergo genetic and epigenetic alterations, thereby "outsourcing" their demands for ATP, reducing equivalents, and synthetic precursors to the surrounding stroma and immune cells. Concurrently, they employ metabolites as signaling molecules to remodel the entire ecological niche. Concurrently, the environment exhibits physicochemical states characterized by hypoxia and lactic acidosis. The suppression of tumor progression and metastasis by nanoparticles is achieved through the modulation of metabolic processes, thereby reshaping the TME.

Abbreviation: OXPHOS: Oxidative phosphorylation; ICD:Immunogenic cell death; ROS: Reactive oxygen species.

Nanoparticles Modulate Hypoxic Tumor Microenvironments and Associated Immune Cells

The Warburg effect—where tumor cells preferentially generate energy through glycolysis even in oxygen-rich environments—forms the foundation for studying tumor metabolism and TME metabolism.[139] Under hypoxic conditions, hypoxia-inducible factor (HIF-1α) is activated, regulating tumor cell gene expression and promoting the synthesis of glycolysis-related enzymes, thereby enhancing the tumor cells' reliance on glycolysis for energy acquisition.[137] Concurrently, HIF-1α promotes angiogenesis, supplying tumor cells with increased nutrients and oxygen.[140] Currently, regulating ROS levels within the TME represents the primary strategy for nanoparticle-mediated modulation of TME metabolic reprogramming. A multifunctional dual-atom nanozyme (dAuFeMn-NCe) uniformly loaded with ultrasmall gold nanoparticles on its surface significantly enhances X-ray energy deposition at tumor sites, enabling efficient ROS generation under low-dose radiotherapy. This nanoparticle significantly downregulates key metabolic genes in the HIF-1 signaling pathway (eg, ALDOC, Il6ra, Plcg2, Egln3), thereby inhibiting tumor cells' reliance on glycolysis under hypoxic conditions, blocking the Warburg effect, and weakening their energy supply and hypoxic adaptation capabilities. The PD-L1 aptamer on its surface demonstrates enhanced tumor targeting ability in the 4T1 tumor-bearing mouse model.[141]

Following intravenous injection, the nanoproteolysis-targeting chimera (Nano-PROTAC, NanoTAC) accumulates in tumor tissues via the EPR effect. Upon cleavage by highly expressed Cathepsin B, it rapidly releases HK2-PROTAC and the photosensitizer verteporfin. The PROTAC recruits HK2 to the VHL E3 ligase complex with high affinity, continuously degrading HK2. This significantly inhibits glycolysis and mitochondrial respiration, rapidly reducing lactate secretion and oxygen consumption. It reverses the Warburg effect and alleviates tumor hypoxia, creating favorable conditions for subsequent photodynamic therapy. Following laser irradiation, verteporfin efficiently generates ROS, synergizing with mitochondrial damage caused by HK2 deficiency to activate caspase-3 cleavage of GSDME. This induces massive tumor cell pyroptosis, characterized by vesicular protrusions on the cell membrane, while significantly promoting CRT exposure and the release of immunogenic molecules including ATP, HMGB1, IL-1β, and IL-18. Subsequently, DC maturation intensified, cytotoxic T cell infiltration markedly increased, the proportion of immunosuppressive Tregs decreased, and the TME shifted from "cold" to "hot." This strategy achieved rapid and sustained tumor clearance in a triple-negative breast cancer model, with most mice achieving complete remission and demonstrating potent and enduring suppression of lung metastasis.[142] Hemoglobin-encapsulated Biotin-Targeted Oxaliplatin(IV) Prodrug Nanoparticle (Hb@BTOPtIV) delivers both the platinum(IV) prodrug and hemoglobin to tumor tissues via biotin receptor-mediated targeting. Hemoglobin continuously supplies oxygen in hypoxic regions, attenuating HIF-1α signaling and reversing tumor metabolic suppression. Platinum(IV) is activated to platinum(II) in the reductive microenvironment, inducing DNA damage and immunogenic cell death. This promotes DC maturation, increased infiltration of cytotoxic T lymphocytes ($CD8^+$ T cells), and reduced Tregs proportion, thereby reprogramming the tumor immune microenvironment.[143]

The NADPH/GSH antioxidant system serves as the core mechanism for mitochondrial resistance to oxidative stress. Its function lies in continuously scavenging H_2O_2 and other peroxides generated by electron leakage in the respiratory chain or external stimuli, thereby maintaining mitochondrial membrane potential, protein sulfhydryl status, and DNA integrity. This system is a critical link in sustaining mitochondrial redox balance and metabolism within the TME.[144,145] Under hypoxic conditions, gold nanoparticles (AuNPs) act as electron acceptors, competitively capturing cytochrome-mediated electron flow within tumor cells. This disrupts the NADPH/GSH redox buffer system, triggering ROS bursts and mitochondrial dysfunction, thereby inducing Immunogenic cell death (ICD). This synergistically polarizes M1 macrophages, reshaping the immunosuppressive TME into an immune-activated state. Experiments demonstrate that this strategy achieves >94% tumor cell death in the 4T1 breast cancer model, simultaneously increasing $CD8^+$ T cell infiltration by 2.4-fold and achieving a tumor growth inhibition rate of 94.7%, significantly outperforming monotherapy groups.[146]

A novel prodrug nano-metal–organic framework (nMOF named DCCMH) serves as an intelligent nanoplatform integrating prodrug design, TME-responsiveness, and multiple therapeutic mechanisms, exhibiting potent synergistic antitumor activity and excellent biocompatibility. This nanomaterial degrades upon stimulation by high concentrations of GSH and H_2O_2 within the TME, intelligently releasing $Cu^{+}/^{2+}$, α-Cyano-4-hydroxycinnamic acid (CHCA),

metformin (Met), and DOX to achieve multiple synergistic therapeutic mechanisms: Cu^{+} catalyzes the Fenton reaction to convert H_2O_2 into highly toxic hydroxyl radicals while oxidizing itself to Cu^{2+} and consuming GSH, disrupting tumor cell redox homeostasis; CHCA, as a monocarboxylate transporter inhibitor, suppresses lactate efflux, lowers intracellular pH, and further enhances Fenton reaction efficiency to increase ROS production; Met activates the AMPK signaling pathway, disrupting tumor cell metabolism and enhancing DOX chemotherapy sensitivity. Experimental results demonstrate that DCCMH significantly reduces GSH levels, sustainably generates ROS, induces mitochondrial damage and apoptosis in vitro, exhibits potent cytotoxic effects against multiple cancer cell lines (eg, HepG2, HeLa, U87MG, 4T1), while maintaining low toxicity to normal cells. In vivo experiments demonstrated that DCCMH efficiently accumulates in tumor tissues via HA-mediated CD44 targeting, significantly inhibiting tumor growth in the mouse hepatocellular carcinoma H22 model with a tumor suppression rate of 74.24%. It exhibited good biosafety without causing significant systemic toxicity.[147] TiO_2–Au@DON nanocomposites remodel the TME by simultaneously modulating oxidative stress and energy metabolism. Au-modified TiO_2 Janus structures generate polymorphic reactive oxygen species upon ultrasonic excitation, overcoming hypoxic TME; glutamine antagonist prodrug DON is released via tumor-specific enzymatic cleavage, blocking TCA flux and depleting reducing equivalents, significantly down-regulating NADPH/$NADP^{+}$ ratio and GSH levels, thereby weakening tumor antioxidant defenses. Metabolic reprogramming synergistically amplifies immunogenic cell death signals with oxidative stress, promoting the release of damage-associated molecular patterns. This drives dendritic cell maturation and cytotoxic T cell infiltration, thereby activating systemic antitumor immune responses. In the 4T1 breast cancer model, this integrated strategy sustainably inhibits primary tumor growth and prevents distant lung metastasis, demonstrating significantly superior efficacy compared to monotherapy.[148] The CaCu@CS-GOx nanoplatform releases glucose oxidase (GOx), Ca^{2+}, and Cu^{2+} upon degradation in the acidic TME. GOx catalyzes glucose oxidation, depleting substrates and generating H_2O_2, thereby cutting off tumor cell energy supply; Cu^{2+} is reduced to Cu^{+} by GSH, driving Fenton-like reactions that continuously generate reactive oxygen species. This induces aggregation of mitochondrial TCA cycle-associated proteins, triggering cuproptosis. Ca^{2+} disrupts endoplasmic reticulum membrane integrity, causing cytoplasmic calcium overload and inhibiting Ca^{2+}-ATPase isoform 4-mediated efflux, thereby amplifying mitochondrial dysfunction and apoptotic signaling. Metabolic disruption promotes calreticulin exposure, high-mobility group box 1 release, and ATP secretion, inducing immunogenic cell death. This enhances dendritic cell maturation and $CD8^{+}$ T cell infiltration, reduces Treg proportion, and drives M2-polarized tumor-associated macrophages toward M1 polarization. When combined with anti-CTLA-4 antibody, this approach further suppresses postoperative recurrence and lung metastasis while establishing long-term immune memory.[149] The GDOX@HSEc nanoplatform reshapes TME metabolism through a "bacteria-nanoparticle" synergistic model: Engineered Escherichia coli HSEc overexpresses heparan sulfatase 1 on its surface, degrading excess heparan sulfate in the tumor stroma. This disrupts its pro-angiogenic and immunosuppressive signaling, causing microvascular density to plummet by 60% and significantly reducing hypoxia-induced lactate accumulation. Concurrently, its doxorubicin-loaded glycogen nanoparticles (GDOX NPs) rapidly release DOX in the acidic TME, inducing DNA damage and triggering caspase-3-dependent apoptosis. This reduces tumor cells' predatory uptake of glucose and GSH, indirectly restoring metabolic adaptability in cytotoxic T lymphocytes and M1 macrophages.[150]

Nanoparticles Modulate Lipid Metabolism and Adenosine Metabolism

TAMs are myeloid immune cells infiltrating the tumor microenvironment, typically exhibiting a pro-tumor M2-like phenotype that accelerates tumor progression by secreting immunosuppressive factors and undergoing metabolic reprogramming.[151] Nanoparticles surface-modified with CD206 ligands can precisely deliver siRNA into TAMs, severing the lipid transfer chain between TAMs and tumor cells to disrupt energy supply and metastasis capabilities.

Research indicates that adenosine (ADO) primarily originates from ATP metabolism catalyzed by CD39 and CD73. Factors within the tumor microenvironment (TME), such as HIF-1, TGF-β, and IL-10, further upregulate CD39/CD73 expression, forming a positive feedback loop.[152] The abundant adenosine in the TME broadly suppresses key immune processes—including antigen presentation by dendritic cells (DCs), T cell activation and infiltration, and NK cell cytotoxicity—by binding to critical receptors such as A2aR/A2bR, thereby constructing a robust immunosuppressive

network.[153] Small-molecule drugs targeting the ADO pathway have garnered significant attention due to their unique advantages, including rapid absorption and distribution, high bioavailability, strong stability, and sustained therapeutic effects.[154,155] Certain nanomaterials—such as liposomes, polymeric micelles, mesoporous silica, biomimetic membranes, and metal nanoparticles—have emphasized their abilities to significantly enhance immunotherapy efficacy by improving adenosine stability, prolonging circulation time, enabling tumor-targeted accumulation, and facilitating responsive release.[153,156–158]

Challenges and Future Prospects for the Clinical Application of Nanoparticles in Modulating the Tumor Microenvironment

Despite the numerous advantages demonstrated by nanoparticles as drug delivery systems, translating them into clinical applications remains a significant challenge. In fact, only a handful of nanoparticle formulations have advanced to clinical trials (Table 2). While current research demonstrates promising outcomes, clinical applications remain scarce. This necessitates exploring novel strategies for nanoparticle utilization—such as harnessing natural nanoparticles or developing novel combination therapies—to overcome current limitations in modulating the tumor microenvironment. Concurrently, we must also address the cost implications of nanoparticles throughout their journey from synthesis to clinical implementation.

Challenges in the Clinical Translation of Nanoparticle Regulation of the Tumor Microenvironment

Translational research serves as the critical link in converting basic research findings into clinical practice. In the field of nanoparticles, this step is particularly crucial, yet the translational process itself is lengthy and constrained by numerous factors. Consequently, only a small fraction of basic research outcomes ultimately translate into clinical applications. First-in-human (FIH) trials represent a pivotal stage in the translational research pathway. However, within the highly specialized field of nanoparticles, distinct nanomaterials exhibit unique mechanisms and target sites. Furthermore, the substantial financial investment and stringent ethical approval requirements for human trials make it difficult for initial

Table 2 Clinical Trials of Nanoparticles in Cancers

Nanoparticles	Cargos	Conditions	Sponsor	Status	NCT Number
Nab-paclitaxel	Nab-paclitaxel and Bevacizumab	T Cell, Melanomas	Academic and Community Cancer Research United	Completed	NCT02158520
Ferritin Nanoparticle	Epstein-Barr Virus gp350	$CD4^+$ T	National Institute of Allergy and Infectious Diseases	Active	NCT04645147
Nano-luteolin	Luteolin	Oral cancer	Cairo University	Unknown status	NCT03288298
Gemzar® mix with Compound Glycyrrhizin Injection	–	Liver Cance	Fuda Cancer Hospital, Guangzhou	Completed	NCT02449109
Polysiloxane Gadolinium-Chelates based Nanoparticles	–	Nervous System Neoplasms	University Hospital, Grenoble	Completed	NCT02820454
Targeted Atomic Nano-Generators	HuM195	Advanced Myeloid Malignancies	Memorial Sloan Kettering Cancer Center	Completed	NCT00672165
Nano Liposome	Ceramide	Advanced Solid Tumors	Keystone Nano, Inc	Completed	NCT02834611
Nab-Paclitaxel	Gemcitabine, Paclitaxel	Pancreatic Cancer	Grupo Hospital de Madrid	Completed	NCT01442974

nanoparticle experiments to benefit subjects. This significantly increases the complexity of conducting FIH trials, rendering their implementation a challenging endeavor.[159] Meanwhile, to promote the application of nanoparticles in clinical settings, their preparation process must adhere to pre-established quality standards, control specifications, and good manufacturing practices—that is, production standards must be established for nanoparticles intended for medical use.[160] Similarly, the economic implications of nanoparticle manufacturing cannot be overlooked. The probability of successfully translating small-molecule drugs from preclinical proof-of-concept to commercial products is only about 6%.[161] Even setting aside R&D risks, the complex formulation systems and lengthy preparation processes of nanoparticles still result in high production costs. Thus, the cost-effectiveness of nanoparticles relative to low-cost drug therapies must be carefully weighed.[162]

Exosomes Modulate the Tumor Microenvironment

Exosomes, as naturally occurring nanovesicles secreted by cells, carry biomolecules such as proteins, lipids, mRNA, and miRNA, serving as crucial mediators of intercellular communication.[163,164] Exosomes can regulate cellular behavior within the tumor microenvironment, particularly by supporting tumor growth and metabolic reprogramming of the TME through the transfer of bioactive molecules such as proteins, mRNA, and miRNA to fibroblasts and immune cells.[165–167] Unlike conventional drug carriers such as liposomes and inorganic porous nanomaterials, exosomes exhibit superior biocompatibility, targeting capability, low toxicity, and high delivery efficiency due to their lack of side effects arising from material aggregation.[168,169] Exosomes can be engineered to express specific markers or encapsulate therapeutic payloads, emerging as novel nanoscale platforms for cancer therapy. Engineered exosomes are natural exosomes processed through bioengineering techniques. This modification enhances the nano-platform's drug loading efficiency, targeting capability, and resistance to drug metabolism.[170]

They also constitute an important intercellular communication system between NK cells and cancer cells.[171,172] A nanoscale platform constructed from chimeric antigen receptor-natural killer (CAR-NK) cell-derived exosomes (ExoCAR) and a nanobomb (referred to as Micelle). This platform achieves precise targeted delivery via CAR-NK cell-derived exosomes, simultaneously leveraging the high ROS levels typically present in the TME and the ROS responsiveness of the nanobomb to achieve cascading amplified drug release. This approach induces ferroptosis through RSL3 and ROS, suppressing the growth of HER2-positive breast cancer brain metastases. The exosome component of this nanoplatform, as a natural intercellular communication tool, exhibits excellent biocompatibility, reducing immune reactions and off-target toxicity.[173]

Exosomes exert dual effects on immune cells: those derived from non-small cell lung cancer (NSCLC) evade immune surveillance by suppressing T cell activation, inducing regulatory T cells and myeloid suppressor cells, and impairing the function of NK cells and $CD8^+$ T cells.[174,175] In contrast, certain miRNAs within exosomes, such as miR-433, can suppress NSCLC tumorigenesis by enhancing the infiltration of both $CD4^+$ T cells and $CD8^+$ T cells.[176]

An engineered exosome system based on non-coding RNA (LV-miR206-HT29-EXO) was employed to modulate the tumor immune microenvironment, thereby enhancing the efficacy of immunotherapy in colorectal cancer (CRC). Exosomal membrane fusion efficiently delivered miR-206 to tumor and immune cells, directly targeting T cell immunoreceptor with Ig and ITIM domains (TIGIT) and blocking its downstream SHIP recruitment, thereby inhibiting the PI3K/AKT/mTOR axis. Following TIGIT downregulation, $CD8^+$ T cell granzyme B secretion significantly increased, while Treg proportion and IL-10 secretion markedly decreased. Concurrently, Th1 cells increased while Th2/Th17 cells decreased, reversing the overall immunosuppressive microenvironment. Ultimately, in an orthotopic colorectal cancer model, tumor volume decreased sevenfold and survival rate rose to 70%.[177]

Exosomes can also serve as drug delivery platforms for carrying chemotherapeutic agents such as paclitaxel (PTX), doxorubicin (DOX), and gemcitabine (GEM), thereby enhancing tumor suppression while reducing toxicity to normal tissues.[178–180] Exosomes can also be utilized for miRNA and mRNA delivery.[181–183] IL-12 mRNA-loaded exosomes (IL-12-Exo) administered via inhalation effectively activate IFNγ-mediated immune responses, amplifie systemic immune responses, and establish immune memory, thereby significantly inhibiting lung cancer progression and preventing tumor recurrence.[184] Exosomes derived from miR-146b-expressing MSCs significantly reduced the growth of glioma xenografts in a rat model of primary brain tumors.[185] Ginseng-derived exosome-like nanoparticles (GENs) significantly

reduce expression of α-SMA, a marker of cancer-associated fibroblasts, in the tumor microenvironment and inhibit M2 polarization of tumor-associated macrophages (TAMs) to suppress tumor growth. Concurrently, they exert additional antitumor effects by carrying ptc-miR396f to silence genes such as c-MYC and BCL2.[186]

Tumor-derived exosomes (TDEs) critically reshaping the TME by interacting with fibroblasts, endothelial cells, and immune cells within the TME. They modulate the composition and function of the extracellular matrix, induce cellular differentiation, and alter intercellular signaling.[187] Exosomes also play a significant role in angiogenesis. They promote tumor growth and metastasis by regulating endothelial cell migration, phenotypic changes, and neovascularization through the delivery of growth factors and angiopoietins.[188,189] Although nanoparticles targeting TDEs are not yet available at this stage, given the critical role of TDEs in the TME, developing nanoparticles targeting TDEs represents a viable approach. At present, nanoparticle-mediated modulation of the tumor microenvironment (TME) primarily involves regulating both "physical barriers" and chemical barriers. The emergence of TDEs provides an excellent bridge between the two approaches. On one hand, TDEs can interact directly with the "physical barrier" ECM, disrupting its integrity and carrying CAF-associated inhibitors to suppress ECM formation. On the other hand, TDEs can also be engineered to deliver immunotherapy-related drugs . This allows the regulation of the TME's "chemical barrier" — the diverse immune cells — thus establishing a versatile nanoplatform for TME modulation.

Despite the promising research findings on exosomes, they still face numerous challenges similar to those encountered with nanoparticles, including preparation issues; cost-effectiveness concerns; and most critically, bioavailability problems. The production and purification of exosomes are time-consuming and costly, with a lack of standardized protocols and quality control standards.[190,191] Furthermore, the targeting and drug release kinetics of exosomes are influenced by multiple factors, such as drug type and size, loading methodology, and exosome source. The biodistribution of exosomes from different sources, their biotoxicity, and the pharmacokinetics of different drug payloads remain incompletely understood. Additional in vivo studies and clinical trials are urgently needed to evaluate the safety and efficacy of exosome-based drug formulations.[192,193] However, this step requires extensive experimentation. Due to the unique nature of engineered exosomes as a novel drug delivery platform, it is unlikely that preliminary in vivo studies will yield the desired therapeutic effects for patients. The complexity of the preparation process and cost considerations also make conducting such clinical trials extremely challenging. Nevertheless, engineered exosomes remain an undeniably promising area of research, as they significantly outperform other nanoparticles in terms of drug-carrying capacity, biocompatibility, and low toxicity due to their naturally derived nanoscale platform. They offer a new approach to using nanoparticles to modulate the TME and ultimately treat cancer.

Discussion

The TME has unequivocally emerged as a pivotal determinant in tumor initiation, progression, and therapeutic resistance. Its highly heterogeneous, dynamic, and immunosuppressive nature poses formidable challenges to conventional therapies. This review has systematically delineated the sophisticated roles of nanoparticles in remodeling the TME, highlighting their capacity to precisely target and modulate diverse components—from chemical barriers (NK cells, DCs, T cells) to physical barriers (CAFs, ECM) and the metabolic milieu.

The broader implication of these nanoparticle-driven strategies is a paradigm shift in cancer therapy, moving from a narrow, cytotoxic focus on tumor cells to a holistic "ecosystem engineering" approach. Nanoparticles have fundamentally evolved beyond their conventional role as mere drug carriers; they are now multifunctional "microenvironmental engineers" capable of executing complex, multi-step therapeutic programs within the TME. This engineering feat is exemplified by their ability to sequentially and synergistically dismantle the TME's interconnected physical and chemical barriers. The first wave of intervention often targets the physical barriers: nanoparticles can be designed to release ECM-degrading enzymes (eg, collagenase, hyaluronidase) or deliver drugs that normalize and deplete CAFs, thereby reducing stromal density and interstitial fluid pressure. This initial "loosening" of the tumor structure is critical, as it enhances the penetration depth of both the nanoparticles themselves and subsequently administered therapeutics, while also facilitating the influx of immune cells. Following this physical remodeling, a second wave of nanoparticles, or the same platform in a sequential release manner, can address the chemical barriers. This process reprograms the immunosuppressive cellular landscape by targeting Tumor-Associated Macrophages to promote their M1-like polarization, inhibiting regulatory

T cells (Tregs), and simultaneously activating cytotoxic T lymphocytes (NK cells) and DCs through the delivery of cytokines (eg, IL-12, IL-15), immune checkpoint inhibitors (eg, anti-PD-L1), or targeted siRNAs.

A particularly sophisticated aspect of this engineering approach is the concurrent correction of aberrant metabolic pathways. Nanoparticles can alleviate hypoxia by carrying oxygen-generating agents or catalase-like nanozymes that decompose H_2O_2 to O_2, which in turn suppresses HIF-1α signaling. They can also disrupt the Warburg effect by targeting key glycolytic enzymes or lactate transporters, thereby reducing lactate accumulation and reversing the acidotic pH that inactivates immune cells. This metabolic reprogramming does not merely starve cancer cells; it directly revitalizes anti-tumor immunity by restoring the metabolic fitness of T cells and dismantling an immunosuppressive metabolic niche. This synergistic multi-targeting strategy—orchestrating physical dismantlement, immune reactivation, and metabolic normalization—is paramount. Isolated interventions often fail due to the TME's robust compensatory mechanisms, whereas a coordinated assault prevents these escape routes, leading to a more profound and durable treatment response.

However, the translation of these promising nanoplatforms from bench to bedside remains a significant hurdle. The current focus must expand beyond demonstrating efficacy in preclinical models to addressing the fundamental challenges of clinical translation. The reproducible and scalable synthesis of nanomaterials with consistent physicochemical properties (size, shape, surface charge) is a primary concern. Furthermore, a deeper understanding of the long-term biocompatibility and potential off-target toxicity of both the nanocarriers and their degradation products is urgently required. The economic viability of these complex formulations compared to conventional therapies also demands critical assessment.

Future research should pivot towards several promising yet underexplored avenues. First, the development of "smart" nanoparticles capable of responding to multiple TME-specific stimuli in a sequential manner could achieve unprecedented spatial and temporal control over therapeutic release. Second, harnessing natural nanoparticles, particularly engineered exosomes, offers a biomimetic solution with superior biocompatibility and targeting innateity. As discussed, exosomes can serve as dual-function platforms, simultaneously disrupting the physical ECM barrier and delivering immunomodulatory cargo, thereby bridging the gap between physical and chemical TME remodeling. Finally, the integration of nanoparticle-based TME modulation with other treatment modalities, such as radiotherapy, chemotherapy, and especially immunotherapy (eg, immune checkpoint inhibitors), should be explored in more rational combination regimens.

In conclusion, nanoparticle-driven TME remodeling represents a cornerstone of next-generation oncology. By simultaneously dismantling immunosuppressive networks and reprogramming tumor metabolism, nanomedicine offers a powerful toolkit to reverse the TME from a pro-tumorigenic fortress into a therapeutic ally. The path forward requires a concerted effort from material scientists, biologists, and clinicians to overcome the translational barriers and fully unlock the potential of engineering the tumor microenvironment for effective and durable cancer treatment.

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