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REVIEW

Preclinical Nanoparticle Approaches Targeting Tumor-Associated Macrophages in Breast Cancer: From Mechanisms to Therapeutic Strategies

Jiahui Teng[1,2], Xiaorong Zhang[2], Chunxiao Shen[1,2], Ling Wang[2], Jiali Hu[2], Zefen Li[1,2], Yan Liu[2,3], Jinyan Liu[1,2], Shufei Wei[1,2], Liangliang Wang[1,2]

[1]The First Clinical Medical School, Jiujiang University, Jiujiang, Jiangxi,People's Republic of China; [2]Department of Pathology, Affiliated Hospital of Jiujiang University, Jiujiang, Jiangxi, People's Republic of China; [3]The First Clinical Medical School, Gannan Medical University, Ganzhou, Jiangxi, People's Republic of China

Correspondence: Shufei Wei; Liangliang Wang, Email weishufei0429@163.com; jjwangliangliang@163.com

Abstract: Breast cancer is the most common malignancy among women worldwide, with high incidence and mortality rates. Tumor-associated macrophages (TAMs) are key mediators in the immunosuppressive tumor microenvironment (TME), contributing to poor prognosis and reducing immunotherapy efficacy. This review examines the dual roles of TAMs in breast cancer progression. TAMs are known to promote tumor development through angiogenesis, immune evasion, and metastasis, while M1-polarized TAMs conversely enhance antitumor immunity. Herein, the nanoparticle-based strategies targeting TAMs presented in preclinical research are explored, including reprogramming M2 to M1 macrophages, delivering MYC inhibitors, depleting TAMs, and inhibiting TAM recruitment. Integration with immune checkpoint inhibitors is also discussed. Challenges in translating these nanoparticle approaches from preclinical models to clinical practice are further addressed, with an emphasis placed on human-relevant models, optimized production processes, and personalized therapeutic approaches.

Keywords: breast cancer, tumor-associated macrophages, nanotechnology, nanoparticles, M1/M2 Polarization, immune checkpoint inhibitors

Introduction

According to GLOBOCAN 2022, breast cancer is the most common cancer type among women, with approximately 2.3 million new cases reported annually, comprising 11.6% of all newly diagnosed cancer cases, second only to lung cancer (12.4%).[1] Immunotherapy has demonstrated promising outcomes in breast cancer treatment; however, its overall efficacy remains limited due to the immunosuppression of the tumor microenvironment (TME). Tumor-associated macrophages (TAMs) constitute a key component of the TME, influencing tumor cell adaptation and host immune responses. The high prevalence of anti-inflammatory immune cells and the associated immunosuppressive network can reduce the efficacy of cancer immunotherapy.[2] Strategies such as reprogramming TAMs from the M2 tumor-promoting phenotype to the M1 anti-tumor phenotype, depleting TAMs, and inhibiting their recruitment have all been extensively studied. Nanotechnology-based targeting of TAMs presents novel opportunities to enhance breast cancer immunotherapy by overcoming tumor immune evasion and improving immune checkpoint blockade efficacy. Substantial progress in efficient TAM modulation has helped to enhance the efficacy of breast cancer immunotherapy.

To provide a comprehensive understanding of nanotechnology-based targeting of TAMs, this review summarizes the role of TAMs in breast cancer immunotherapy; examines the application of nanotechnology in modulating TAM polarization and its impact on treatment outcomes; and discusses the prospects, challenges, and future directions of nano-immunotherapy.

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Literature Search Strategy

This narrative review was conducted following systematic literature searches of the PubMed, Web of Science, and Scopus databases from January 2018 to March 2026. The search strategy employed Boolean operators to combine relevant Medical Subject Headings terms and keywords. Primary search terms included "tumor-associated macrophages", "breast cancer", "nanoparticles", "nanotechnology", "immunotherapy", "M1/M2 polarization", "targeted drug delivery", and "immune checkpoint inhibitors". The exact search string used was: ("tumor-associated macrophages" OR "TAMs") AND ("breast cancer" OR "breast neoplasm") AND ("nanoparticles" OR "nanotechnology" OR "nano-delivery").

Inclusion criteria focused on preclinical studies employing nanoparticle-based strategies specifically targeting TAMs in breast cancer models; clinical trials or translational studies involving TAM-directed nanotherapies in breast cancer; and mechanistic studies elucidating TAM biology in the breast tumor microenvironment. Pan-cancer studies were included only when they provided foundational mechanisms or technological advances directly applicable to breast cancer. Exclusion criteria included non-English publications, abstracts without full-text availability, and studies lacking specific focus on macrophage modulation.

The initial search yielded approximately 2800 records. After removal of duplicates and screening of titles and abstracts, over 300 full-text articles were assessed for eligibility. Ultimately, 205 publications were included in this review, including both breast cancer-specific studies and pan-cancer investigations with direct relevance to breast cancer TAM targeting. The reference lists of included articles were manually screened to identify additional relevant studies. The most recent literature search was conducted in March 2026.

TAM Biology in Breast Cancer

Breast cancer heterogeneity arises from multiple factors, including genomic instability, epigenetic remodeling, and dynamic evolution of the TME.[3] Traditional PAM50 gene expression profiling classifies breast cancer into five intrinsic subtypes: Luminal A, Luminal B, HER2-enriched, basal-like, and Normal-like.[4] These subtypes display distinct TME compositions, immune cell infiltration patterns, and clinical outcomes.

Immune checkpoint inhibitors have revolutionized the treatment landscape for triple-negative breast cancer (TNBC), with utilization rates rapidly increasing from less than 5% in 2017 to 48.0% (early-stage) and 38.8% (metastatic) by 2021.[5] Compared to chemotherapy alone, combination immunotherapy significantly improves prognosis; Five year event-free survival increased from 71.8% to 80.0% in early-stage TNBC, reaching 92.0% in patients achieving pathological complete response.[6] Further, the objective response rate rose from 32.4% to 48.2% in metastatic TNBC, with the median overall survival extended from 12.6 months to 17.9 months.[7] However, only hormone receptor-positive /HER2-negative subtype show benefits from PD-L1-, while HER2-positive subtype shows limited efficacy.[6] The immunosuppressive TME, dominated by M2-type TAMs, remains the primary cause of primary and acquired resistance in the majority of patients.[8]

Therefore, understanding the molecular subtype-specific roles of TAMs is essential for designing targeted nanotherapeutic strategies. The following sections will elaborate in detail on the dual roles of TAMs in breast cancer progression and nanoparticle-based approaches to modulate their function in a subtype-specific manner.

Composition of the TME and Polarization of TAMs

The TME is a complex system comprising primarily tumor cells, mesenchymal stromal cells, and immune cells. It plays a crucial role in tumor progression, immune evasion, and response to immunotherapy. Immune cells within the TME include T lymphocytes, regulatory T cells (Tregs), B lymphocytes, TAMs, neutrophils, monocytes, and dendritic cells (DCs).[9,10] TAMs, a predominant immune cell type in the TME, may originate from circulating monocyte precursors in the bone marrow (BM), and from tissue-resident macrophages (TRM) established during embryonic development. Their origins in tumor tissues vary according to tissue- or organ-specificity, thereby exhibiting diverse functions in tumors.[11,12]

TAMs are involved at multiple stages of tumorigenesis and progression. Under different stimuli, TAMs can polarize into two functionally distinct subtypes: classically activated M1-type and selectively activated M2-subtype TAMs.[13] M1-type TAMs are pro-inflammatory and tumor-suppressive, while M2-type are anti-inflammatory and promote tumor

progression.[14] M1-type macrophages are induced by cytokines secreted by type I T-helper cells (Th1) or bacterial lipopolysaccharides (LPS), driving the production of pro-inflammatory mediators such as interleukin (IL)-12, tumor necrosis factor-α (TNF-α), high nitric oxide (NO), and reactive oxygen species (ROS) levels. These macrophages exhibit strong antimicrobial properties and antitumor activity, contributing to innate immune defense and tumor cell eradication. In contrast, M2-type macrophages are activated by Th2 cytokines (eg, IL-4 and IL-13) to secrete anti-inflammatory cytokines (eg, IL-10 and IL-13) M2-type macrophages are involved in cellular debris clearance, angiogenesis, tissue remodeling, damaged tissue repair, and promotion of pro-tumorigenesis and progression.[15] Although the exact timing of monocyte differentiation into TAMs remains unclear, the tissue microenvironment has been shown to induce substantial alterations in their transcriptional profiles.[16] These cells are closely associated with poor prognosis in patients with breast cancer, particularly with the malignant and hormone receptor-negative subtypes.[17]

Pro-Tumorigenic Role of TAMS

TAMs play an important role in tumor progression, predominantly promoting tumor cell proliferation and survival, tumorigenic angiogenesis, inhibiting T-cell-mediated tumor immune responses, and promoting epithelial mesenchymal transition and cellular remodeling for the stroma. Therefore, TAMs represent a potential new target for tumor therapy (Figure 1).

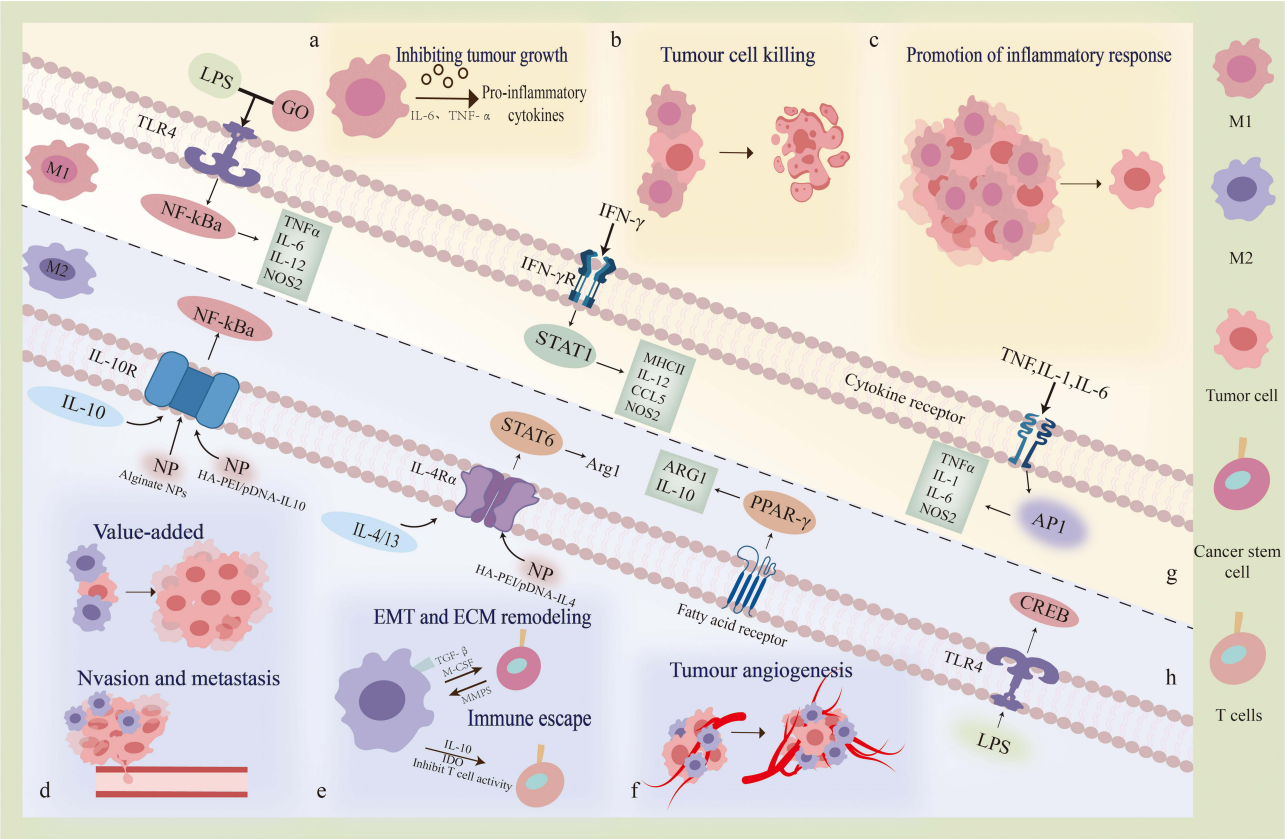

Figure 1 The dual role and regulatory mechanisms of macrophages in the tumor microenvironment: Macrophages exert dichotomous roles in the tumor microenvironment. (**a**) M1 macrophages are activated by LPS or Th1-type cytokines (eg, IFN-γ), enhance the NF-κB signaling pathway, and secrete pro-inflammatory cytokines (eg, IL-6, TNF-α) to suppress tumor growth (**b**) IFN-γ activates STAT1 to reinforce the cytotoxic functions of M1 macrophages, inducing the release of IL-12, TNF-α, NO and other pro-inflammatory mediators to exert anti-tumor effects. (**c**) M1 macrophages secrete IL-6, TNF-α, IL-1β and other pro-inflammatory factors to amplify immune responses and promote inflammation. (**d**) M2 macrophages secrete IL-10, TGF-β and other factors that enhance tumor-cell invasion and metastatic capacity. (**e**) M2 macrophages promote EMT and ECM remodeling by secreting IL-4/13 and TGF-β, thereby facilitating tumor invasion. (**f**) M2 macrophages secrete pro-angiogenic factors such as VEGF, TGF-β and IL-8 to stimulate tumor neovascularization. (**g**) M1 polarization is triggered by IFN-γ and TLR4 signals. IFN-γ, via STAT1, up-regulates pro-inflammatory cytokines (TNF-α, IL-6, IL-12) and NOS2, enhancing pro-inflammatory and anti-tumor functions. The TLR4 pathway activates NF-κB to further amplify inflammation and M1 polarization. (**h**) M2 polarization is driven by IL-4 and IL-13, which activate STAT6 and induce PPARγ expression, mediating anti-inflammatory responses, tissue repair and the establishment of an immunosuppressive microenvironment. These two macrophage subsets finely regulate immune responses and tumor progression within the tumor microenvironment through distinct signaling pathways and feedback mechanisms.

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TAMs and Breast Cancer: Value-Added Insight, Invasion, and Metastasis

Tumor cell migration and metastasis are driven by the degradation of the endothelial cell basement membrane within tumor tissues, facilitated by activated TAMs secreting growth factors (eg, VEGF, PDGF, EGF, TGF-β) that activate pathways such as PI3K-Akt, NF-κB, and ILK, leading to ECM degradation and tumor/stromal cell proliferation, invasion, and metastasis[18,19] Injection of MPLA+IFNγ into breast cancer mouse models reduced primary tumor growth and metastasis.[20] Conversely, COX-2^{+}TAMs promote tumor cell growth by upregulating Bcl-2 and downregulating Bax via modulation of the PI3K-Akt pathway.[21,22] Exosomes from M2-like macrophages promote tumor cell invasion and migration by suppressing RASSF4 expression via miRNAs (eg, miR-155, miR-196a-5p).[23]

TAMs and Breast Cancer Tumor Angiogenesis

Blood vessels are essential for sustained tumor growth; in tumors, the "angiogenic switch" initiates vascular formation to supply nutrients and remove waste once the tumor reaches a critical size. TAMs play a key role in promoting tumor angiogenesis in breast cancer, as shown in murine models.[24] M2-type TAMs secrete various pro-angiogenic cytokines, including VEGF, PDGF, EGF, TGF-β, matrix metalloproteinases, TNF-α, IL-1β, and IL-8.[14,25] VEGF, a potent pro-angiogenic factor, stimulates endothelial cell proliferation, migration, and lumen formation, and is secreted by both breast cancer cells and TAMs, with the latter amplifying angiogenic signaling. This synergistic effect significantly promotes tumor angiogenesis.[26,27] In vitro, co-incubation of macrophages with MDA-MB-231 breast cancer cells upregulated angiogenesis-related factors such as CXC and CC chemokines, and induced IL-6 production in TAMs via the p38-MAPK pathway. IL-6 subsequently activated TAMs via the STAT-3 pathway, enriching cancer stem cells and promoting breast cancer cell propagation.[28,29] In transgenic murine models with reduced mTORC1 activity in TAMs, reprogramming via the TSC–mTORC1 axis redirected TAMs to perivascular niches, where they competed for endothelial progenitor cells, inhibiting tumor neoangiogenesis.[30,31] Thus, these results show that TAMs drive tumor angiogenesis in breast cancer, and their inhibition or reprogramming can suppress tumor neoangiogenesis.

TAMs Promote the Epithelial Mesenchymal Transition and Extracellular Matrix Remodeling

In breast cancer, TAMs drive tumor progression and metastasis by secreting cytokines, chemokines (such as CCL2), and growth factors. These factors activate TGF-β signaling and upregulate transcription factors such as Snail and Slug, thereby promoting EMT and enhancing tumor invasion and metastasis, including in TNBC.[32,33] TAMs secrete enzymes such as matrix metalloproteinases, serine proteases, and histone proteases, which disrupt the basement membrane and ECM, thereby facilitating tumor invasion.[34] They also contribute to ECM synthesis by producing collagens I, VI, and XIV, promoting ECM deposition, cross-linking, and fibrosis. This increases ECM rigidity and creates a favorable microenvironment for tumor cell migration.[35]

Immune Escape Mediated by TAMs

In the breast cancer TME, TAMs regulate local immune responses through multiple mechanisms. M2-type TAMs highly express arginase-1 (Arg1), hydrolyzing L-arginine into urea and L-ornithine, while secreting immunosuppressive factors such as IL-10 and IDO to inhibit T cell and NK cell activity.[36–42] Additionally, TAMs can impair cytotoxic T lymphocyte (CTL) proliferation and IFN-γ production through COX-2 overexpression and GM-CSF-induced PD-L1 upregulation.[43,44] TAMs also modulate PI3K/Akt signaling pathways (eg, CCL2/PI3K/Akt/mTOR, EGFR/PI3K/Akt) to enhance tumor cell survival and autophagy[45–48] Therefore, targeting TAMs and their associated signaling pathways may enhance immunotherapeutic efficacy.

TAMs Promote Chemotherapy and Radiotherapy Resistance

In the TME, TAMs significantly enhance the resistance of cancer cells to chemotherapy and radiotherapy by secreting cytokines and chemokines that modulate immunosuppression, thereby reducing treatment efficacy.[49] Additionally, TAMs activate pro-survival signaling pathways such as PI3K/Akt and MAPK in tumor cells by secreting specific cytokines (eg, CXCL5, THBS1) and exosomes carrying miR-223, thereby significantly enhancing tumor cell drug resistance[50] Chemotherapeutic agents alter TAM polarization to the M2 phenotype, increasing drug tolerance.[45] For example, cisplatin promotes M2 polarization via IL-10 upregulation and STAT3 activation, consequently increasing

chemoresistance.[51] Similarly, chemotherapeutic agents stimulate TAMs to secrete CXCL7, which activates the STAT1/PHGDH-serine metabolic axis and the SAM paracrine feedback loop, promoting M2 polarization and chemoresistance.[52] Additionally, TAMs deliver drug resistance-associated microRNAs (eg, miR-21, miR-155) via exosomes to modulate signaling pathways in tumor cells, thereby further enhancing drug resistance[53] Therefore, TAMs facilitate chemotherapy and radiotherapy resistance through multiple pathways within the TME, underscoring the therapeutic potential of TAM-targeted strategies.

Tumor Suppressive Role of TAMS

In addition to their tumor-promoting effects, TAMS also exert tumor-suppressive functions by promoting inflammatory responses, mediating tumor cell cytotoxicity, and inhibiting tumor growth and metastasis.

Promotion of Inflammatory Response and Tumor Cell Killing

M1-type macrophages mediate anti-tumor activity through multiple mechanisms. Firstly, they secrete pro-inflammatory cytokines and express high levels of MHC-II-like and co-stimulatory molecules, thereby conferring efficient antigen-presenting capacity and exhibiting pro-inflammatory and anti-tumor properties.[54,55] M1-type macrophages eliminate tumor cells via two direct mechanisms: direct cytotoxicity and antibody-dependent cell-mediated cytotoxicity. M1-type macrophages induce programmed necrosis in tumor cells by releasing lysosomal enzymes and cytotoxic mediators, such as reactive oxygen species (ROS) and nitric oxide (NO), which slowly but directly target and destroy infected or neoplastic cells.[56] In the presence of specific anti-tumor IgG antibodies, M1-type macrophages recognize the Fc region via the recognition of Fcγ receptors expressed on tumor cells, and induce cytotoxic responses.[57] By secreting pro-inflammatory cytokines and NO, M1-type macrophages suppress cellular proliferation, induce tissue damage, and activate NK cells and CTLs. This activation is mediated by cytokines such as IFN-γ, IL-1β, and Th1-type cytokines such as lipopolysaccharide (LPS), which exert cytotoxic effects on tumor cells.[58–60]

Inhibiting Tumor Growth and Metastasis

M1-type TAMs induce tumor cell apoptosis through the secretion of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), thereby inhibiting tumor growth and metastasis. Additionally, they can directly inhibit CTL proliferation via L-arginine metabolism by arginase 1, inducible NO synthase, ROS, or nitrogen species, thereby limiting immune escape by tumors.[61–63] M1-type TAMs promote the maturation and activation of DCs, thereby enhancing tumor antigen presentation and activating T cell-mediated immune responses.[64] They further reduce the secretion of pro-angiogenic factors (eg, VEGF and bFGF), thereby inhibiting tumor angiogenesis and limiting nutrient supply and metastatic pathways[65] Notably, macrophages were commonly localized at the rupture sites of the basement membrane and at the infiltration fronts of malignant tumors, potentially influencing the early tumor invasion and metastasis.

Current Immunotherapeutic Challenges in Breast Cancer

Immunosuppressive TME

Within the breast-cancer milieu, highly expressed immunosuppressive molecules and cells constitute the principal barrier to immunotherapy. TAMs continuously secrete IL-10, TGF-β, CCL22, and VEGF-A, thereby recruiting regulatory T cells and steering newly infiltrated monocytes towards an M2 phenotype, effectively preventing $CD8^+$ T-cell extravasation[66] Under hypoxia, TAMs up-regulate SPP1 and LGALS3, engage $CXCR2^+$ neutrophils, and jointly establish a "myeloid suppressive network" that markedly attenuates $CD8^+$ T-cell cytotoxicity.[67] Concurrently, TAMs display elevated levels of PD-L1, PD-L2, Galectin-9, and VISTA, which deliver inhibitory signals upon binding to PD-1 or TIM-3 on $CD8^+$ T cells, thereby crippling effector functions.[68] Metabolically, arginase-1, iNOS, and reactive oxygen species released by TAMs deplete local arginine and cysteine, thereby suppressing T-cell proliferation and IFN-γ production.[43] TAM-derived exosomal miR-21-5p further targets endothelial LATS1/VHL, activating YAP1/HIF-1α signaling, and indirectly exacerbating the hypoxic immunosuppressive microenvironment.[69] Additionally, MMP-9 and cathepsins produced by TAMs degrade collagen and laminin, physically encapsulating tumor nests and restricting T-cell infiltration, ultimately generating an immune-excluded phenotype.[70]

Therapy Resistance

Clinical resistance to immunotherapy in breast cancer is initiated when TAMs act as an "antibody sink", highly expressing PD-L1/PD-L2 to sequester anti-PD-1 agents and weaken direct tumor blockade.[71–73] Moreover, VEGF-A, IL-1β, and CXCL8 from TAMs induce vascular resistance: VEGF-A down-regulates ICAM-1/VCAM-1 on endothelial cells, thereby impeding T-cell adhesion and extravasation;[74] IL-1β reduces tight-junction proteins;[75] and CXCL8 activates CXCR2 signaling, promoting aberrant angiogenesis and further excluding T cells.[76] At the metabolic level, TAMs up-regulate IDO-1, COX-2, and CD73, jointly constructing metabolic immune suppression. IDO-1 converts tryptophan to kynurenine, activating the AHR pathway and driving $CD8^+$ T-cell terminal exhaustion; COX-2-derived PGE_2 binds EP4, inhibiting T-cell activation; CD73-generated adenosine activates A2A receptors, curbing $CD8^+$ T-cell cytotoxicity.[77–79] As discussed below, nanotechnology-enabled TAM targeting offers unique advantages to overcome these immunotherapeutic challenges.

Nanoparticle Classes, Targeting Rationales, and Distinct Advantages of This Approach

Distinct Advantages of Nanotechnology in TAM Targeting

Nanocarriers possess inherent targeting capability, allowing the selective concentration and localization of drugs in target tissues, organs, cells, or organelles, thereby reducing toxicity to healthy tissue and improving the therapeutic index.[80] Their 10–100 nm size and large surface area facilitate deep tumor penetration and high drug loading, while minimizing off-target exposure.[81,82] Unlike conventional cytotoxic agents that cannot distinguish between normal and cancer cells, nanoparticles exploit the enhanced permeability and retention (EPR) effect to preferentially accumulate within the tumor region.[83,84] The EPR effect arises from the leaky tumor vasculature (400–600 nm fenestrations) and impaired lymphatic drainage, enabling nanoparticles of 10–200 nm to extravasate and achieve tumor-to-blood concentration ratios 10–50-fold higher than small-molecule drugs.[85,86]

In addition to passive tumor accumulation, nanocarriers can be functionalized with ligands that specifically recognize overexpressed receptors on TAMs, such as CD206, CSF1R, or mannose receptors, consequently converting TAMs into an active targeting hub for drug delivery.[87,88] For example, mannose-conjugated nanoparticles bind CD206 with nanomolar affinity, triggering receptor-mediated endocytosis and enabling intracellular payload delivery.[89]

Nanoparticles can also overcome tumor-microenvironment barriers. Through responsive design, they release payloads under specific conditions, such as acidity, hypoxia, or immunosuppression characteristic of the breast-cancer microenvironment, thereby enhancing therapeutic efficacy.[90] Moreover, modern nano-systems integrate diagnostic and therapeutic functions to achieve "theranostics". Within a single material scaffold, they simultaneously incorporate imaging signals and therapeutic modules, thereby eliminating the need for multiple components and yielding structurally defined, reproducible, and biocompatible theranostic platforms through simple fabrication.[91] For example, single-component upconversion nanoparticles (UCNPs) achieve a closed loop of "NIR excitation–visible emission–photosensitizer activation" within a single particle, thereby enabling synchronous deep-tumor imaging and photodynamic therapy without the use of any additional contrast agents or drugs; their simple composition and well-defined structure facilitate batch-to-batch consistency under current GMP standards, and markedly reduce in-vivo metabolic complexity, thereby accelerating clinical translation.[92] These capabilities align with broader advances in optical molecular imaging, which continues to evolve as a critical tool for cancer diagnosis and therapy guidance with an expanding clinical impact.[93]

Nanocarrier Classification and TAM-Targeted Delivery Strategies in Breast Cancer

The nano-carriers commonly employed in breast-cancer therapy can be grouped into four major families: carbon-based, lipid-based, polymer-based, and metallic systems.

Carbon-based nanomaterials: Single- or multi-walled carbon nanotubes and graphene oxide possess large interior cavities or inter-layer galleries that can accommodate hydrophobic drugs, affording exceptionally high loading capacities and surface areas.[94] However, pristine carbon allotropes are poorly hydrophilic and tend to aggregate under physiological conditions. Surface PEGylation or carboxylation markedly improves dispersibility and biocompatibility, while reducing

immunogenicity.[95] For TAM targeting, mannose-functionalized graphene oxide loaded with sorafenib has demonstrated selective uptake in $CD206^+$ macrophages and efficient M2-to-M1 repolarization in breast cancer models.[96]

Lipid-based platforms: Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers assembled from natural phospholipids or solid lipids, are biodegradable and biocompatible, and can encapsulate both hydrophilic and lipophilic drugs.[97,98] Their bilayer rigidity is tunable, affording controllable release kinetics, prolonged circulation, and enhanced stability.[99] In hormone-dependent breast cancer, TAMs are the primary source of immunosuppression, and impede endocrine therapy efficacy.[100] For example, the lipid nanoparticles developed by Al-Janabi et al target folate receptor β overexpressed on perivascular TAMs, loaded with STING agonists to reprogram these TAMs, thus demonstrating significant synergistic effects with endocrine therapy, and providing an important paradigm for breast cancer treatment.[101]

Polymeric nanoparticles: These are fabricated from biocompatible and biodegradable polymers such as PLGA.[102] PEGylation confers sustained release, protects payloads from enzymatic or plasma-protein degradation, and offers excellent reproducibility.[103,104] These systems can efficiently deliver siRNA, natural products, and cytotoxics.[105] For TAM targeting, mannose-PEG-PLGA nanoparticles specifically recognize CD206 receptors overexpressed on M2-type TAMs through surface mannose modification, thereby enabling selective uptake and intracellular delivery.[106] For example, the mannose-modified PLGA nanoparticles developed by Xiao Wei et al were found to be efficiently internalized by M2-type TAMs and induced M2-to-M1 phenotypic repolarization through reactive oxygen species photogeneration strategy, thereby inhibiting tumor growth and metastasis.[107]

Metallic nanostructures: Gold nanorods, super-paramagnetic iron oxide nanoparticles (SPIONs), and related materials possess unique photothermal, magnetic, and imaging properties.[108] Hollow gold nanoshells absorb strongly in the NIR, and exhibit high X-ray attenuation, enabling concurrent photothermal therapy and CT imaging.[109] SPIONs are biodegradable, clinically approved MR contrast agents which can also generate heat under NIR irradiation.[110] Mannose-decorated SPIONs can exploit surface mannose ligands to specifically bind the CD206 receptors abundantly expressed on M2-polarized TAMs, thereby facilitating selective cellular uptake and magnetic enrichment.[106] For example, the hyaluronic acid-mannose dual-modified iron oxide nanoparticles (HA-man@Fe_3O_4) designed by Zhang et al achieve precise targeting through the synergistic effect of the two ligands, with uptake by M2-like TAMs shown to be twice that of clinically approved ferumoxytol, and can induce M2-to-M1 repolarization. Furthermore, combined use with neoantigen peptide vaccines was shown to significantly enhance antigen presentation capability and improve $CD8^+$ T cell infiltration and activation, achieving a 40% tumor complete regression rate in mouse breast cancer models.[111] In addition, the Polyporus umbellatus polysaccharide iron-based nanocomposite (PUPN) developed by Liu et al combines natural polysaccharides with Fe_3O_4, inducing TAMs M1 polarization through the multi-pathway synergistic mechanism of "IFN-γ-Fenton-NF-κB/MAPK", significantly inhibiting breast cancer cell proliferation and invasion, providing a novel strategy for iron-based nanomaterials to regulate the TME.[112] Beyond conventional metallic systems, emerging organic nanomaterials with aggregation-induced emission properties now expand the radiotherapeutic arsenal, enabling X-ray triggered continuous generation of reactive oxygen species to potentiate cancer radioimmunotherapy.[113]

Strategies for Targeting TAMs

TAMs are predominantly immunosuppressive M2 cells that promote breast-cancer growth and metastasis.[114] Multiple strategies have been tested to target TAMs, including exosome-mediated delivery, magnetic targeting strategies, microenvironment-responsive nanosystems, and immune-signal modulation.

Exosome-mediated delivery: Exosomes, as natural nanocarriers, exhibit excellent biocompatibility and inherent targeting capacity.[115] For example, Kamerkar et al engineered exoASO-STAT6, an exosome specifically delivering STAT6 antisense oligonucleotides to silence the "undruggable" STAT6 in TAMs. This treatment efficiently repolarized TAMs toward the M1 phenotype, thereby achieving genetic reprogramming.[116]

Magnetic targeting strategies: These exploit the superparamagnetism of SPIONs to achieve active drug enrichment at the tumor site under the guidance of an externally applied magnetic field.[117] For example, folate-conjugated magnetic SPIONs enable selective TAM accumulation and quantitative [Fe]-MRI imaging in TNBC mice,[118] while one study demonstrated their potential for targeted drug delivery and magnetic hyperthermia in breast-cancer therapy.[119]

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Microenvironment-responsive nanosystems: These have evolved from single pH triggers to four-modal platforms that simultaneously sense acidity, ROS, enzymes, and hypoxia. Combined with folate/mannose ligands, magnetic guidance, or exosome camouflage, these systems can achieve highly selective delivery to M2-type TAMs.[120,121]

Immune-signal modulation: siRNAs or small-molecule inhibitors targeting NF-κB, mTOR, and other pathways block M2 polarization.[122] For example, mannose-decorated nanoparticles targeting CD206 mediate TAM endocytosis and disrupt M2 polarization.[123] Simultaneous delivery of mTOR inhibitors and STAT6 siRNA via mannose-targeted liposomes has shown synergistic effects, achieving more complete M2-to-M1 repolarization than single agents.[124]

Nanotechnology Applications in Breast Cancer: TAM-Focused Perspectives

Nanotechnologies have been extensively applied in medicine, particularly in oncological therapeutics, including in the fields of chemotherapeutic drug delivery, gene therapy construction, and enhancement of immunotherapeutic efficacy. The following section reviews current applications of nanotechnology in oncology.

Chemotherapeutic Delivery with Concurrent TAM Targeting

Nanoparticles enhance chemotherapeutic efficacy in breast cancer by concurrently targeting TAM-mediated immunosuppression. For example, M1 macrophage-derived exosome-coated nanoparticles incorporating SR780, Fe^{3+}, and catalase inhibit CD47-SIRPα checkpoint signaling, facilitating macrophage-mediated phagocytosis and reversing TAM immunosuppression in breast cancer models.[125] Mannose-modified nanoparticles specifically target CD206 overexpression on M2-type TAMs in breast tumors, minimizing off-target effects.[126,127] Co-delivery of paclitaxel with STAT6 siRNA or CSF-1R inhibitors synergistically kills breast cancer cells, while repolarizing TAMs from the M2 to M1 phenotype, thereby remodeling the anti-tumor immune microenvironment.[128] Thus, nanoparticles provide innovative strategies for remodeling breast cancer drug delivery systems and overcoming TAM-mediated immunosuppression.

Constructing Gene Therapies

Tumor gene therapy involves gene editing or silencing through the delivery of exogenous nucleic acid molecules to the target cells.[129] However, the targeted delivery of therapeutic genes to specific cells and tissues remains a significant challenge. Nanoparticles offer a promising alternative as non-viral vectors for gene delivery, with low immunogenicity and high transfection efficiency.[130]

Nanoparticles enable TAM-targeted gene delivery in breast cancer by recognizing TAM surface markers, such as CD206 and F4/80. These systems deliver siRNA or mRNA to silence pro-tumorigenic genes in TAMs, thereby reprogramming them from the M2 to M1 phenotype, restoring phagocytic function and antigen presentation, and consequently reversing immunosuppression in the breast cancer microenvironment.[131] Furthermore, nanoscale natural carriers, such as exosomes, with their excellent biocompatibility, low immunogenicity, and ability to penetrate physiological barriers, provide an ideal platform for TAM-targeted delivery of gene editing tools.[132]

Enhancing Immunotherapy Efficacy Through TAM Modulation

CSF-1R inhibitors delivered via nanoparticles relieve T cell barriers in breast cancer by repolarizing TAMs from the M2 to M1 phenotype.[133,134] Nanocarriers responsive to pH, enzymes, or redox states in the TAM-rich breast tumor microenvironment achieve site-specific drug release, maximizing immune activation, while avoiding systemic toxicity[135–137] Furthermore, nanoparticles modulate the breast cancer microenvironment through multi-node TAM-centered strategies. BEN nanoparticles achieve TME regulation by reprogramming TAMs, inhibiting MDSCs, and blocking PD-1/PD-L1, significantly increasing NK and $CD8^+$ T cell effector function in breast tumors.[138] Hypoxia-alleviating LDH nanozymes induce TAM polarization toward M1 phenotype in breast cancer models, promoting immune microenvironment reprogramming.[139,140]

Preclinical Outcomes

Nanoparticles, including carbon-based, lipid-based, polymer-based, and metal-based nanostructures, have all been extensively utilized in breast cancer treatment.[141,142] These platforms facilitate the delivery of chemotherapeutic agents

and natural compounds, thereby enhancing cytotoxicity and mitigating drug resistance.[143] They also serve as vectors for gene therapy tools, including CRISPR/Cas9, non-coding RNA, and RNAi,[144] while stimulus-responsive nanocarriers enable targeted inhibition of breast tumors.[145,146] Nanoparticles facilitate the co-delivery of drugs and genetic material via endocytosis,[147] while nanostructures integrated with photothermal and photodynamic therapies induce tumor ablation.[148]

Nanoparticles modulate the TME and induce macrophage repolarization, which enhances the anti-tumor immune response.[149] Macrophages bind to CD47 on cancer cells, inhibiting their phagocytosis,[150] while tumor-secreted factors drive TAM polarization toward the pro-tumorigenic M2 phenotype. Comprising over 50% of the TME, TAMs are pivotal in tumor progression. Strategies targeting TAMs—including inhibiting recruitment, depleting populations, and modulating polarization—activate anti-tumor immunity to suppress tumor growth, angiogenesis, and metastasis.[151] Nanomaterials further enable targeted drug transport, precise release localization, and improved bioavailability,[152,153] with core–shell nanoparticles effectively remodeling the TME and promoting macrophage repolarization.[141,154,155] Therefore, nanoparticles offer promising strategies for both targeting and modulating TAMs, remodeling the TME, and activating anti-tumor immune responses[156] (Figure 2).

Reprogramming M2-Type TAMs into M1-Type

In breast cancer treatment, nanotechnological strategies have been shown to effectively reprogram TAMs from the tumor-promoting M2 to the anti-tumor M1 phenotype through engineered exosome delivery, magnetic targeting, microenvironment-responsive drug release, and synergistic modulation of immune signaling pathways, thereby reversing the tumor-immunosuppressive microenvironment and initiating a systemic anti-tumor immune response.

Exosome Engineered Delivery

In certain tumors, including breast cancer, the TME exhibits hypoxia and immunosuppression, and is enriched with TAMs, which represent a potential target for antitumor therapy.[157] In one study, novel hybrid nanovesicles of M1 macrophage-derived exosomes comprising AS1411 aptamer-coupled liposomes (AApt-Lips), termed M1E/AALs, were co-loaded with perfluorotributylamine (PFTBA) and IR780 as photosensitisers (P-I) to form a P-I@M1E/AALs nanoplatform. This nanoplatform achieved TAM reprogramming through multiple synergistic mechanisms. First, the AS1411 aptamer ensures precise tumor targeting of the nanovesicles. During treatment, PFTBA decomposes to produce oxygen upon laser irradiation, thereby alleviating tumor hypoxia. Further, IR780 generates reactive oxygen species (ROS) under 808 nm laser excitation, directly killing tumor cells. More importantly, characteristic proteins on the M1-Exos membrane surface are transferred to TAMs through membrane fusion, inducing their phenotypic conversion to an anti-tumor type, thereby enhancing immune responses.[158] In addition, recent research by Jorquera-Cordero et al has demonstrated that M1 macrophage-derived exosomes (MM1-EVs) loaded with doxorubicin (MM1-DOX) and pretreated with hyaluronic acid (HA) and the β-blocker carvedilol (CV) can convert M2-type TAMs into M1-type through membrane fusion-mediated transfer of M1-type characteristic proteins (such as CD86 and iNOS), thereby enhancing anti-tumor immunity. This nanosystem showed significant anti-tumor efficacy in a 4T1 metastatic breast cancer model.[159] Beyond macrophage-derived exosomes, platelet-derived exosomes hybridized with liposomes provide an alternative cell source for uninterrupted singlet oxygen generation, further expanding the repertoire of exosomal platforms for breast cancer immunotherapy.[93]

Magnetic Nanoparticle-Targeted Modulation

A synergistic effect between TAM phenotypic reprogramming and antitumor activity has previously been achieved through a multidimensional strategy. Fe_3O4 nanoparticle-based chemo dynamic therapy generates ROS via the Fenton reaction, which induces macrophage polarization towards a pro-inflammatory M1 phenotype, while simultaneously killing tumor cells.[160] Accordingly, Fe_3O_4 nanoparticles encapsulated within myeloid-derived suppressor cell membranes were engineered to enhance tumor targeting by mimicking membrane-surface homing molecules, thereby enabling simultaneous M2 TAM repolarization and inducing immunogenic cell death.[161] Rao et al previously developed genetically engineered cell membrane-coated magnetic nanoparticles (gCM-MNs) by wrapping MN cores with gCMs

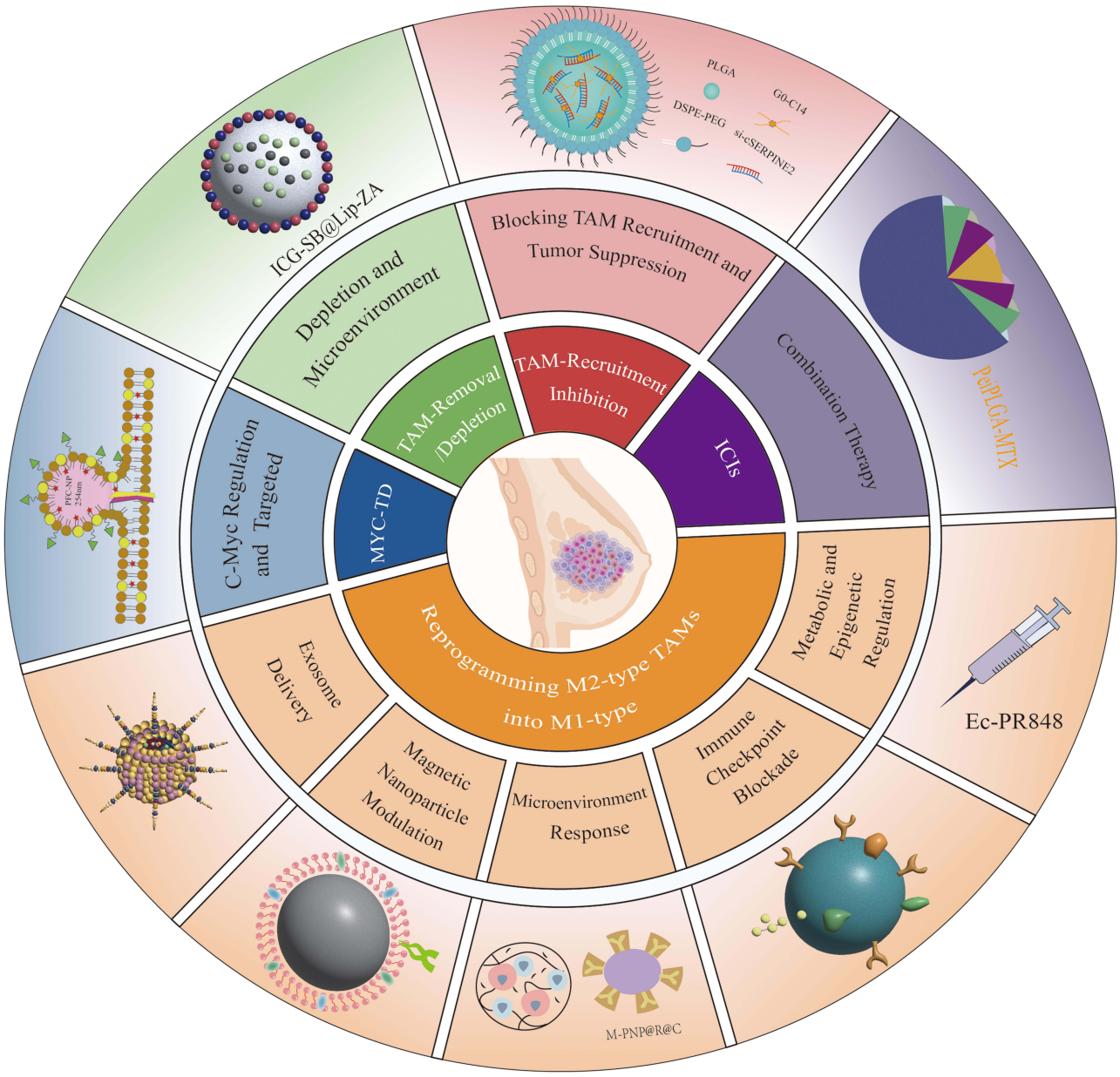

Figure 2 The figure depicts nanoparticle (NP)-based strategies targeting tumor-associated macrophages (TAMs) in breast cancer. Nanoparticles deliver drugs to reprogram M2 TAMs into M1, enhancing antitumor activity. They also carry MYC inhibitors to the tumor site, specifically targeting TAMs to suppress their pro-tumor functions. Additionally, nanoparticles can selectively deplete TAMs, reducing their presence in the tumor microenvironment. By blocking chemokine and growth factor signaling, TAM recruitment to the tumor is inhibited. Combining these nanoparticle strategies with immune checkpoint inhibitors further enhances the antitumor effects of T cells and natural killer cells. Nanoparticles ensure precise drug delivery and release at the tumor site, improving efficacy and reducing side effects.

overexpressing SIRPα variants.[162] Under magnetic navigation, this system actively targets tumor tissues, where the gCM shell competitively blocks the CD47-SIRPα "don't eat me" signaling pathway through high-affinity SIRPα variants to relieve phagocytic inhibition, while the Fe_3O_4 core synergistically repolarizes TAMs from the M2 to M1 phenotype, promoting cancer cell phagocytosis and triggering antitumor T-cell immunity. In murine models of malignant melanoma (B16F10) and TNBC (4T1), gCM-MN treatment significantly suppressed primary tumor growth and reduced distant lung metastasis. These innovations overcome the single-function limitations of traditional magnetic nanoparticles, establishing a "three-in-one" precision intervention system integrating physical targeting, immunomodulation, and synergistic therapy.

Microenvironment Response

While developing microenvironment-responsive intelligent systems, TAM spatiotemporal regulation was achieved through the precise sensing of TME features. pH-responsive M-PNP@R@C nanocarriers released the TLR7/8 agonist R848 and the STING agonist cGAMP in acidic TME, thereby synergistically driving M1 polarization through dual pattern-recognition receptor activation.[163] Previously, Liu et al designed TME-responsive nanoparticles (PMM NPs) that simultaneously activate the STING pathway and TLR4 (Toll-like receptor 4) pathway, utilizing TLR4-mediated NF-κB signaling to amplify STING signal transduction.[164] PMM NPs alleviated TME immunosuppression by reducing regulatory T cell proportions and repolarizing M2 macrophages towards the M1 phenotype, consequently generating an immunosupportive TME that unleashed cascading adaptive immune responses. This nanosystem demonstrated remarkable synergistic efficacy when combined with anti-PD-1 antibody (checkpoint inhibitor) treatment in non-inflammatory metastatic breast cancer models. These TME-responsive nanoparticles provide novel insights for achieving spatiotemporal precision control of STING activation, offering promising clinical candidates for cancer immunotherapy.

Additionally, GSH/ROS dual-responsive nanoparticles exploited the redox imbalance property in the tumor region to achieve the sequential release of paclitaxel and baicalin—inducing immunogenic cell death via chemotherapy and reversing M2 polarization, respectively—thereby enhancing antitumor efficacy while significantly reducing the systemic toxicity associated with chemotherapeutic agents.[165] This synergy between TME remodeling and immunotherapy is achieved through the closed-loop regulation mechanism of "sense-response-drug release".

Immune Checkpoint Blockade Strategies

In immune checkpoint blockade strategies, multi-targeted interventions have been employed to alleviate macrophage inhibition and remodel antitumor immunity. Beyond the adaptive immune checkpoints (eg, PD-1/PD-L1), emerging targets within the innate immune compartment offer several distinct therapeutic opportunities Firstly, CD47 is highly expressed in breast cancer cells, binding to SIRPα on TAMs to deliver a potent "don't eat me" signal that inhibits phagocytosis and promotes immune escape[166] gCM-MNs further markedly enhances macrophage-mediated phagocytosis by competitively blocking the CD47-SIRPα "don't eat me" signal, an innate immune checkpoint independent of adaptive immunity.[162]

Beyond CD47-SIRPα, the MHC class I-LILRB1/2 axis represents another critical phagocytic checkpoint in breast cancer, in which tumor-derived MHC I engages LILRB1 to suppress macrophage activation. Therapeutic targeting of this axis enhances antibody-dependent cellular phagocytosis.[167] Additionally, hyaluronic acid-MnO_2 nanoparticles (Man-HA-MnO_2 NPs) have been engineered to specifically target the mannose receptors overexpressed on TAMs in breast cancer, reprogramming M2-TAMs toward the M1 phenotype, while relieving tumor hypoxia to enhance immunotherapy efficacy.[168] M-PNP@R@C nanocarriers further downregulated inhibitory SIRPα expression, restoring innate immune recognition and phagocytic capacity against breast cancer cells.[163] This multi-layered innate checkpoint modulation—spanning CD47-SIRPα, MHC I-LILRB, and mannose receptor targeting—establishes a sequence from "signal disinhibition" to "functional activation", thereby offering breast cancer-specific strategies to enhance TAM-mediated tumor clearance independent of T cell engagement.

Epigenetic Regulation and Microbial Synergy

The precise regulation of macrophage polarization has been achieved through modulation of energy metabolism and epigenetic mechanisms during metabolic reprogramming and epigenetic regulation. For example, Lijuan Chong et al constructed M2-like TAM-mimetic biomimetic nanoparticles (HMMDN-Met@PM) comprising mesoporous manganese dioxide loaded with metformin Metformin promoted M2-to-M1 polarization by modulating macrophage glycolipid metabolism via the inhibition of mitochondrial complex I. Under tumor acidic (pH) and high glutathione (GSH) conditions, HMMDN decomposed into Mn^{2+}, achieving MRI contrast enhancement and controlled drug release. In vitro and in vivo studies both demonstrated downregulation of M2 markers (CD206, Arg-1, IL-10) and upregulation of M1 markers (CD80, TNF-α, iNOS), successfully achieving M2 macrophage repolarization toward the M1 phenotype and effectively suppressing tumor growth.[169,170] Leonard et al also previously discovered that treatment with a mesoporous silica particle-based nanotherapy loaded with albumin-bound paclitaxel (MSV-nab-PTX) promoted macrophage

polarization towards the M1 phenotype in breast cancer liver metastasis (BCLM) MSV-nab-PTX particles released zinc ions (Zn^{2+}) in the TME; Zn^{2+} acted as a histone deacetylase (HDAC) inhibitor, suppressing HDAC activity and triggering epigenetic activation of pro-inflammatory genes to facilitate M1 polarization.[171] This "precision epigenetic immunotherapy" paradigm provides novel insights for overcoming drug resistance in aggressive subtypes such as TNBC, particularly poorly perfused or severely immunosuppressed metastatic breast cancer cases.

Microbial-nano synergistic systems and combined therapeutic potentiation strategies have overcome traditional therapeutic limitations through biomaterial synergies. For example, the Ec-PR848 nano-loading system leveraged the immunomodulatory properties of engineered bacteria to regulate M1/M2 balance through the microbial-host interactions. When combined with PDOX chemotherapy, the polarization ratio was elevated to 1.59.[172] In contrast, Bif@P Bi-R nanomotors combined the hypoxia-targeting capability of *Bifidobacterium bifidum* with the photothermal properties of bismuth-based nanoparticles to enable the targeted delivery and photothermal-immunothermal spatio-temporal synergistic therapy of R848.[173] In combination therapy, PMNPs remodeled the immune microenvironment via dual mechanisms involving TLR7/8 activation and PI3Kδ inhibition, resulting in a 2.3-fold increase in radiotherapy response rate.[174] These microbial-nano synergistic systems further provide a novel therapeutic paradigm for breast cancer immunotherapy through precise M1/M2 polarization modulation and spatiotemporal synergistic effects.

Targeted Delivery of MYC Inhibitors

Breast cancer progression is closely linked to changes in the TME and immune evasion.[175] c-Myc is a key oncogene, the dysregulation of which is typically not caused by the activation other oncogenic lesions, rather than by direct mutation. These signaling pathways converge on MYC to initiate a transcriptional program leading to uncontrolled proliferation of cancer cells.[176] c-Myc is a well-defined M2-polarizing transcription factor, activated by IL-4, that regulates the expression of M2-specific genes (eg, SCARB1, ALOX15, and CD206)[177] Antigen presentation gene expression was reduced in MCF10A cells overexpressing ectopic MYC compared to parental MCF10A cells, indicating that MYC overexpression alone is sufficient to repress MHC-I-related genes in human mammary epithelial cells. Additionally, MYC-overexpressing tumors exhibit reduced sensitivity to anti-PD-L1 therapy, while immune checkpoint blockade (eg, PD-1 and PD-L1) can restore the cytotoxic activity of $CD8^+$ T cells.[178,179] The therapeutic potential of MYC inhibitors can further by enhanced by encapsulating the MYC-inhibitor precursor MI3-PD in perfluorocarbon nanoparticles, employing an αvβ3-targeted delivery system to transport the drug directly to the cytoplasmic compartment of target cells. This approach inhibits M2-type TAMs within the TME, while preserving the anti-tumor M1-type activity.[180] Thus, targeted nanoparticle delivery of MYC inhibitors represents a viable therapeutic strategy for breast cancer.

Removal of TAMs and TAM Depletion

Depleting TAMs is another strategy for cancer immunotherapy. MMP-2-responsive PEG-FA-Lip liposomes deliver drugs via folate receptor targeting, induced immunogenic cell death, depleted M2-type TAMs, and reduced immunosuppressive Treg cell infiltration for multiple antitumor effects.[181] In a prior study, Li et al co-loaded pexidartinib (PLX)-encapsulated dextran nanoparticles (PLX-NPs) and anti-programmed death-1 (PD-1) antibody-conjugated platelets (P-aPD-1) into an alginate hydrogel In this model, the dextran nanoparticles encapsulated PLX to target and block CSF1R, specifically depleting TAMs Furthermore, in hydrogel-treated mice (CT26 and B16F10 tumor recurrence models, as well as metastatic 4T1 breast tumor recurrence models), depleted TAMs enhanced systemic aPD-1 immunotherapy efficacy, promoted CD8+ T cell infiltration, and suppressed lung metastasis.[182] This nanoparticle system broke immune barriers by depleting immunosuppressive M2 TAMs, thereby effectively inhibiting lung metastasis and recurrent lesion growth, demonstrating significant clinical value, particularly in refractory metastatic breast cancer.

To counteract post-photothermal deterioration of the TME, Yi Cao et al designed a multifunctional ICG-SB@Lip-ZA nanosystem integrating photothermal ablation, zoledronic acid-mediated depletion of M2-type TAMs, and TGF-β pathway inhibition via SB-505124 In breast cancer models, the proportion of M2-like TAMs in the TME was found to be significantly reduced, while cancer-associated fibroblast (CAF) proliferation was suppressed, barriers to T cell infiltration were eliminated, and the microenvironment was transformed from an inflammatory-immunosuppressive state to an immune-activated state, consequently achieving a tumor eradication rate of 94%[183] This provides a more efficient

approach for clinical photothermal-immunotherapy combination, particularly applicable to aggressive breast cancer subtypes in which immunosuppressive microenvironments need to be overcome.

Termination of TAM Recruitment

The immunosuppressive TME has previously been targeted by inhibiting TAM recruitment to suppress tumor progression. A cationic nanoparticle encapsulating CCR2 siRNA (CNP/siCCR2) effectively blocked the CCL2–CCR2 axis, inhibited macrophage recruitment in an in situ murine breast cancer model, alleviated the immunosuppressive microenvironment, and suppressed tumor invasion, metastasis, and angiogenesis.[184] Additionally, the oncogene SERPINE2-derived circRNA, scSERPINE2, was found to be significantly elevated in breast cancer. Tumor-derived exosomal circSERPINE2 entered TAMs, enhanced IL-6 secretion, and promoted TAM recruitment, thereby facilitating breast cancer cell proliferation and invasion. A polylactic acid-hydroxy glycolic acid copolymer (PLGA)-based nanoparticle containing si-cSERPINE2 was effective at attenuating breast cancer progression in vivo.[185] Thus, modulation of the immunosuppressive TME via nanocarriers regulating TAM recruitment, abundance, or phenotype, combined with vascular remodeling, immune checkpoint blockade, physical barrier disruption, and chemotactic signaling inhibition, offers a novel strategy for combinatorial immunotherapy in breast cancer.

Immune Checkpoint Inhibitors

Due to immune escape, TAM enrichment, and cytokine-driven immunosuppression, a TAM-dominated immunosuppressive TME limits the efficacy of immune checkpoint inhibitors (ICIs).[186] To overcome this, Yu-Li et al developed a pH-responsive solid lipid nanoparticle (SLN) system that induces endoplasmic reticulum stress and immune reprogramming When functionalized with PD-L1/EGFR-binding peptides and an ER-homing peptide, these SLNs increase CD4+ and CD8+ T cell infiltration, while reducing the levels of Tregs and M2-TAMs in CT-26 models This TME-responsive nanoplatform, constructed through multi-dimensional ERS-immune-metabolic regulation, offers a precision therapeutic paradigm for immune-refractory TNBC that surpasses traditional ICIs.[187] Its modular design allows interchangeable targeting peptides (eg, HER2 replacing EGFR), demonstrating broad adaptability across breast cancer subtypes.

During tumor immune escape, elevated expression of immune checkpoint molecules significantly impairs the cytotoxic activity of CTLs to kill tumor cells.[175] Therefore, anti-PD-1 or anti-PD-L1 drugs, as conventional ICIs, have demonstrated substantial promise in tumor therapy.[73] Methotrexate-loaded PLGA nanocarriers (PeiPLGA-MTX) inhibit the STAT3/NF-κB pathway, disrupting immune cell-tumor interactions, and reducing tumor volume and metastasis in 4T1 models.[188] M1 macrophage membrane-coated PLGA nanoparticles co-loaded with IR780 and catalase (M1/PLGA@IR780/CAT) combined with anti-PD-L1 promote DC maturation, remodel the TME, and establish robust immune memory, preventing metastasis and recurrence.[189,190] These nanosystems shift ICI therapy from "passive blockade" to "active remodeling" through TAM polarization modulation and dynamic PD-L1 suppression, thus holding significant translational value for refractory TNBC.

Clinical Translation Progress

Current clinical trends indicate that monotherapies targeting TAMs demonstrate limited efficacy, with increasing research focus consequently shifting toward combination strategies. Studies support combining TAM targeting strategies with immune checkpoint inhibitors or precision nanodelivery systems to achieve synergistic enhancement. For example, M2-targeted peptide-chitosan-curcumin nanoparticles (M2pep-Cs-Cur NPs) combined with anti-PD-L1 therapy improved TNBC survival rates by approximately 50%.[191] Ionizable STING-activating nanoadjuvants were further found to reshape the immune microenvironment through tumor-restricted delivery, significantly enhancing checkpoint inhibitor efficacy.[192] Concurrently, nanotechnology has evolved from a "passive carrier" to an "active therapeutic" role: FDA-approved ferumoxytol enables both TAM-specific MRI imaging and intrinsic antitumor activity through M1 polarization induction.[118,193] The combination of the next-generation SIRPα-Fc fusion protein HCB101 with chemotherapy and PD-1 antibody for TNBC treatment has additionally demonstrated controllable safety and antitumor activity in Phase Ib/IIa trials.[194] These advances signify that TAM-targeted nanotherapies are transitioning from preclinical research into larger-scale translational studies (Table 1).

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Table 1 Comprehensive Summary of Nanoparticle-Based Strategies for TAM Targeting in Breast Cancer

Nanoparticle Platform	Carrier Type	TAM-Targeting Strategy	Cargo/Active Component	Mechanism of TAM Modulation	Key Molecular Targets	Breast Cancer Model	Key Outcomes
M1-derived exosomes[158]	Exosome/biomimetic vesicle	Membrane fusion	IR780, PFTBA, catalase	M1 membrane protein transfer induces M2→M1 repolarization; ROS generation; hypoxia alleviation	CD86, iNOS, AS1411 aptamer	4T1 (TNBC)	Enhanced T-cell infiltration; prolonged survival; metastasis inhibition
MM1-EVs/HA/CV[159]	Exosome/biomimetic vesicle	Exosome engineering + HA/β-blocker modification	Doxorubicin	Membrane fusion-mediated M1 marker transfer converts M2→M1	CD86, iNOS	4T1 metastatic	Enhanced anti-tumor immunity; potentiated DOX efficacy
Fe_3O_4 nanoparticles[160]	Magnetic/inorganic	Fenton reaction-driven	—	ROS generation induces M1 polarization and tumor cell death	Fenton chemistry	Breast cancer mouse model	Tumor growth inhibition; M1 polarization
Fe_3O_4@MDSC membrane[161]	Magnetic/biomimetic	Membrane coating	—	MDSC membrane homing; simultaneous M2 repolarization and ICD	MDSC surface molecules	Breast cancer mouse model	Tumor growth inhibition; immune activation
gCM-MNs[162]	Magnetic/biomimetic	Magnetic navigation + engineered cell membrane	SIRPα variants	Competitive CD47-SIRPα blockade; Fe_3O_4 core synergistically repolarizes M2→M1	CD47-SIRPα axis	4T1 (TNBC), B16F10	Primary tumor suppression; reduced lung metastasis; enhanced phagocytosis
M-PNP@R@C[163]	Polymer-based	pH-responsive release	R848 (TLR7/8 agonist), cGAMP (STING agonist)	Dual pattern-recognition receptor activation drives M1 polarization	TLR7/8, STING, NF-κB	Breast cancer mouse model	Tumor growth inhibition; innate immune restoration
PMM NPs[164]	Polymer-based	TME-responsive STING/TLR4 amplification	STING agonist + TLR4 activator	TLR4-NF-κB amplifies STING signaling; reduces Tregs; repolarizes M2→M1	STING, TLR4, NF-κB	Non-inflammatory metastatic BC	Synergistic efficacy with anti-PD-1; adaptive immune response
GSH/ROS dual-responsive NPs[165]	Polymer-based	Redox-responsive sequential release	Paclitaxel, baicalin	PTX induces ICD; baicalin reverses M2 polarization	Redox imbalance, STAT3	Breast cancer model	Enhanced anti-tumor efficacy; reduced systemic toxicity
HMMDN-Met@PM[169,170]	Inorganic/biomimetic	M2-TAM-mimetic targeting	Metformin	Metformin inhibits mitochondrial complex I; Mn^{2+} release for MRI and drug release	Mitochondrial complex I, CD206	Breast cancer model	M2↓ (CD206, Arg-1, IL-10); M1↑ (CD80, TNF-α, iNOS); tumor suppression
MSV-nab-PTX[171]	Inorganic (mesoporous silica)	Mathematical model-guided	nab-PTX, Zn^{2+}	Zn^{2+} as HDAC inhibitor triggers epigenetic activation of pro-inflammatory genes	HDAC, pro-inflammatory genes	BCLM	M1 polarization; precision epigenetic immunotherapy
Ec-PR848[172]	Engineered bacteria	Bacteria-nano hybrid	R848	Microbial-host interactions regulate M1/M2 balance	TLRs, NOD-like receptors	Breast cancer model	Polarization ratio 1.59; combined with chemotherapy
Bif@P Bi-R nanomotors[173]	Engineered bacteria	Bifidobacterium hypoxia targeting	R848, bismuth-based NPs	Photothermal-immunothermal spatiotemporal synergy	TLRs, photothermal conversion	Breast cancer model	Targeted delivery; photothermal-immune synergy
PMNPs[174]	Polymer-based	TLR7/8 activation + PI3Kδ inhibition	—	Dual mechanisms remodel immune microenvironment	TLR7/8, PI3Kδ	Breast cancer model	2.3-fold increase in radiotherapy response
αvβ3-targeted PFC NPs[180]	Polymer/lipid hybrid	Integrin αvβ3 targeting	MYC inhibitor prodrug (MI3-PD)	Inhibits c-Myc-driven M2 polarization; preserves M1 activity	αvβ3 integrin, c-Myc	Breast cancer model	Selective M2 inhibition; M1 preservation
CaBP-PEG[144]	Inorganic	TAM depletion	—	Normalizes tumor vasculature; alleviates hypoxia	TAM metabolism	Breast cancer model	Tumor growth inhibition; vascular normalization
PEG-FA-Lip[181]	Lipid-based	Folate receptor β targeting (MMP-2-responsive)	—	Depletes M2-TAMs; induces ICD; reduces Treg infiltration	Folate receptor β, MMP-2	Breast cancer model	Multiple anti-tumor effects

PLX-NPs + P-aPD-1@hydrogel[182]	Polymer-based/hybrid	CSF1R blockade + platelet-mediated ICB	Pexidartinib (PLX), anti-PD-1	CSF1R inhibition depletes TAMs; platelets enhance aPD-1 delivery	CSF1R, PD-1	4T1 metastatic, CT26, B16F10	Enhanced $CD8^+$ T cell infiltration; suppressed metastasis; prevented recurrence
ICG-SB@Lip-ZA[183]	Lipid-based	Photothermal-immune integration	ICG, zoledronic acid, SB-505124	ZA depletes M2-TAMs; SB-505124 inhibits TGF-β; photothermal ablation	TGF-β, M2-TAMs	Breast cancer model	94% tumor eradication; TME transformation to immune-activated state
CNP/siCCR2[184]	Polymer-based	CCR2 siRNA delivery	siCCR2	Blocks CCL2-CCR2 axis; inhibits macrophage recruitment	CCR2, CCL2	Orthotopic BC model	Reduced invasion, metastasis, angiogenesis; alleviated immunosuppression
si-cSERPINE2@PLGA[185]	Polymer-based	Exosomal circRNA targeting	si-cSERPINE2	Inhibits tumor exosomal circSERPINE2; suppresses MALT1-NF-κB-IL-6 axis	MALT1-NF-κB-IL-6	Breast cancer model	Attenuated breast cancer progression
M2pep-Cs-Cur NPs + anti-PD-L1[191]	Polymer-based	M2-targeted peptide delivery	Curcumin	M2pep targets M2-TAMs; curcumin repolarizes TAMs; combined with ICB	M2pep, PD-L1	TNBC model	~50% improvement in survival rates
Ionizable STING nanoadjuvants[192]	Lipid-based	Tumor-restricted delivery	STING agonist	Tumor-specific STING activation reshapes immune microenvironment	STING pathway	Solid tumors (including BC)	Enhanced checkpoint inhibitor efficacy
PeiPLGA-MTX[188]	Polymer-based	STAT3/NF-κB pathway inhibition	Methotrexate	Disrupts immune cell-tumor interactions	STAT3, NF-κB	4T1 model	Reduced tumor volume and metastasis
M1/PLGA@IR780/CAT + anti-PD-L1[189,190]	Polymer/biomimetic	M1 macrophage membrane coating	IR780, catalase	Promotes DC maturation; remodels TME; establishes immune memory	PD-L1, CD80/CD86	Breast cancer model	Metastasis and recurrence prevention
Man-HA-MnO_2 NPs[168]	Inorganic	Mannose receptor targeting	Hyaluronic acid, MnO_2	Reprograms M2-TAMs to M1; relieves tumor hypoxia	CD206 (mannose receptor), HIF-1α	Breast cancer model	Enhanced immunotherapy efficacy

Note: Carrier types are categorized as: exosome/biomimetic vesicle, magnetic/inorganic, polymer-based, lipid-based, inorganic, engineered bacteria, or hybrid systems.

Abbreviations: TAM, tumor-associated macrophage; TNBC, triple-negative breast cancer; BC, breast cancer; BCLM, breast cancer liver metastasis; MDSC, myeloid-derived suppressor cell; gCM-MNs, genetically engineered cell membrane-coated magnetic nanoparticles; PFTBA, perfluorotributylamine; HA, hyaluronic acid; CV, carvedilol; ICD, immunogenic cell death; PFC, perfluorocarbon; ICG, indocyanine green; ZA, zoledronic acid; SB-505124, TGF-β receptor inhibitor; PLX, pexidartinib; aPD-1/aPD-L1, anti-PD-1/anti-PD-L1 antibody; M2pep, M2-targeting peptide; Cs, chitosan; Cur, curcumin; CAT, catalase; Man, mannose.

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Translational Bottlenecks

Despite the substantial promise shown by nanotechnologies in breast-cancer therapy, the journey from pre-clinical proof-of-concept to bedside application remains fraught with hurdles. First, the inherent complexity of TAMs complicates therapeutic intervention.[195] Single-cell analyses have shown the existence of numerous context-dependent subpopulations of cells that defy simple M1/M2 classification, necessitating multidimensional taxonomies to accurately capture TAM heterogeneity.[196] Moreover, TAMs undergo adaptive rewiring in response to the tissue milieu, exhibiting distinct functions and phenotypes (exemplified by the functional divergence between Kupffer-cell-like TAMs in hepatocellular carcinoma and microglia-derived TAMs in glioblastoma), underscoring their tissue-specific adaptability.[68]

Current animal models inadequately recapitulate the complexity and heterogeneity of human tumors, particularly in regards to immune-cell composition, angiogenic patterns, and intercellular crosstalk within the TME; consequently, many nanotherapeutic strategies that show robust efficacy in mice display disappointing outcomes in clinical trials, impeding translational applications.[157] For example, CSF-1R inhibitors rapidly deplete M2-TAMs in rodents, yet tumors recruit alternative myeloid populations via the CX3CR1/CCR2 axis to sustain immune suppression, resulting in limited clinical benefit.[197]

The metabolic plasticity of TAMs further complicates therapy: M1 TAMs rely heavily on glycolysis, whereas M2 TAMs prefer oxidative phosphorylation—a dichotomy influenced by metabolites such as succinate and itaconate.[37,68,198] Pharmacokinetic and biodistribution studies of nanoparticles remain scarce; most reports have focused on short-term outcomes, meaning that long-term metabolic fate, accumulation sites and final excretion routes in humans are still undefined, necessitating validation in non-human primate studies.[199] Furthermore, the long-term sequestration of metal-based nanomaterials in mononuclear-phagocyte organs (liver, spleen, lung) raises toxicity and safety concerns.[200]

Meanwhile, problems with the large-scale production, formulation stability, and batch-to-batch consistency of nanoparticles remain unresolved: complex multi-material synthesis routes, storage-induced aggregation, and degradation or surface-ligand shedding all compromise therapeutic performance and safety, posing significant clinical risks.[195] Nanotherapy regulation and approval therefore face formidable challenges, the innovative and intricate nature of nanotechnology outstrips the adaptability of current drug-regulatory frameworks and review procedures,[201] resulting in protracted and convoluted translational pathways that can escalate development costs and timelines.[199]

Despite the formidable potential of nanotechnology in breast-cancer management, clinical realization demands an integrated consideration of TAM diversity, tissue-specific adaptability, metabolic flexibility, and compensatory mechanisms, alongside concerted efforts to resolve pharmacokinetic, biodistribution, scalable manufacturing, formulation-stability, and regulatory hurdles, so as to devise more precise and effective therapeutic strategies (Table 2).

Challenges and Future Directions

Overall, significant progress has been made in the production of nanotechnology-based strategies targeting TAMs in breast cancer immunotherapy. Multifunctional nanoparticles can modulate TAM phenotype, abundance, and recruitment, reversing the immunosuppressive tumor microenvironment. Key mechanisms include repolarizing M2 TAMs to M1 phenotypes via polarization modulators, checkpoint blockade, or metabolic/epigenetic interference. Specific advances include the development of M1E/AALs nanovesicles and Fe_3O_4 nanoparticles for photothermal-immuno-synergy, CaBP-PEG, and ICG-SB@Lip-ZA systems for vascular normalization and hypoxia alleviation, and the development of nano-delivery platforms targeting chemotactic signals or exosomal circRNA for metastasis inhibition. However, clinical translation faces substantial bottlenecks. Notably, incomplete understanding of nanoparticle pharmacokinetics limits long-term toxicity assessment, while the commonly used murine models inadequately replicate human TME complexity, leading to poor clinical translation. Furthermore, issues regarding large-scale production, formulation stability, and batch-to-batch consistency remain unresolved. TAM heterogeneity, metabolic plasticity, and compensatory recruitment mechanisms further complicate therapeutic design.

Future directions should address these gaps through the development of specific, actionable strategies. The design of organoid and humanized models to better recapitulate human TAM biology could help to overcome these issues. In addition, synergistic combinations with radiotherapy, CAR-T therapy, or microbial therapy should be further explored. The co-delivery of immune agonists with epigenetic modulators may achieve coordinated repolarization and immune memory. Standardized pharmacokinetic and safety studies are also essential to establish long-term biocompatibility. Finally, at the

Table 2 Strategic Classification of TAM-Targeted Nanotherapies

Therapeutic Strategy	Mechanism Category	Representative Nanoparticle Platforms	Key Molecular Targets	Immunological Outcome
M2→M1 Repolarization	Metabolic reprogramming	HMMDN-Met@PM[169,170]	Mitochondrial complex I	M1 phenotype restoration; pro-inflammatory cytokine production
	Epigenetic modulation	MSV-nab-PTX[171]	HDAC	Transcriptional reprogramming to M1
	Pattern recognition receptor activation	M-PNP@R@C,[163] PMM NPs[164]	TLR7/8, STING, TLR4-NF-κB	Innate immune activation; type I IFN response
	Exosomal membrane transfer	M1E/AALs,[158] MM1-EVs[159]	CD86, iNOS	Phenotypic conversion via membrane fusion
	Microbial-nano synergy	Ec-PR848,[172] Bif@P Bi-R[173]	TLRs, NOD-like receptors	M1/M2 balance regulation
TAM Depletion	CSF1R inhibition	PLX-NPs[182]	CSF1R	Elimination of immunosuppressive M2 population
	Bisphosphonate-mediated	ICG-SB@Lip-ZA,[183] CaBP-PEG[144]	TAM metabolism, TGF-β	M2-TAM elimination; vascular normalization
	Folate receptor targeting	PEG-FA-Lip[181]	Folate receptor β	Selective M2-TAM depletion; ICD induction
Recruitment Inhibition	CCL2-CCR2 axis blockade	CNP/siCCR2[184]	CCR2, CCL2	Reduced monocyte/macrophage infiltration
	Exosomal circRNA interference	si-cSERPINE2@PLGA[185]	MALT1-NF-κB-IL-6	Disrupted TAM-tumor communication
Combination with ICB	PD-1/PD-L1 pathway enhancement	M2pep-Cs-Cur + aPD-L1,[191] M1/PLGA@IR780/CAT + aPD-L1[189,190]	PD-L1, CD80/CD86	Synergistic T cell activation; immune memory
	Innate checkpoint modulation	gCM-MNs,[162] Man-HA-MnO_2[168]	CD47-SIRPα, CD206	Restored phagocytic capacity; M2→M1 conversion
M2→M1 Repolarization	Metabolic reprogramming	HMMDN-Met@PM[169,170]	Mitochondrial complex I	M1 phenotype restoration; pro-inflammatory cytokine production
	Epigenetic modulation	MSV-nab-PTX[171]	HDAC	Transcriptional reprogramming to M1
	Pattern recognition receptor activation	M-PNP@R@C,[163] PMM NPs[164]	TLR7/8, STING, TLR4-NF-κB	Innate immune activation; type I IFN response
	Exosomal membrane transfer	M1E/AALs,[158] MM1-EVs[159]	CD86, iNOS	Phenotypic conversion via membrane fusion

Notes: This classification aligns with the mechanistic framework presented in Figure 2. Strategies are categorized by primary mechanism; overlapping approaches are assigned to the dominant therapeutic strategy.
Abbreviations: ICB, immune checkpoint blockade; HDAC, histone deacetylase.

interface of materials science, immunology, and AI, future research should develop theranostic nanoparticles and customize TAM-targeted therapies by breast cancer subtype, to expedite clinical translation and improve patient outcomes.

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Disclosure

The author(s) report no conflicts of interest in this work.

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