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REVIEW

Nanoparticles Modulating the Immune Microenvironment in Breast Cancer Treatment

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Abstract: Breast cancer remains a significant therapeutic challenge, with the immune microenvironment playing a crucial role in its progression and treatment response. This review investigates the potential of nanoparticles to modulate the immune microenvironment in breast cancer therapy. Initially, we discuss the composition and influence of the immune microenvironment on breast cancer, followed by current strategies targeting these components. We then provide strategies of nanoparticles for targeting immune cells such as macrophages, dendritic cells, and T-cells. The role of nanoparticles in enhancing immune checkpoint blockade (ICB) and their application in cancer vaccines is also examined. Additionally, we explore the synergistic effects of combining nanoparticles with conventional therapies. The review addresses the challenges in clinical translation, focusing on safety, biocompatibility, and toxicity. Finally, we outline future research directions and the potential advancements in nanoparticle-based immunotherapy, emphasizing their transformative impact on breast cancer treatment.

Keywords: nanoparticle, breast cancer, immune cells

Introduction

Breast cancer remains a significant cause of morbidity and mortality worldwide, presenting substantial challenges in treatment due to its heterogeneous nature and the complexity of its microenvironment. Advances in surgery, chemotherapy, radiotherapy, and targeted therapies have improved outcomes, but the dynamic interactions within the tumor microenvironment continue to impede treatment efficacy.[1,2] The immune microenvironment, in particular, plays a pivotal role in tumor progression, metastasis, and response to therapies. It comprises various immune cells, cytokines, and signaling molecules that can either suppress or promote tumor growth, significantly impacting the effectiveness of conventional treatments.[3]

The immune microenvironment in breast cancer exhibits a dual role, with elements that can both support and inhibit tumor growth. Generally, tumor-associated macrophages (TAM), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs) contribute to an immunosuppressive milieu that fosters tumor progression and therapeutic resistance.[4,5] In contrast, effector T cells, natural killer (NK) cells, and dendritic cells (DCs) can initiate potent anti-tumor responses when adequately stimulated.[6,7] Thus, a deeper understanding and strategic modulation of the immune microenvironment are essential for enhancing breast cancer treatment outcomes.

Nanoparticles have emerged as a promising modality in cancer therapy due to their unique properties, such as nanoscale size, high surface area-to-volume ratio, and the capacity for functionalization to enable targeted delivery.[8] These features render nanoparticles highly suitable for delivering therapeutic agents directly to tumor sites or specific immune cells within the tumor microenvironment. Nanoparticles can be engineered to modulate immune responses, either by activating anti-tumor immune cells or by inhibiting immunosuppressive components within the tumor microenvironment.[9,10]

This review aims to elucidate the potential of nanoparticles in modulating the immune microenvironment for breast cancer treatment. Initially, we will provide an overview of the immune microenvironment in breast cancer, detailing its composition and its role in disease progression and therapeutic response. Subsequently, we will discuss strategies of

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nanoparticles for targeting different immune cells. Furthermore, we will examine the use of nanoparticles in enhancing ICB, developing cancer vaccines, and their synergistic effects when combined with conventional therapies such as chemotherapy and radiotherapy. Finally, we will address the challenges and future directions in the clinical translation of nanoparticle-based therapies, emphasizing their potential to revolutionize breast cancer treatment through immune modulation.

Immune Microenvironment of Breast Cancer

The immune microenvironment in breast cancer is a multifaceted and dynamic system comprising various immune cells, cytokines, chemokines, and signaling molecules. Key components include TAMs, Tregs, MDSCs, DCs, NK cells, and effector T cells. TAMs, often polarized towards a pro-tumorigenic M2 phenotype, facilitate tumor growth, angiogenesis, and metastasis while suppressing anti-tumor immunity.[11] Tregs and MDSCs contribute to immunosuppression by inhibiting effector T cells and NK cells, thus creating an environment that supports tumor progression.[12,13] In contrast, DCs, NK cells, and effector T cells are crucial for initiating effective anti-tumor responses, although their functions can be impaired within the tumor microenvironment (Figure 1).[14–16] Therefore, strategies aimed at reprogramming the immune microenvironment from a suppressive to an activating state hold significant promise for enhancing breast cancer therapy.

Therapeutic strategies targeting the immune microenvironment are focused on augmenting anti-tumor immunity. Immune checkpoint inhibitors, such as antibodies against PD-1/PD-L1 and CTLA-4, block inhibitory signals that suppress T cell activity.[17,18] Cytokine therapy, using agents like IL-2, IL-12, and Chi3l1, aims to activate and proliferate immune cells within the tumor microenvironment.[19,20] Adoptive cell therapy involves the ex vivo expansion and activation of immune cells, followed by their infusion into the patient. Oncolytic viruses selectively infect and destroy tumor cells while stimulating an anti-tumor immune response.[21] Additionally, strategies to deplete or reprogram immunosuppressive cells, including TAMs, Tregs, and MDSCs, are being investigated to reduce immunosuppression and enhance anti-tumor immunity.[22] Comprehensive understanding and manipulation of the immune microenvironment are essential for the advancement of effective breast cancer treatments.

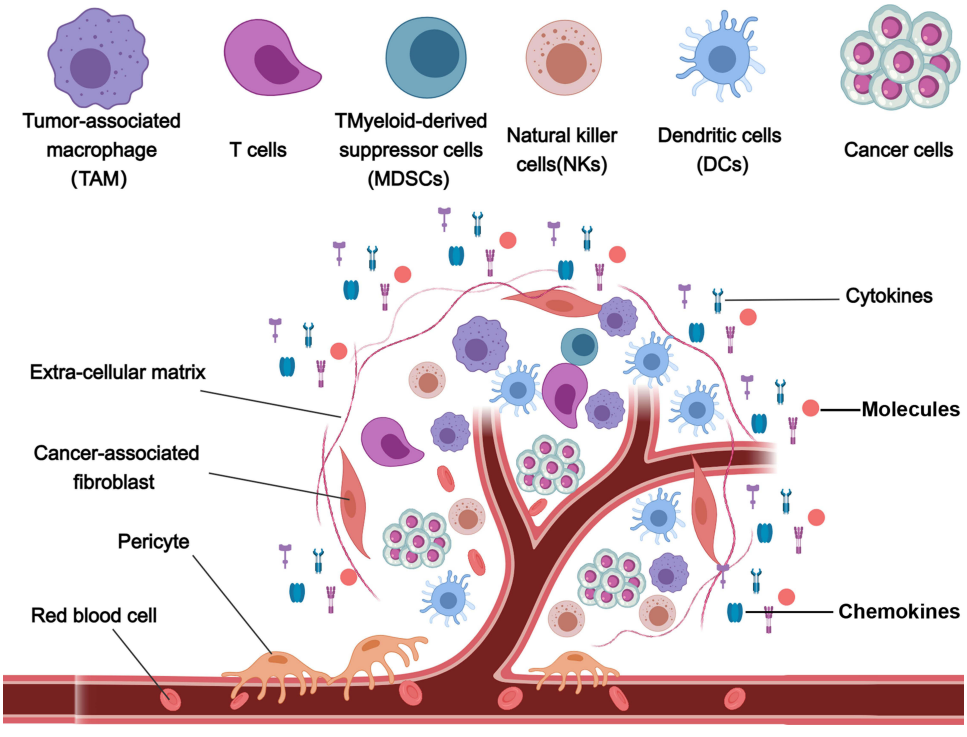

Figure 1 The immune microenvironment in breast cancer is a complex and ever-changing network made up of diverse immune cells (eg TAM, T cells, MDSCs, NKs, DCs, Cancers cells), cytokines, chemokines, and molecules.
Abbreviations: TAM, Tumor-associated macrophage; MDSCs, TMyeloid-derived suppressor cells; NKs, Natural killer cells; DCs, Dendritic cells.

Targeting Strategies With Nanoparticle for Different Immune Cells

TAMs

Nanoparticles have emerged as a crucial tool in regulating TAMs for breast cancer treatment. One approach utilizes hybrid cellular membrane nanovesicles (hNVs) displaying SIRPα variants that inhibit the CD47-SIRPα signaling axis and promote M2-to-M1 repolarization. These hNVs significantly prevent cancer recurrence and metastasis by enhancing macrophage immune responses.[23] Similarly, supramolecular peptide amphiphile nanosystems (SPADS) target M2-type macrophages (M2-Mφ), reprogramming them into M1-type macrophages, thereby reshaping the immune microenvironment, disrupting tumor immune evasion, and enhances the efficacy of anti-PD-1 therapy (Figure 2).[24] Another promising strategy involves polyaniline-coated iron oxide nanoparticles (Pani/γ-Fe2O3), which re-educate IL-10-stimulated macrophages towards a pro-inflammatory M1 profile, thereby decreasing the proportion of CD163+ macrophages and increasing CD86+ macrophages, which in turn improve their antitumor activity.[25] Additionally, dual inhibition of CSF1R and MAPK pathways using supramolecular nanoparticles (DSNs) effectively re-polarizes M2 macrophages to an M1 phenotype. This concurrent inhibition enhances antitumor immunity and reduces tumor growth in aggressive breast cancer models.[26] Moreover, targeted delivery of a c-MYC inhibitor using perfluorocarbon nanoparticles (αvβ3-MI3-PD NPs) specifically reduces M2-like TAMs while preserving M1-like macrophages, which approach mitigates tumor growth by modulating the macrophage population within the TME.[27] Collectively, nanoparticle-based strategies underscore the critical role of TAMs in breast cancer progression and demonstrate the potential of nanoparticles in reprogramming TAMs to improve therapeutic outcomes.

Tregs

Nanoparticles have shown significant potential in Tregs for breast cancer treatment. For instance, one approach involves the use of shikonin and chitosan-silver nanoparticles (MUC1@ACS) that induce necroptotic immunogenic cell death (ICD) in triple-negative breast cancer (TNBC). This combination effectively triggers ICD, enhances dendritic cell maturation, and inhibits Tregs infiltration, thereby reducing primary and distal tumor growth and metastasis.[28] Another strategy employs ursolic acid (UA)-liposomes for their potent immunomodulatory effects. UA-liposomes reduce the numbers of Tregs in tumor tissues by inhibiting STAT5 phosphorylation and IL-10 secretion, thereby correcting the tumor-mediated immunosuppressive microenvironment and deterring tumor growth.[29] Additionally, a mitochondrial-targeting nanotrapper (I@MSN-Im-PEG) has been developed to alleviate tumor hypoxia by chelating copper ions, thereby reducing oxygen consumption and enhancing photodynamic therapy (PDT). This nanotrapper not only improves PDT-induced ICD but also reverses Treg-mediated immune suppression, significantly enhancing photoimmunotherapy in breast cancer (Figure 3).[30] Furthermore, the combination of silibinin and IPI-549 encapsulated in nanoparticles targets tumor-associated fibroblasts and inhibits PI3Kγ, respectively. This dual approach remodels the TME, reduces Treg, resulting in increased apoptotic tumor tissue.[31] Overall, nanoparticle-based strategies underscore the critical role of Tregs in breast cancer progression and highlight the potential of nanoparticles in reprogramming the Tregs to improve therapeutic outcomes.

MDSCs

Nanoparticles have demonstrated significant potential in regulating MDSCs for breast cancer treatment. One approach employs a dual-function nanodrug composed of gemcitabine-celecoxib (GEM-CXB NPs) that effectively depletes both MDSCs and tumor cells. This method induces ICD, alleviates MDSC-mediated immunosuppression, thereby enhancing antitumor and anti-metastasis efficacy.[32] Another strategy involves the use of micellar nanoparticles loaded with doxorubicin and α-galactosylceramide (RLA/DOX/αGC NP), which inhibit MDSC recruitment and promote their depletion. This modulation significantly improves the inflammatory and immunosuppressive microenvironment of the lung and tumor sites, inhibiting the formation of the pre-metastatic niche.[33] A sponge-like neutrophil membrane-coated nano-system (NM/PPcDG/D) has been developed to suppress tumor recurrence and metastasis by inhibiting MDSC recruitment and functions. This system enhances antitumor immunity and prevents the establishment of immunosuppression in postoperative inflammatory regions, presenting a promising therapeutic strategy for postoperative malignant tumors.[34] Synthetic Nanoparticle Antibodies (SNAbs) offer another solution by targeting and depleting MDSCs, and thus overcoming local immunosuppression (Figure 4).[35] Furthermore, cargo-free immunomodulatory nanoparticles combined

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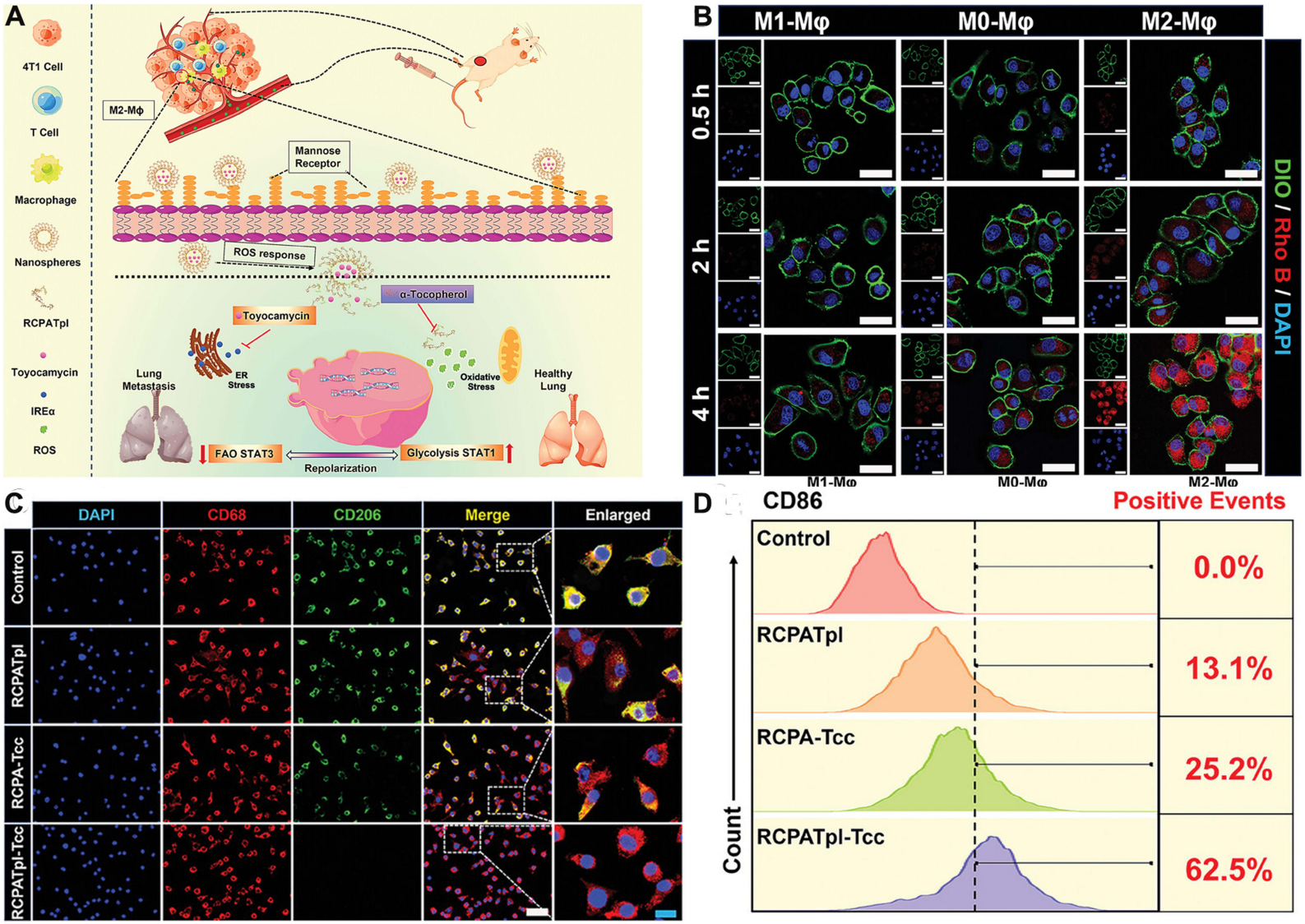

Figure 2 RCPA Reprogramming of macrophages to suppress breast cancer progression. (**A**) Diagram showing M2 macrophage (M2-Mφ) reprogramming through targeted delivery, inhibiting endoplasmic reticulum and oxidative stress to suppress breast cancer and lung metastasis. (**B**) Fluorescence images of M1, M0, and M2 macrophages treated with Rho B-loaded RCPAs at 0.5, 2, and 4 hours, scale bar: 30 μm. (**C**) Immunofluorescence showing CD206 in M2-Mφ after 24 hours with different RCPAs, white scale bar: 50 μm, blue scale bar: 14 μm. (**D**) Flow cytometry showing CD86 in M2-Mφ after 24 hours of RCPA treatment. Reprinted from Xiao Q, Huang J, Wang X, et al. Supramolecular Peptide Amphiphile Nanospheres Reprogram Tumor-associated Macrophage to Reshape the Immune Microenvironment for Enhanced Breast Cancer Immunotherapy. *Small*. 2024;20(21):e2307390. © 2023 Wiley-VCH GmbH.[24]

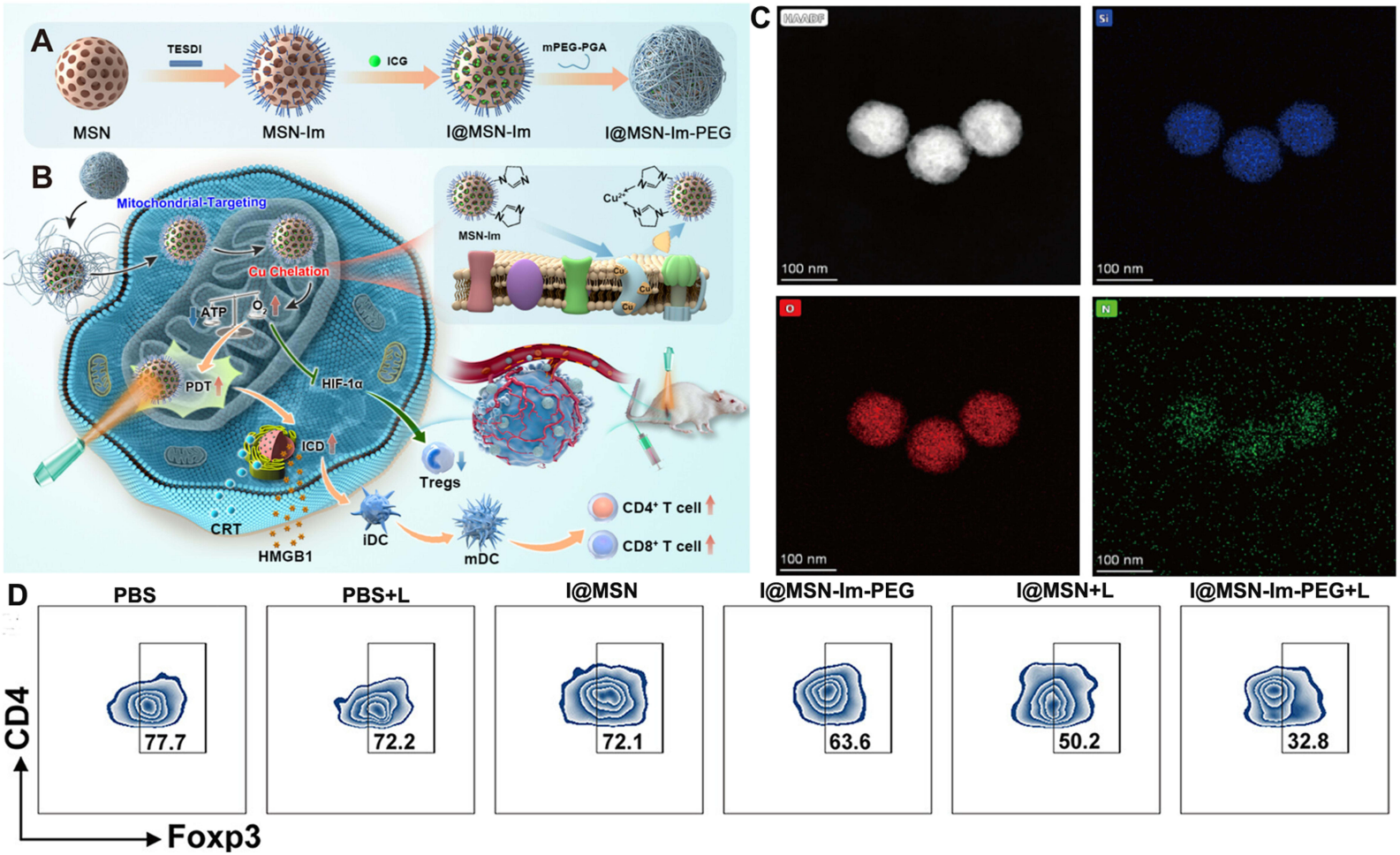

Figure 3 Nanotrapper enhances photoimmunotherapy in breast cancer via Treg modulation. (**A** and **B**) Diagram of a mitochondrial-targeting nanotrapper (I@MSN-Im-PEG) designed to modulate Treg cells and boost photoimmunotherapy. (**C**) HAADF-STEM image with elemental mapping (Si, O, N) of I@MSN-Im-PEG. (**D**) Flow cytometry showing intratumoral Treg cells (CD4+Foxp3+). Adapted with permission from Huang W, Yu M, Sun S, et al. Mitochondrial-Targeting Nanotrapper Captured Copper Ions to Alleviate Tumor Hypoxia for Amplified Photoimmunotherapy in Breast Cancer. *ACS Appl Mater Interfaces*. 2024;16(2):2166–2179. Copyright 2024 American Chemical Society.[30]

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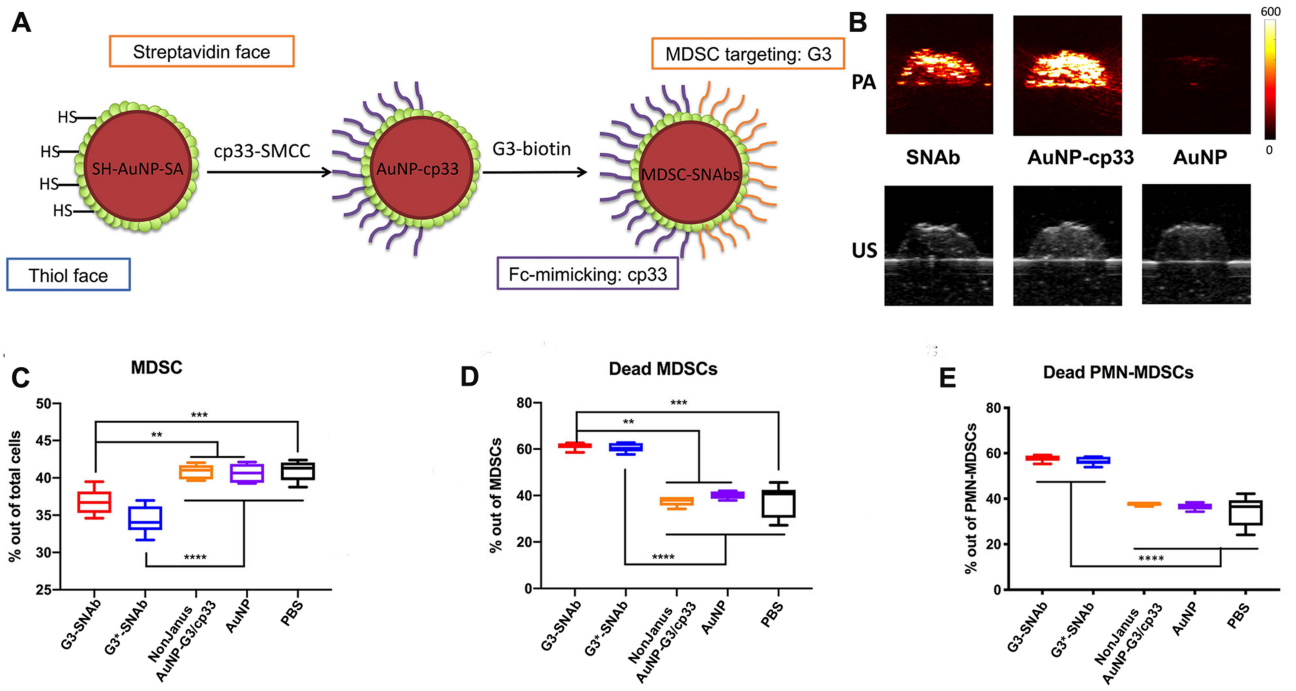

Figure 4 Targeted Janus Au nanoparticles for enhanced MDSC binding in breast cancer. (**A**) Janus Au nanoparticles were modified with ligands cp33 and G3 for targeted binding. (**B**) Photoacoustic and ultrasound images of nanoparticle-treated mouse MDSCs. (**C**–**E**) Flow cytometry analysis of MDSCs from treated mouse splenocytes, showing live/dead cell percentages. G3: WGWSLSHGYQVK; G3*: KSLWVQWSGGHY. **** $p < 0.0001$, *** $p < 0.0002$, ** $p < 0.0021$. Adapted with permission from Liu J, Toy R, Vantucci C, et al. Bifunctional Janus Particles as Multivalent Synthetic Nanoparticle Antibodies (SNAbs) for Selective Depletion of Target Cells. *Nano Lett*. 2021;21(1):875–886. Copyright 2021 American Chemical Society.[35]

with anti-PD-1 antibody divert immune cells from the TME, reducing MDSC abundance and enhancing the efficacy of immunotherapy in metastatic TNBC models. These nanoparticles decrease the expression of MCP-1 and increase TNF-α expression, promoting a pro-inflammatory environment that supports anti-tumor immunity.[36] Collectively, the nanoparticle-based strategies highlight the pivotal role of MDSCs in breast cancer progression and demonstrate the potential of nanoparticles in reprogramming the TME to improve therapeutic outcomes.

DCs

Nanoparticles play a crucial role in regulating DCs for breast cancer treatment by modulating the tumor microenvironment (TME) and enhancing antitumor immunity. Firstly, the use of genetically edited cascade nanozymes (gCM@MnAu) designed to promote DC maturation. This strategy has demonstrated significant efficacy in breast cancer and lung metastasis models, prolonging survival and eliciting systemic antitumor responses.[37] Secondly, the application of a Ca & Mn dual-ion hybrid nanostimulator (CMS) that induce ferroptosis and activates innate immunity. This nanostimulator enhances DC activation and antigen presentation, leading to increased infiltration of tumor-specific cytotoxic T lymphocytes (CTLs) into tumor tissues (Figure 5).[38] Additionally, a nanodrug (GM@LR) co-delivering a GSDME-expressing plasmid and manganese carbonyl (MnCO) into TNBC cells promotes DC maturation via the STING signaling pathway, which results in increased infiltration of cytotoxic lymphocytes and robust immune responses.[39] Furthermore, a nano-ultrasonic contrast agent (Pt(IV)/CQ/PFH NPs-DPPA-1) boosts the ratio of mature DCs by reprogramming the metabolism of immature DCs. This agent enhances chemoimmunotherapy by leveraging cisplatin-induced ROS production and chloroquine to inhibit tumor cell autophagy.[40] Lastly, TRAIL-modified, doxorubicin-embedded periodic mesoporous organosilica nanoparticles (PMOs) have shown the ability to activate DCs, significantly suppressing tumor growth in a TNBC mouse model.[41] Overall, nanoparticle-based strategies underscore the pivotal role of DCs in breast cancer immunotherapy, offering new perspectives for effective treatment.

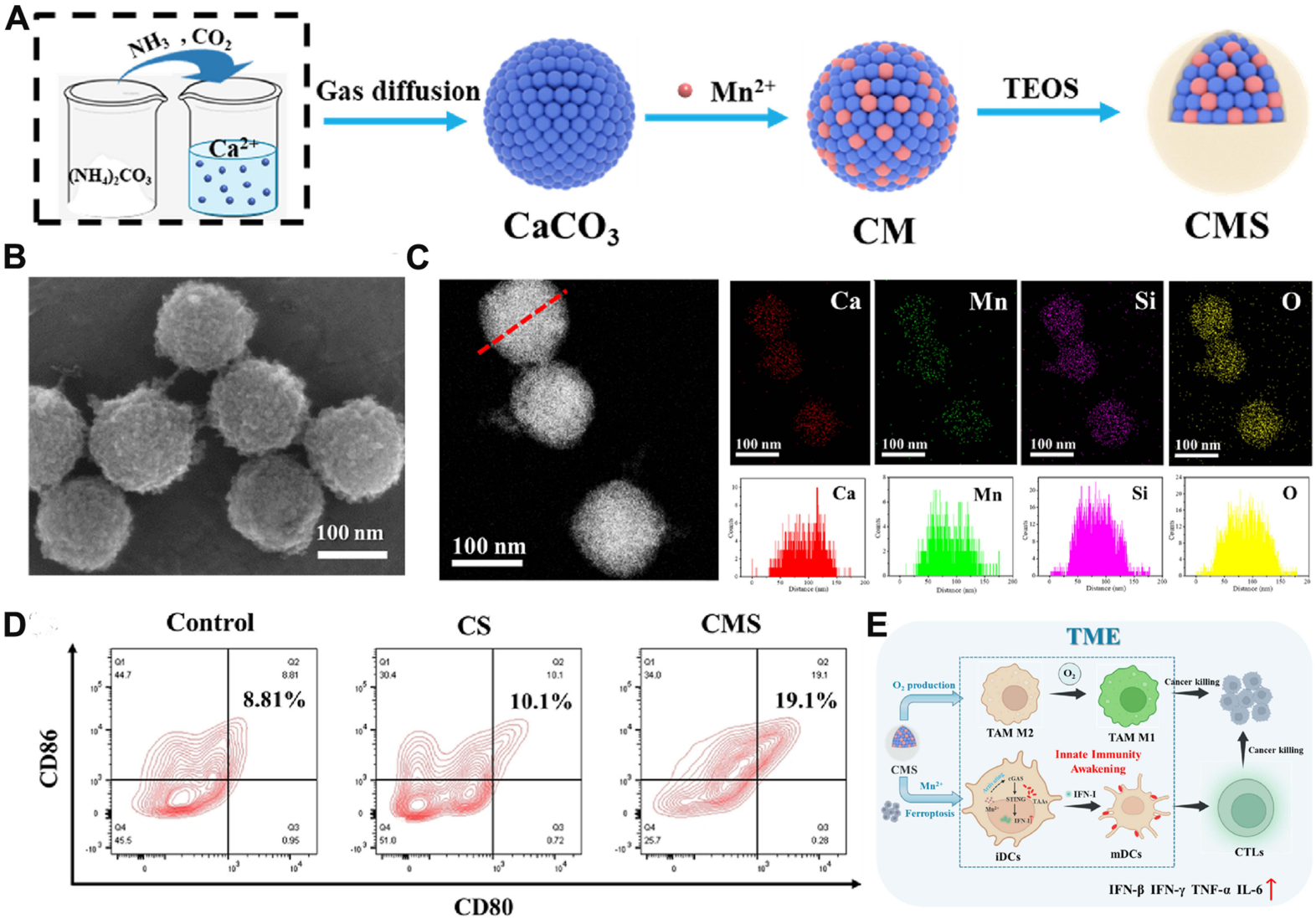

Figure 5 CMS Nanoparticles enhance DC activation to fight against breast cancer. (**A**) Diagram showing the synthesis process of CMS. (**B**) SEM image of CMS nanoparticles. (**C**) Dark-field STEM image of CMS with EDS element mapping and line scanning. (**D**) Flow cytometry plots of matured DCs (CD80+CD86+ on CD11c+) in lymph nodes of 4T1 tumor-bearing mice post-treatment. (**E**) Illustration of CMS activating TAMs and DCs to enhance the anti-tumor immune response. Adapted from *Bioact Mater.* Volume 33, Deng X, Liu T, Zhu Y, et al. Ca & Mn dual-ion hybrid nanostimulator boosting anti-tumor immunity via ferroptosis and innate immunity awakening. 483–496, copyright 2024, with permission from Elsevier.[38]

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NK Cells

Nanoparticles have demonstrated significant potential in regulating NK cells to enhance breast cancer treatment by overcoming immunosuppressive barriers. One approach involves the use of multifunctional nanosonosensitizers (FA-MnPs) for sonodynamic therapy (SDT). These nanoparticles, when activated by ultrasound, generate reactive oxygen species and activate NK cells, thereby inhibiting tumor growth in TNBC models.[42] Another strategy employs triadic drug delivery nanoparticles (BEN) that co-deliver an MDSC inhibitor (entinostat) and an immune checkpoint inhibitor (BMS-1), which target multiple nodes within the immunosuppressive network to activate NK cells, thereby suppressing tumor growth and metastasis (Figure 6).[43] Additionally, nanoengineered disruption of heat shock protein 90 (Hsp90) using a chimeric nanotherapeutic tool comprising taxanes and a cholesterol-tethered Hsp90 inhibitor (radicicol) has been shown to overcome drug-induced resistance and invigorate NK cell activity, which approach enhances NK cell immune surveillance and reduces tumor persistence, emphasizing the critical role of NK cells in combating drug-tolerant cancer cells.[44] Collectively, the nanoparticle-based strategy highlights the crucial role of NK cells in breast cancer treatment and demonstrates the potential of nanoparticles in regulating NK cells to improve therapeutic outcomes.

Effector T Cells

Nanoparticles have demonstrated substantial potential in regulating effector T cells to enhance breast cancer treatment. Firstly, PEG-sheddable nanodrugs that incorporate Signal Transducer and Activator of Transcription 6 inhibitor (AS) and

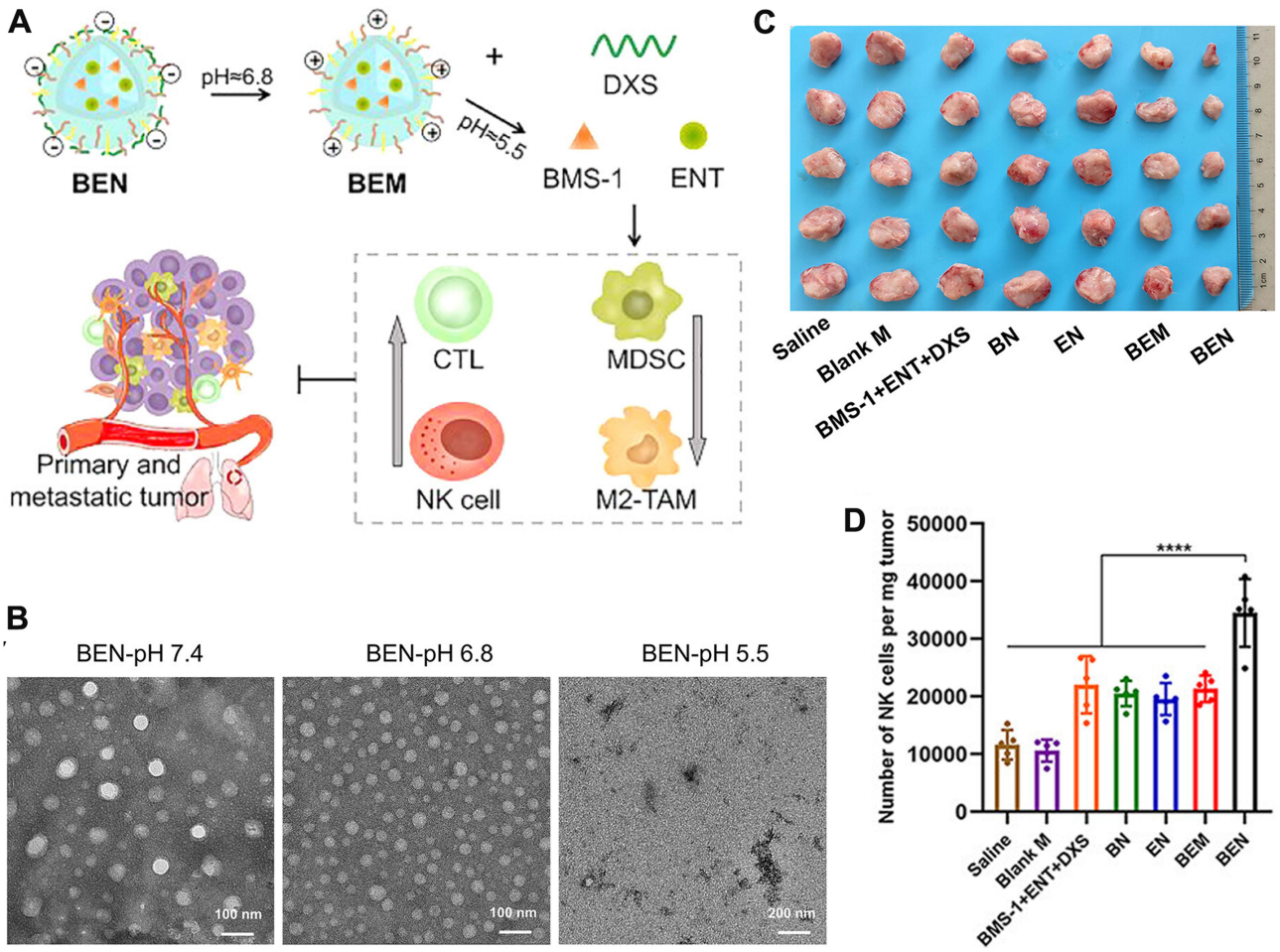

Figure 6 BEN Nanoparticles activate NK cells to suppress tumor growth. (**A**) Diagram showing how BEN targets tumors in breast cancer immunotherapy. In the acidic tumor environment, DXS detaches, blocking SR-A, promoting TAM polarization to M1, and increasing NK cells. (**B**) TEM images of BEN at different pH levels (7.4, 6.8, 5.5). (**C**) Tumor images after 21 days of treatment. (**D**) NK cell count in tumors. ****p < 0.0001. Adapted from Yan W, Li Y, Zou Y, et al. Breaking Tumor Immunosuppressive Network by Regulating Multiple Nodes with Triadic Drug Delivery Nanoparticles. *ACS Nano*. 2023;17(18):17826–17844. Copyright 2023 American Chemical Society.[43]

anti-Galectin-9 antibody (aG-9) are significant advancements. These nanodrugs respond to the acidic TME by shedding their PEG corona and releasing aG-9, which locally blocks PD-1/Galectin-9/TIM-3 interactions to reverse T cell exhaustion, thereby promoting effector T cell infiltration and enhancing therapeutic efficacy (Figure 7).[45] Secondly, docetaxel-loaded pH/ROS dual-responsive nanoparticles generate reactive ROS to induce ICD, thereby activate effector T cells to improve the outcomes of anti-PD-1 antibody therapy by inhibiting tumor growth and metastasis.[46] Additionally, programmable bispecific nano-immunoengagers (NIE) bind to tumor cells and effector T cells, transforming into nanofibrillar networks within the TME, which networks capture effector T cells and release immunomodulatory agents, significantly enhancing the therapeutic efficacy of ICB therapy.[47] Furthermore, Prussian blue nanoparticle-based photothermal therapy (PBNP-PTT) has been utilized to generate tumor-specific T cells ex vivo. These T cells exhibit robust antitumor activity, significantly reducing tumor growth and enhancing long-term survival in murine models.[48] Collectively, the nanoparticle-based strategy highlights the crucial role of nanoparticles in regulating effector T cells and improving the effectiveness of breast cancer immunotherapy.

Nanoparticles for Immune Modulation

Nanoparticles in Enhancing ICB

Nanoparticles have demonstrated significant potential in enhancing ICB therapy for breast cancer by addressing challenges such as immunosuppression and inefficient drug delivery. Traditional ICB therapies often face limitations

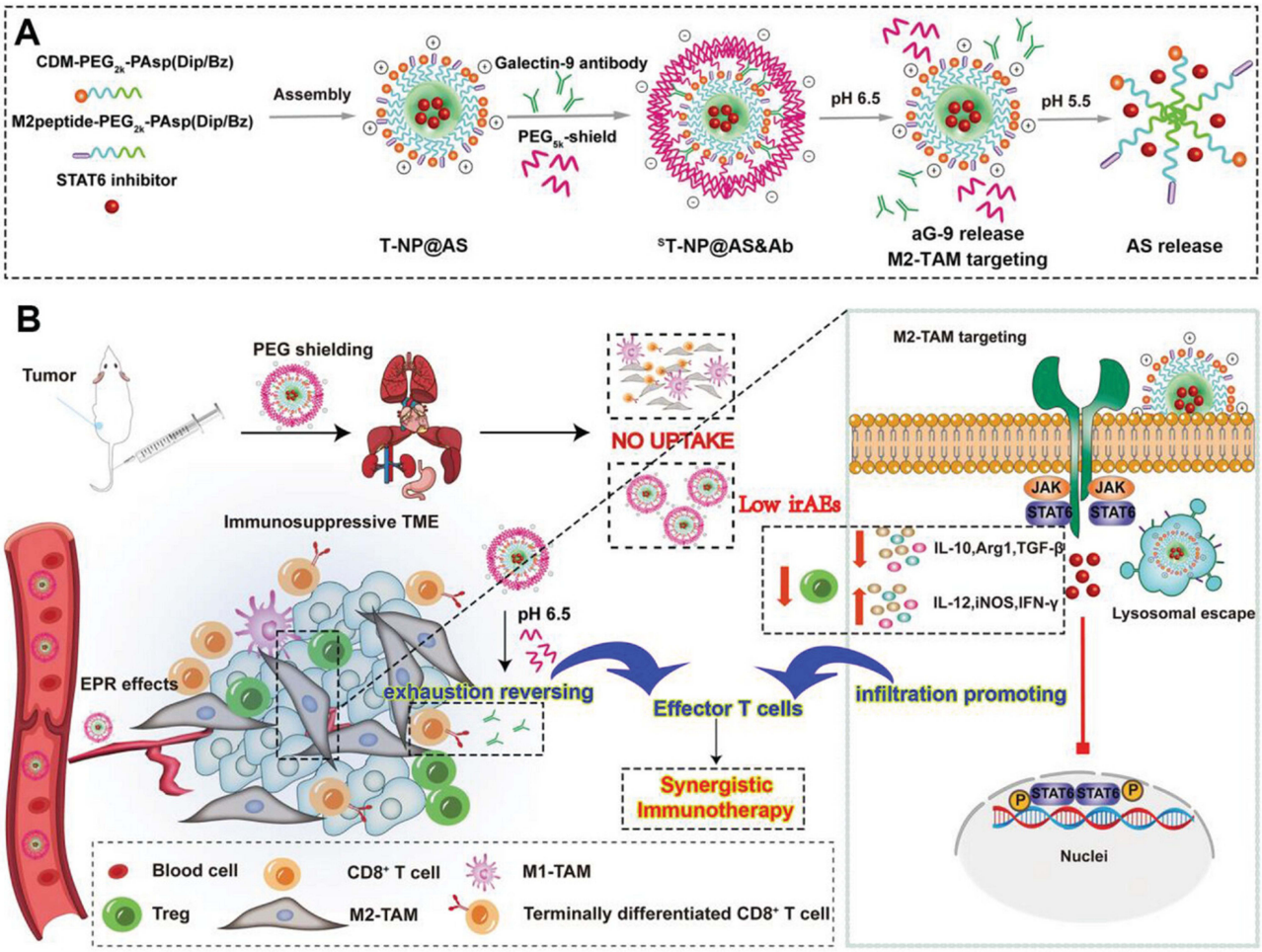

Figure 7 ST-NP@AS&Ab Nanodrug promotes effector T cell infiltration and enhances therapeutic efficacy in breast cancer. (**A**) Illustration of the ST-NP@AS&Ab nanodrug preparation, targeting M2-TAMs with a PEG-shedding polymeric micelle loaded with a STAT6 inhibitor (AS) and anti-Galectin-9 antibody (aG-9). (**B**) Schematic showing the nanodrug's dual action: repolarizing M2-TAMs and reducing T cell exhaustion for enhanced immunotherapy. Reprinted from Huang T, Zhang Q, Yi J, et al. PEG-Sheddable Nanodrug Remodels Tumor Microenvironment to Promote Effector T Cell Infiltration and Revise Their Exhaustion for Breast Cancer Immunotherapy. *Small*. 2023;19(38):e2301749. © 2023 Wiley-VCH GmbH.[45]

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due to adverse events and drug resistance, particularly within the immunosuppressive TME.[49] A notable advancement involves lactate oxidase nanocapsules, which lower lactate levels and release immunostimulatory hydrogen peroxide, thus improving the efficacy of ICB by mitigating tumor-induced immunosuppression.[50] In TNBC, liposomal co-delivery of TLR3 and TLR7 agonists effectively converts the TME from a "cold" to a "hot" immunogenic state, significantly enhancing ICB therapy.[51] Additionally, bio-nanoparticle-based vaccines targeting ASPH, in combination with PD-1 blockade, have demonstrated substantial suppression of primary tumors and metastases by expanding activated T cells and reducing immunosuppressive regulatory T cells.[52] Another approach utilizes relaxin-encapsulated polymeric metformin nanoparticles to deplete cancer-associated fibroblasts (CAFs) and remodel the TME, thereby enhancing cytotoxic T cell infiltration and efficacy when combined with PD-L1 antibodies.[53] Furthermore, nanoparticle-integrated dissolving microneedles co-delivering TLR7/8 agonist R848 and aPD-1 have been shown to mature tumor-infiltrating dendritic cells and promote CD8+ T cell infiltration, significantly improving therapeutic outcomes in TNBC models.[54] Therefore, these advancements in nanoparticles boost ICB therapy by enhancing immune responses, optimizing drug delivery, and overcoming immunosuppressive barriers in breast cancer.

Nanoparticle-Based Cancer Vaccines and Their Efficacy

Nanoparticle-based cancer vaccines represent a promising frontier in breast cancer therapy by leveraging the unique properties of nanoparticles to enhance vaccine efficacy and immune responses. Traditional breast cancer vaccines, including peptide, protein, and nucleic acid-based types, have shown limited effectiveness in clinical trials.[55] Recent advances in nanotechnology have addressed these limitations by designing nanoplatforms that efficiently deliver molecular, cellular, or subcellular vaccines directly to breast cancer cells, thereby boosting anti-tumor immunity and minimizing side effects.[55] For instance, an injectable nano-in-gel vaccine (NIGel-Vax) demonstrated significant post-operative breast cancer therapy efficacy by achieving up to a 96% tumor suppression rate and a 50% cure rate in TNBC models (Figure 8).[56] Another approach involves DC-based vaccines, where down-regulating PD-L1 on DCs and silencing PD-1 on T cells using siRNA-loaded nanoparticles enhance T-cell priming and anti-tumor responses.[57] Additionally, self-assembled vaccines combining tumor-specific antigens and TLR2 agonists have shown substantial efficacy in promoting DCs maturation and CD8+ T cell activation, leading to a 70% tumor inhibition rate in vivo.[58] These strategies highlight the potential of nanoparticle-based vaccines to improve the clinical outcomes of breast cancer immunotherapy by enhancing the delivery, stability, and immune activation of vaccine components.

Combination Therapies Involving Nanoparticles

Combination therapies involving nanoparticles offer significant advancements in breast cancer treatment by enhancing therapeutic outcomes and overcoming resistance. Multifunctional nanoplatforms, such as DTX-loaded Zein/CSP-GTP/FeIII nanoparticles, effectively eliminate primary tumors and prevent metastasis through a combination of chemotherapy, immunotherapy, and photothermal therapy. This approach induces ICD and enhances DCs maturation.[59] Similarly, CaCO3-based colloidosomal microreactors modulate the tumor microenvironment by alleviating hypoxia and acidity, thus boosting the efficacy of immunotherapies like anti-PD-1 antibodies and CAR-T cells (Figure 9A).[60] Another strategy employs IR780-based homodimeric nanoassemblies for photodynamic and immunotherapy, demonstrating superior tumor accumulation and immune activation.[61] An injectable thermosensitive hydrogel system (APH) combining near-infrared (NIR) nanoparticles and plasma amine oxidase enhances cancer immunotherapy by alleviating tumor hypoxia, boosting carbonyl stress, and synergistically suppressing tumor growth, metastasis, and recurrence while promoting immune memory.[62] A heterogenic membrane-based biomimetic hybrid nanoplatform synergizes radiotherapy and immunotherapy by enhancing radiosensitivity and triggering robust immune responses.[63] Additionally, biodegradable NIR-II fluorescence image-guided surgery nanoprobes improve the outcomes of breast cancer radiotherapy while minimizing long-term toxicity.[64] Finally, engineered multifunctional nanoplatforms, such as MoS2/Fe@CPT-11-PEG-iRGD, facilitate low-temperature photothermal therapy and ferroptosis, significantly extending survival in tumor-bearing mice (Figure 9B).[65] In previous studies, an APH hydrogel system leveraging photothermal therapy and carbonyl stress, and a THL photosensitizer combined with cold exposure, effectively enhance cancer immunotherapy by overcoming tumor hypoxia, boosting ROS production, and promoting immune responses, offering promising advances in breast tumor treatment.[66,67] Therefore, nanoparticle-based combination

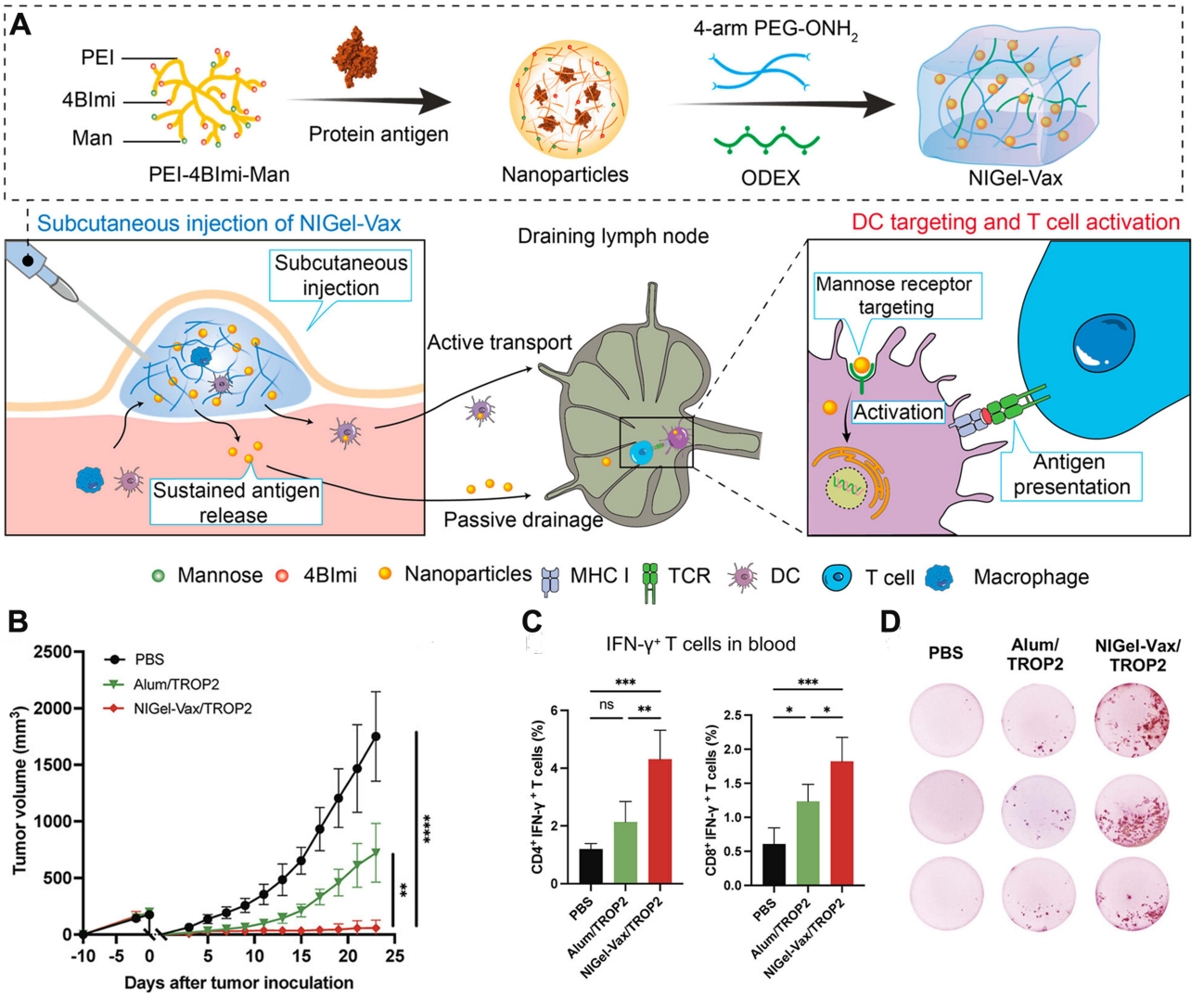

Figure 8 Injectable hydrogel vaccine for immune activation of breast cancer. (**A**) NIGel-Vax preparation involves mixing PEI-4BImi-Man with protein antigens to form nanoparticles, then loading into a hydrogel. After injection, nanoparticles release, reach lymph nodes, activate dendritic cells, and stimulate T cells for immune response. (**B**) Tumor growth curves for different treatments. (**C**) Levels of CD4+ and CD8+ IFN-γ+ T cells in blood 23 days after vaccination. (**D**) ELISPOT results for splenocytes across treatment groups. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001; ns, no significance. Adapted with permission from Liu T, Si X, Liu L, et al. Injectable Nano-in-Gel Vaccine for Spatial and Temporal Control of Vaccine Kinetics and Breast Cancer Postsurgical Therapy. *ACS Nano.* 2024;18(4):3087–3100. Copyright 2024 American Chemical Society.[56]

therapies represent promising breast cancer treatment by integrating multiple therapeutic modalities, addressing the limitations of conventional treatments, and enhancing overall efficacy.

Challenges and Future Directions

Breast cancer presents unique challenges in tumor immunotherapy, particularly due to its immunosuppressive microenvironment. Compared to other cancers, breast tumors are often characterized by low immunogenicity, the presence of TAMs with immunosuppressive phenotypes, and high levels of Tregs, all of which contribute to immune evasion. Additionally, the stromal-rich architecture of breast cancer creates physical and biochemical barriers that hinder the effective delivery of immunotherapies, including nanoparticle-based strategies.[68] These factors necessitate tailored approaches to address the specific immunosuppressive mechanisms active in breast cancer.

The clinical translation of nanoparticle-based therapies for breast cancer presents several significant challenges. The heterogeneity of the tumor microenvironment and the variability in immune responses among patients often result in inconsistent therapeutic outcomes, complicating the prediction and optimization of treatment efficacy.[69,70] Additionally, the production and scalability of nanoparticles with precise characteristics necessary for targeting specific immune cells

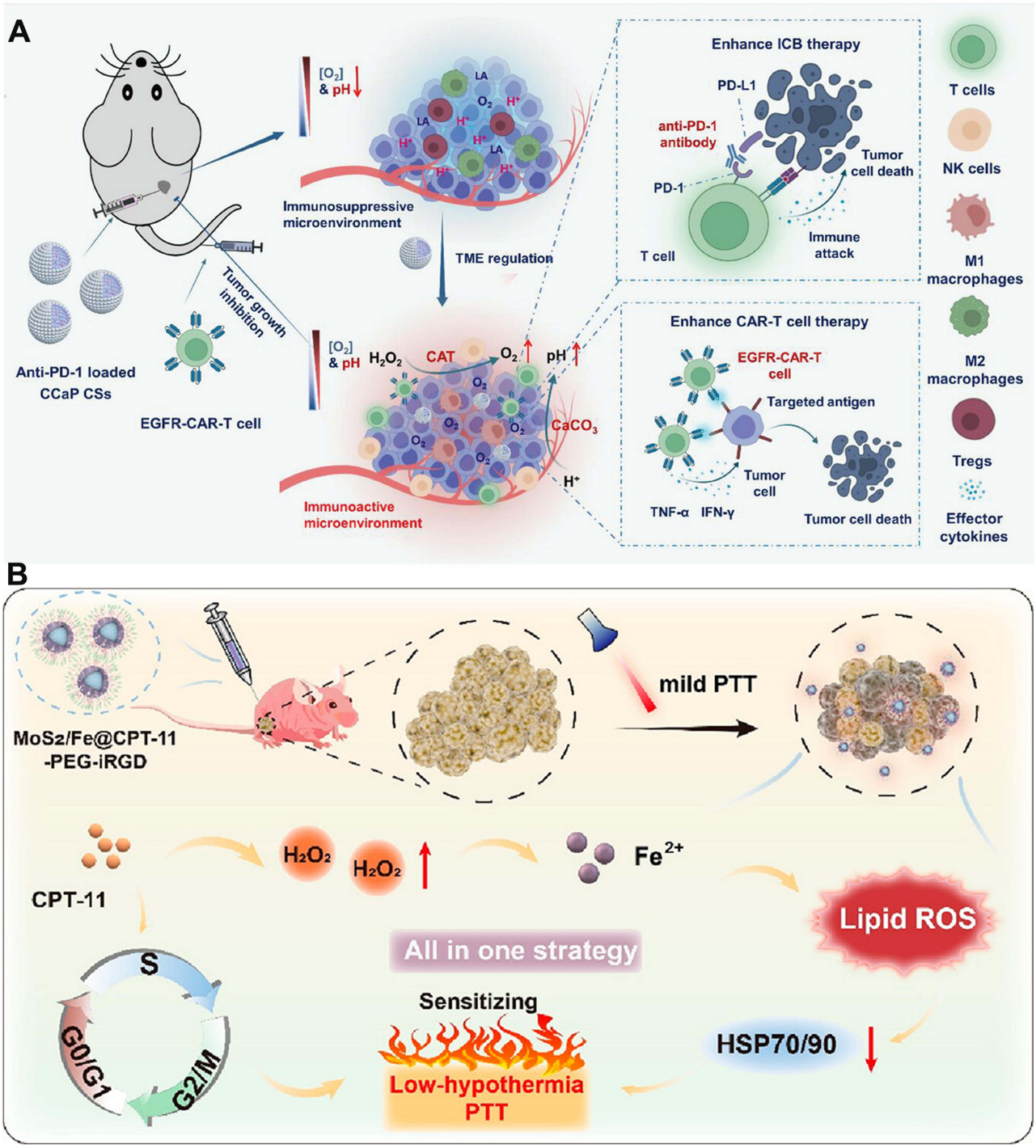

Figure 9 Combined therapy for enhanced breast cancer treatment. (**A**) Diagram of colloidosomal microreactors that modify the TME for improved immunotherapy. Reprinted from Dong Z, Liu Y, Wang C, et al. Tumor Microenvironment Modulating CaCO(3) -Based Colloidosomal Microreactors Can Generally Reinforce Cancer Immunotherapy. *Adv Mater*. 2024;36(9):e2308254. © 2023 Wiley-VCH GmbH.[60] (**B**) Illustration showing how chemotherapy, ferroptosis, and low-temperature PTT work together to kill tumor cells and slow tumor growth. Reprinted with permission from Li K, Xu K, Liu S, et al. All-in-One Engineering Multifunctional Nanoplatforms for Sensitizing Tumor Low-Temperature Photothermal Therapy In Vivo. *ACS Nano*. 2023;17(20):20218–20236. Copyright 2023 American Chemical Society.[65]

are technically demanding and cost-intensive.[71,72] Regulatory challenges further complicate the process, as extensive evaluation of nanoparticle safety, efficacy, and quality control is required, which can be both time-consuming and costly.

Addressing safety, biocompatibility, and toxicity concerns is essential for the successful clinical application of nanoparticle-based therapies.[73] Nanoparticles must be engineered to minimize adverse immune reactions and off-target effects while ensuring biodegradability and non-toxicity.[74] Long-term studies on the biodistribution, clearance, and

potential tissue accumulation of nanoparticles are crucial to fully understanding their safety profiles. Establishing standardized protocols for evaluating the biocompatibility and toxicity of various nanoparticles will facilitate regulatory approval and clinical translation.

Future research directions in nanoparticle-based immunotherapy should focus on overcoming these challenges and advancing the field. The development of multifunctional nanoparticles capable of targeting multiple components of the immune microenvironment simultaneously could enhance therapeutic efficacy.[75] Innovations in nanoparticle design, such as stimuli-responsive and self-assembling nanoparticles, offer promising avenues for more precise and controlled drug delivery. Integrating artificial intelligence and machine learning into the design and optimization of nanoparticle therapies could accelerate the discovery of effective formulations.[76,77] Clinical trials designed to assess the efficacy of these advanced nanoparticles, particularly in combination with existing therapies like immune checkpoint inhibitors and adoptive cell therapies, are crucial to determining their synergistic potential.[78] Ultimately, the goal is to translate these advancements into safe, effective, and widely accessible treatments that significantly improve outcomes for breast cancer patients.

Conclusion

In summary, nanoparticles have the potential to transform breast cancer treatment by modulating the immune microenvironment. Despite existing challenges related to safety, biocompatibility, and regulatory approval, ongoing advancements in nanoparticle technology and an improved understanding of tumor immunology are likely to propel this field forward. The integration of nanoparticle-based therapies into clinical practice could offer more effective and personalized treatment options for breast cancer patients, marking a significant step forward in cancer therapy.

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Disclosure

The authors declare that they have no competing interests in this work.

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