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REVIEW

Advancements in Cell Membrane-Derived Biomimetic Nanotherapeutics for Breast Cancer

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Abstract: Breast cancer remains the leading cause of female mortality worldwide, necessitating innovative and multifaceted approaches to address its various subtypes. Nanotechnology has attracted considerable attention due to its nanoscale dimensions, diverse carrier types, suitability for hydrophobic drug delivery, and capacity for controlled and targeted administration. Nano-sized particles have become prevalent carriers for therapeutic agents targeting breast cancer, thanks to their reproducible synthesis and adjustable properties, including size, shape, and surface characteristics. In addition, certain nanoparticles can enhance therapeutic effects synergistically. However, the immune system often detects and removes these nanoparticles, limiting their efficacy. As a promising alternative, cell membrane-based delivery systems have gained attention due to their biocompatibility and targeting specificity. These membrane-coated drug delivery systems are derived from various cell sources, including blood cells, cancer cells, and stem cells. Leveraging the unique properties of these cell membranes enables precise targeting of breast cancer tumors and associated biomarkers. Inspired by natural structures, cell membranes disguise nanoparticles in the bloodstream, enhancing their retention time in vivo and improving tumor targeting. Consequently, cell membrane-derived nanoparticles (CMDNPs) have been investigated for their potential applications in breast cancer diagnostics, photothermal therapy (PTT), and vaccine development. This review comprehensively explores the potential and limitations of cell membrane-derived drug delivery systems in clinical applications against breast cancer.

Keywords: cell membrane-derived nanoparticles, breast cancer, active targeting, combination therapy, biomimetic delivery systems

Introduction

Breast cancer remains one of the most prevalent and deadly malignancies affecting women worldwide. According to recent statistics, over 2.3 million new cases of breast cancer were diagnosed globally in 2022, and it accounted for approximately 665,000 deaths.[1] This makes breast cancer not only the most commonly diagnosed cancer in women but also a significant public health challenge. Despite advances in early detection and treatment, the mortality rate remains high due to the complex nature of the disease and the limitations of current therapeutic strategies.[2] Traditional breast cancer treatments such as surgery, chemotherapy, and radiotherapy have been the cornerstone of clinical management for decades.[3–5] However, these treatments are often associated with several drawbacks, including limited efficacy, high recurrence rates, significant adverse reactions, and narrow therapeutic windows.[6–9] These limitations highlight the urgent need for the development of novel therapeutic approaches that can provide prolonged in vivo circulation, enhanced bioavailability, and more precise targeting of tumor cells to improve patient outcomes.[10–12]

In the past decade, nanoparticles (NPs) have emerged as promising drug carriers for targeted breast cancer therapy.[13] Nanoparticles can be designed for both active and passive targeting. Active targeting involves the use of specific ligands,

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such as antibodies, to facilitate the uptake of nanoparticles by breast cancer cells, thereby improving the precision of drug delivery and minimizing damage to healthy tissues.[14] Passive targeting, on the other hand, relies on the enhanced permeability and retention effect, which allows nanoparticles to accumulate preferentially in breast tumor tissues due to their leaky vasculature.[15] While passive targeting nanoparticles are more commonly used in clinical settings, active targeting remains challenging due to the high interstitial fluid pressure within the breast tumor microenvironment, which hampers efficient nanoparticle accumulation.[16] Moreover, nanoparticle-based therapies face issues related to toxicity and limited efficacy in breast cancer patients.[17]

In recent years, there has been a growing interest in biomimetic drug delivery systems, particularly those derived from cell membranes, to address the challenges of breast cancer treatment.[18] These systems, known as cell membrane-derived biomimetic nanotherapeutics, exploit the natural properties of cell membranes to enhance drug delivery to breast tumors.[19] By harnessing the homotypic and heterotypic adhesive properties of cells, these biomimetic carriers can be engineered through physical or chemical modifications to create drug delivery systems with active targeting capabilities specifically for breast cancer cells.[20] These carriers exhibit high drug loading capacities, controlled release properties, excellent biocompatibility, low immunogenicity, and inherent targeting abilities.[21] Additionally, by mimicking the flexible morphology of living cells, these nanotherapeutics can enhance drug accumulation and efficacy in breast tumor tissues.[22]

Common cell membrane sources for these biomimetic carriers include stem cells, red blood cells, cancer cells, bacteria, and exosomes, each offering unique therapeutic advantages and targeting properties for breast cancer therapy. This comprehensive literature review aims to summarize the drug-loading characteristics and therapeutic applications of various cell membrane-derived biomimetic nanotherapeutics in breast cancer therapy. The literature search for this review was conducted using databases including PubMed, ScienceDirect, Google Scholar, and Web of Science, ensuring a broad and exhaustive collection of pertinent articles. The following keywords were used in various combinations: “cell membrane-derived nanotherapeutics”, “biomimetic nanoparticles”, “breast cancer therapy”, “cell membrane coating”, “biomimetic drug delivery”, and “tumor targeting”. By exploring the latest advancements and current challenges, this review seeks to provide a holistic understanding of the potential of these innovative drug delivery systems in improving breast cancer treatment outcomes.

Stem Cell Membrane-Derived Biomimetic Nanotherapeutics

Stem cells, particularly mesenchymal stem cells (MSCs), have garnered significant attention in the field of drug delivery due to their unique biological properties, including self-renewal, tumor-homing capabilities, and low immunogenicity.[23–25] These properties make MSCs highly attractive for targeted breast cancer therapies.[26] Recent studies have demonstrated that MSC-derived membranes can encapsulate synthetic nanoparticles, forming biomimetic drug delivery systems with great potential for breast cancer treatment. For instance, Cao et al showed that MSCs could effectively deliver SiO_2 nanoparticles containing photosensitizers (PS) to breast tumors for PTT, achieving efficient tumor destruction with minimal side effects.[27] However, the challenge remains in enhancing the penetration depth of PTT, particularly for tumors that are deep-seated or resistant to heat-induced apoptosis. The same challenge applies to other approaches, such as the use of synthetic microcapsules loaded into MSCs, as explored by Litvinova et al, who highlighted MSCs’ ability to carry these microcapsules while maintaining their migratory and tumor-homing abilities.[28] However, issues related to the mechanical stability of the microcapsules and the consistency of drug release still require optimization.[29] Despite these challenges, MSCs’ tumor-targeting ability is crucial for efficient drug delivery.

Another promising approach involves MSC-derived membranes coated onto nanoparticles, such as doxorubicin (Dox)-loaded hollow gold nanoparticles, which have demonstrated significant tumor growth inhibition and improved CT imaging, along with a favorable safety profile.[30] The addition of MUC1 aptamers further enhances targeted drug delivery, although variability in tumor responses, even within the same patient, poses a challenge due to differences in MUC1 expression levels. This suggests that targeting multiple tumor markers in combination with MSC-derived nanocarriers could improve therapeutic efficacy. Photodynamic therapy (PDT) has also emerged as a potential treatment due to its high selectivity and minimal off-target effects. However, the hydrophobic nature of PS makes their solubility and circulation in the bloodstream a challenge. Recent advancements have led to the development of biomimetic PDT platforms using MSC-coated nanoparticles, which show improved tumor-targeting efficiency and reduced macrophage

uptake compared to uncoated PS.[31] Still, the limited light penetration in solid tumors, particularly in advanced stages of breast cancer, remains a significant hurdle that needs to be addressed through the optimization of light delivery systems.

While MSC-based drug delivery systems show considerable promise, issues related to drug loading, release kinetics, and long-term safety need to be addressed. Studies by Kalimuthu et al have shown that Dox-loaded MSCs do not impair their tumor-homing ability, but challenges related to long-term toxicity and immune response need to be better understood.[32] Therefore, future research should focus on improving the mechanical properties of MSC-derived carriers, fine-tuning drug release mechanisms, and exploring combination therapies to optimize therapeutic outcomes. Despite the challenges, MSC-derived nanocarriers offer a promising avenue for advancing breast cancer treatment, particularly through enhanced drug targeting, improved biocompatibility, and better overall efficacy.

Blood Cells as Targeted Drug Delivery Carriers

Based on blood cells, carriers possess numerous characteristics that render them ideal for targeted drug delivery in breast cancer.[33] Such carriers are advantageous because they reduce immunogenicity and prolong the circulation time of drugs within the body. Generally, blood cells are biodegradable and do not produce toxic byproducts as a result of carrier biodegradation.[34] Due to specific protein markers on their membranes, targeted delivery using blood cells is an innate function of the organism.[35] Additionally, drugs are released in a controlled manner due to the constraints or affinities of the blood cell membranes, which significantly reduces fluctuations in the steady-state concentration. Consequently, blood cells constitute a vital source for drug-carrying cells, offering an effective strategy for enhancing the therapeutic efficacy and safety of drug delivery systems in breast cancer treatment (Table 1).

Red Blood Cell Membrane-Derived Biomimetic Nanotherapeutics

Red blood cells (RBCs) are highly promising drug delivery platforms due to their unique biological properties. Their biconcave disc shape provides an approximate membrane surface area of 135 um^2, facilitating the transport of various compounds.[59] Coupled with the CD47-SIRPα mediated immune evasion mechanism, this theoretical advantage allows for a long circulation half-life of around 120 days.[60] RBCs are the most prevalent type of blood cell, distinguished by their biocompatibility, substantial drug-loading capacity, and minimal immunogenicity.[61] The interaction between the CD47 protein on the surface of RBCs and SIRPa regulates the phagocytic uptake of macrophages, enabling prolonged circulation within the body.[62] However, their "natural stealth" property may be limited in terms of solid tumor penetration due to abnormal vascular structures within the tumor microenvironment. To harness the potential of RBCs for drug delivery, engineering strategies can be classified into genetic and non-genetic approaches.[63] Genetic engineering involves using transfection technology to express specific membrane proteins, such as enzyme recognition sites, on the RBC surface to enable covalent anchoring of drugs.[64] However, caution must be exercised as gene editing may alter the mechanical properties of RBC membranes, increasing membrane stiffness by 15%-20% post-transfection, which may affect their deformability within capillaries. Non-genetic engineering includes drug encapsulation, surface absorption, and membrane fusion techniques.[65] For example, Pierige et al encapsulated 2-Fluoro-ara-AMP within RBCs and tested it on breast cancer cell lines (MCF-7, MDA-MB435 cells), demonstrating the drug's ability to inhibit cancer cell proliferation and achieve slow and sustained delivery into the bloodstream.[66] Despite encapsulation efficiencies reaching 60%-85%, in vitro experiments show that 30% of the drug may be released within the first six hours, necessitating the optimization of membrane stability through cross-linking agents.

Recent advancements have led to innovative applications in breast cancer targeted therapy, including metabolic activation carriers and multifunctional nano-composite systems. The 2-Fluoro-ara-AMP/RBC system utilizes intracellular phosphatases to convert the non-permeable prodrug into an active form, reducing IC_{50} by three times in MCF-7 and MDA-MB435 cells compared to the free drug.[66] However, the lack of in vivo data raises doubts about its clinical translation value, and its responsiveness to the acidic conditions of the tumor microenvironment remains unverified. Multifunctional nano-composite systems, such as RBCM@MSNR/DOX/ICG, leverage the high drug-loading capacity of mesoporous silica nanorods (~1200 mg/g) and the long circulation characteristics of RBC membranes, enabling pH/NIR dual-responsive release.[67] The biodegradability of MSNR is controversial, with its silicon-based skeleton showing removal periods exceeding 30 days in vivo. Further innovation is seen with ARISP nanovesicles, which utilize an

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Table 1 The Application of Blood Cell Membrane-Coated Nanoparticles in Breast Cancer Therapy

Cytomembrane	Core	Loaded Drug	Surface Functionalization	Tumor Type	Application
RBCM (Red blood cell membrane)	PLGA	PFC	–	Breast cancer	Relieve tumor hypoxia and enhance cancer radiotherapy.[36]
	MOs2 NPs	Dox	–	Breast cancer	pH dependent targeted release chemotherapy and PTT.[37]
	NR	PTX	IL-2	Breast cancer	TME-responsive drug release and immunotherapy.[38]
PLTM (Platelet membrane)	Fe_3O_4	SAS	–	Breast cancer	Enhancing the efficacy of tumor immunotherapy.[39]
	ZIF-8 MOF	siRNA	–	Breast cancer	Targeted gene silencing.[40]
	MOF	Loc; OXA	–	Breast cancer	Targeting the TIME and enhancing immunotherapy.[41]
	MON	TBP-2	–	Breast cancer	Precise depletion of cancer stem cells and prevention of cancer recurrence after radiotherapy.[42]
	HGNs	–	–	Breast cancer	Biosafe distribution and photothermal oncotherapy.[43]
	PLA	R848	–	Colorectal neoplasms; breast cancer	Local delivery of immune activators.[44]
	PLGA	Dox, IR780	–	Breast cancer	Combination of photothermal diagnosis and targeted chemotherapy.[45]
	PEOz-liposome	Dox	–	Colorectal cancer; breast cancer	pH-responsive drug delivery and enhancing anti-tumor activity.[46]
	PBs	–	HRP; PD-L1 aptamer and 4T1 cell aptamer AS1411	Breast cancer	Immunotherapy and enhance targeting.[47]
	PLGA	ICG	Anti-PD-L1 antibody	Breast cancer	Inhibition of tumor recurrence after thermal ablation therapy.[48]
MCM (Macrophage cell membrane)	PPiP-polymer	PTX	–	Breast cancer	Tumor-targeted chemotherapy.[49]
	Soy lecithin	Dox, QDs	–	Breast cancer	Improving tumor imaging and tumor-targeted chemotherapy.[50]
	UCNP	Rose Bengal	–	Breast cancer	Improving photodynamic immunotherapy.[51]
	Lipid-DNA	Dox-MPK	–	Metastatic breast cancer	Targeting lung metastasis sites for chemotherapy.[52]
NECM (Neutrophils cell membrane)	PPDG/D micelle	Dox	–	TNBC	Restraining myeloid-derived suppressor cells-mediated immunosuppression and formation of pre-metastatic niche.[53]
	BSA	DAC	–	Triple-negative breast cancer	Photothermal-induced tumor Immunotherapy by triggering pyroptosis.[54]
TCM (T-lymphocyte cell membrane)	BSA	ORY-1001	–	4T1 TNBC; B16F10 melanoma; CT26 colon cancer	Tumor-targeted immunotherapy.[55]
NKCM (Natural killer cell membrane)	PLGA	TCPP	–	4T1 breast cancer	Improves blood circulation, enhances proinflammatory M1-macrophages polarization.[56]
	–	OXA; 1-MT	–	Breast cancer	Achieving tumor-targeting and induce macrophages to polarize into M1 type.[57]
	Liposomes	Dox	–	Breast cancer	Tumor-targeted chemotherapy.[58]

Abbreviations: MOs2, molybdenum disulfide; PFC, perfluorocarbon; NR, nanogels; PTX, paclitaxel; Dox, doxorubicin; SAS, Sulfasalazine; Loc, lactate oxidase; OXA, oxaliplatin; MON, mesoporous organosilicon nanoparticles; TBP-2, an AIE photosensitizer; HGNs, hollow gold NPs; PLA, polylactic acid; R848, resiquimod; HRP, horseradish peroxidase; PD-L1, programmed cell death-Ligand 1; PPiP-polymer, amphiphilic bola-pattern polymer was functionalized with a cationic 2-aminoethyldiisopropyl group (PPiP); BSA, bovine serum albumin; DAC, decitabine; ORY-1001, a potent and selective lysine-specific histone demethylase 1 (LSD1) inhibitor; TCPP, 4,4',4',4'-(porphine-5,10,15,20-tetrayl) tetrakis (benzoic acid); 1-MT, 1-methyl-d-tryptophan.

LDLR receptor-mediated hypoxia targeting mechanism to significantly increase tumor accumulation.[68] However, the downregulation of HIF-1α by Salidroside might interfere with the normalization process of tumor vasculature, presenting potential therapeutic contradictions. Jiang et al also developed a multifunctional biomimetic nanoplatform to enhance chemotherapy, chemodynamic therapy, and PTT, employing Cu-doped zeolitic imidazolate frameworks-8 (ZIF-8) coated with polydopamine (PDA) and RBCM. This platform shows effective synergistic therapies under 808 nm laser irradiation but faces challenges in scaling up production and ensuring therapeutic consistency.[69]

Upconversion nanoparticles (UCNPs) have garnered significant interest for their roles in tumor imaging through magnetic resonance imaging (MRI) and upconversion luminescence (UCL) imaging. The limited in vivo applications of UCNPs are attributed to their short blood clearance time and immunogenicity. Coating UCNPs with RBCs presents a promising strategy for pre-targeted multimodal imaging of triple-negative breast cancer, addressing these challenges.[70] Further studies are required to validate these preclinical findings and ensure the safety and efficacy of these platforms in clinical settings. Despite significant progress, key issues such as carrier heterogeneity due to individual differences in RBC sources, metabolic evasion mechanisms through CD47-independent pathways, and scale-up production barriers with current membrane coating techniques must be resolved. Notably, components within the RBCM are directly related to breast cancer therapy. For instance, the presence of n-3 polyunsaturated fatty acids within the RBCM is negatively correlated with the risk of breast cancer among Chinese women.[71] Omega-6 polyunsaturated fatty acids within the RBCM are associated with xerostomia and taste loss in breast cancer patients.[72] Future research directions include developing intelligent responsive systems based on ROS/MMP-9 for "membrane shedding-drug release", employing microfluidic technology for high-throughput preparation of RBCM biomimetic vesicles, and co-delivering PD-L1 inhibitors with RBC-carried antigens to enhance immune responses by utilizing lymph node homing characteristics. Comprehensive analyses of these challenges and potential solutions aim to facilitate the clinical translation and therapeutic success of RBC-derived biomimetic nanotherapeutics in the targeted treatment of breast cancer.

Platelet Membrane-Derived Biomimetic Nanotherapeutics

Platelets (PLT), like red blood cells, are anucleate cells with a lifespan of approximately 9–10 days, making them highly suitable as drug delivery carriers.[73] Their primary physiological function is hemostasis, a critical process for responding to vascular injury resulting from surgery, inflammation, and infection.[74] In addition to this, PLT are rich in bioactive molecules, including growth factors, chemokines, and cytokines, which contribute to vascular regeneration and cell proliferation. These inherent regenerative properties and biological compatibility suggest that PLT offer a highly favorable platform for drug delivery, with a notable safety profile.[75] Furthermore, platelet-derived microparticles are the most abundant particles in the bloodstream, providing a natural, biocompatible alternative to synthetic and polymeric drug delivery systems, which are often associated with adverse immune responses and toxicity. As drug carriers, PLT can be engineered ex vivo to carry and release therapeutic agents into the bloodstream, or they can facilitate targeted drug delivery through the incorporation of prodrugs or nanoparticles in vivo. This versatility allows PLT to be tailored for precise therapeutic applications, including tumor-specific targeting.[76]

In the context of breast cancer, PLT have gained attention for their role in the tumor microenvironment, where they not only maintain vascular integrity but also actively promote tumor progression and metastasis. PLT facilitate chemokine secretion, which contributes to the development of a pro-metastatic environment, aiding the spread of breast cancer cells to distant organs. This dual role (both protective and metastatic) makes PLT a complex yet promising therapeutic target.[77] Recent studies have explored the potential of PLT-coated nanoparticles in enhancing cancer treatment efficacy. For example, Gao et al developed platelet membrane (PLTM)-coated chlorin e6 liposomes, significantly improving tumor-specific targeting and anti-tumor responses in vivo.[78] The PLTM coating enhanced the uptake of chlorin e6-loaded liposomes by cancer cells through immune evasion and targeting capabilities, resulting in significant inhibition of breast cancer growth. Similarly, the Van-ICG@PLT nano-sensing platform, developed using PLTM camouflage and a small-molecule drug self-assembly technique, showed promising results in localized delivery to surgical wound sites, exhibiting substantial cytotoxicity against 4T1 breast cancer cells when exposed to near-infrared laser irradiation.[79] In a postoperative recurrence model using 4T1 tumor-bearing mice, Van-ICG@PLT demonstrated an impressive tumor inhibition rate of approximately 83% and also exhibited notable anti-infective properties in a mouse

abscess model (Figure 1A and B). Additionally, recent research has focused on utilizing platelet membranes (PMs) to create a biochemotactic-targeting nanotherapeutic platform. This platform, based on dendritic large pore mesoporous silica nanoparticles (DLMSNs) co-loaded with chlorin e6 (Ce6) and lapatinib (LAP), combines PDT with EGFR inhibition for targeted breast cancer treatment. The PM@DLMSN/Ce6/Lap nanoparticles effectively target breast tumor cells, enhance drug delivery, and recruit more nanoparticles to the tumor site after PDT-induced vascular damage.

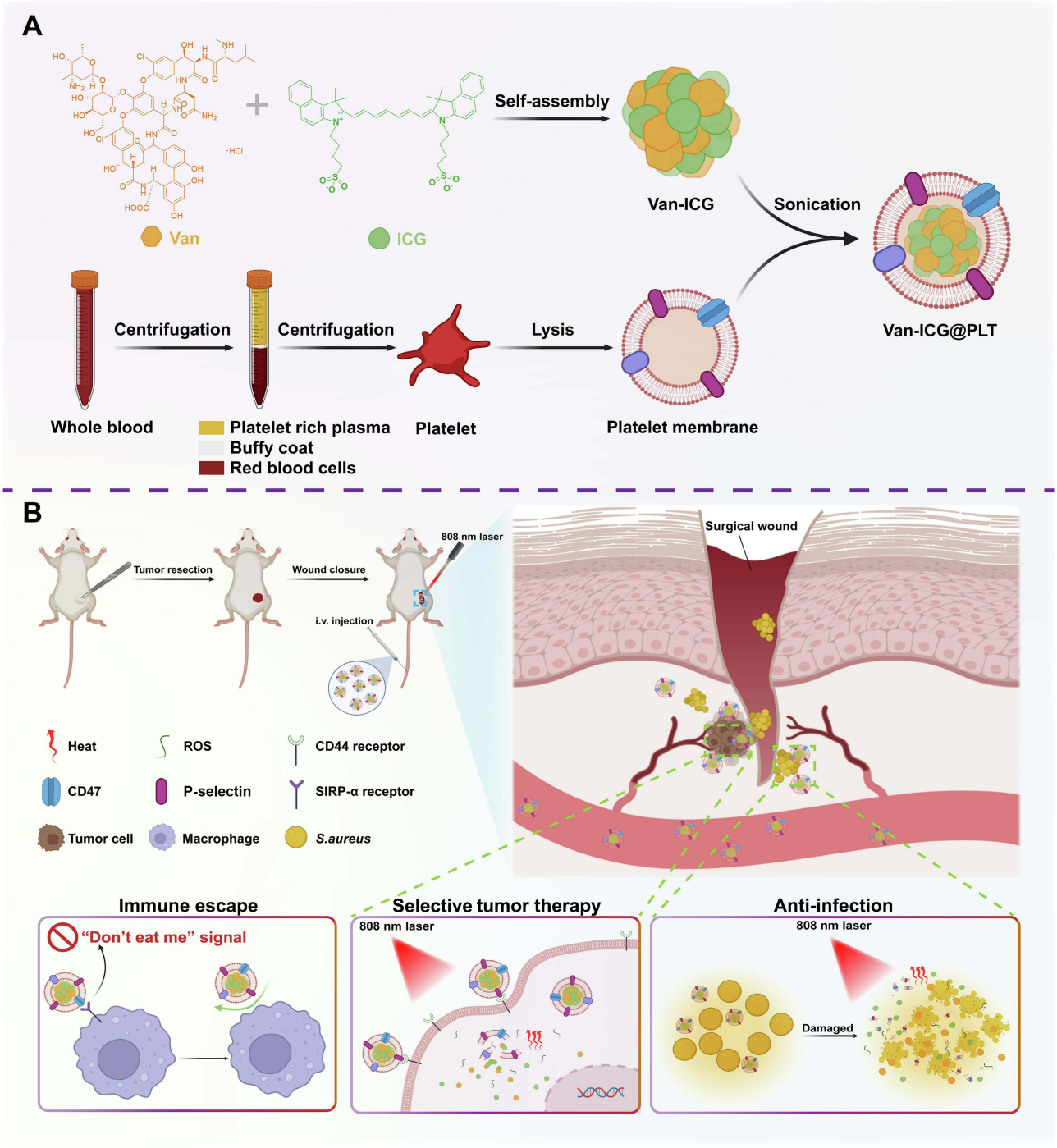

Figure 1 Schematic illustrations of synthetic procedure for Van-ICG@PLT and the mechanism of synergistic therapy. (**A**) The assembly processes of Van-ICG@PLT. (**B**) After intravenous injection, phototherapy and PLT-mediated cascaded delivery of ICG and Van toward synergistically against post-surgical tumor recurrence and wound infection. Reproduced from Liu Y, Qi Y, Chen C, et al. Platelet-mimetic nano-sensor for combating postoperative recurrence and wound infection of triple-negative breast cancer. J Controlled Release. 2023;362:396–408. Copyright 2023, with permission from Elsevier.[79]

This innovative approach not only inhibits tumor cell migration and metastasis but also offers a promising strategy for improving the targeted delivery of anti-tumor drugs, providing a new avenue for the clinical treatment of breast cancer.[80] These findings highlight the potential of platelet-based drug delivery systems in addressing challenges related to tumor recurrence, metastasis, and post-surgical infection. However, further research is needed to better understand the dual role of PLT in tumor progression and to explore their broader clinical applications in oncology and regenerative medicine.

White Blood Cell Membrane-Derived Biomimetic Nanotherapeutics

White blood cells (WBC), as a type of blood cell, are essential to the immune response inside the circulatory system, demonstrating both free circulation and targeted action against inflammation to combat diseases like cancer.[81] The prominent function of WBC lies in their immunological capabilities. Based on their morphological and staining properties, WBC used as immune cells in tumor-targeted drug delivery systems can be classified into three types: neutrophils in polymorphonuclear leukocytes, T cells in lymphocytes, and macrophages in monocytes.[82] These immune cells exhibit inherent and precise targeting skills, minimal immunogenicity, and improved therapeutic effectiveness.[83] Due to their role in the tumor microenvironment and the physical properties they share with tumor cells, WBC can be used as carriers to deliver nanotherapeutic drugs to tumor sites. Nanoparticles can be incorporated into WBC through a "hitchhiking strategy", attached to their surface, or enveloped by membrane components derived from WBC.[84]

Neutrophil-Mediated Nanodrug Delivery

Neutrophils (PMNs) represent the largest population of WBCs in humans, comprising 50%-70% of circulating WBCs. These immune cells are the first responders to inflammatory stimuli and exhibit remarkable selectivity and mobility, rapidly migrating from the bloodstream to sites of inflammation.[85] Due to these properties, PMNs serve as excellent cellular vehicles for drug and nanomedicine delivery, extending the circulation time of therapeutic agents while minimizing clearance by the immune system.[86,87] Importantly, studies have shown that the internalization of nanoparticles does not impair the viability, apoptosis, or activation of PMNs, allowing these cells to effectively transport nanomedicine complexes and address issues related to drug toxicity.[88] In addition to their role in inflammation, PMNs are also present in the tumor microenvironment, where they exhibit anti-tumor functions, intrinsic tumor-homing abilities, and the capacity to carry therapeutic agents.[89] Nanoparticles can enhance therapeutic efficacy by exploiting these properties, either by "hijacking" PMNs in vivo or by promoting neutrophil infiltration through modulation of the tumor microenvironment during cancer treatment.[90]

For instance, Chu et al developed biomimetic supramolecular nanoconstructs consisting of a poly(vinyl pyrrolidone)-tannic acid (PVP-TA) core biofunctionalized with neutrophil cell membranes, resulting in the formation of PVT-NEU NPs.[91] These biomimetic nanoparticles increased the interaction and targeting of breast cancer cells, thereby enhancing the therapeutic efficacy of the model drug, paclitaxel (PTX). This study highlights the potential of PMN-based nanoparticles as a targeted drug delivery platform for advanced breast cancer (Figure 2). Further research has demonstrated that neutrophil membrane-coated biomimetic platforms can actively target lung metastasis in triple-negative breast cancer (TNBC), significantly reducing metastasis to the lungs.[92] Additionally, a multi-site attack nano-platform, camouflaged with neutrophil membranes and encapsulating the hypoxia-responsive dimeric prodrug hQ-MMAE2 (hQNM-PLGA), has been developed to enhance both cancer therapy and anti-metastasis treatment.[93] Neutrophil membrane-coated immunomagnetic nanoparticles (IMNs) have also been employed for the efficient isolation and analysis of circulating tumor cells (CTCs) in breast cancer.[94] Compared to bare IMNs, the neutrophil membrane-coated IMNs (Neu-IMNs) exhibited exceptional separation efficiency, ranging from 41.36% to 96.82%, and significantly increased purity from 40.25% to 90.68%. This approach holds promise for non-invasive early detection of breast cancer. While the use of neutrophil-based drug delivery systems offers substantial promise, several considerations must be addressed to fully realize their potential in clinical settings. One key challenge lies in the potential variability in neutrophil function depending on the tumor microenvironment. Neutrophils are highly dynamic cells whose behavior can be influenced by local factors such as cytokine levels, hypoxia, and the presence of other immune cells. These factors may alter the cells' ability to efficiently target tumor sites or affect their therapeutic efficacy. Therefore, optimizing the conditions under which neutrophils are activated or infiltrate the tumor is critical for maximizing the effectiveness of PMN-based delivery systems.

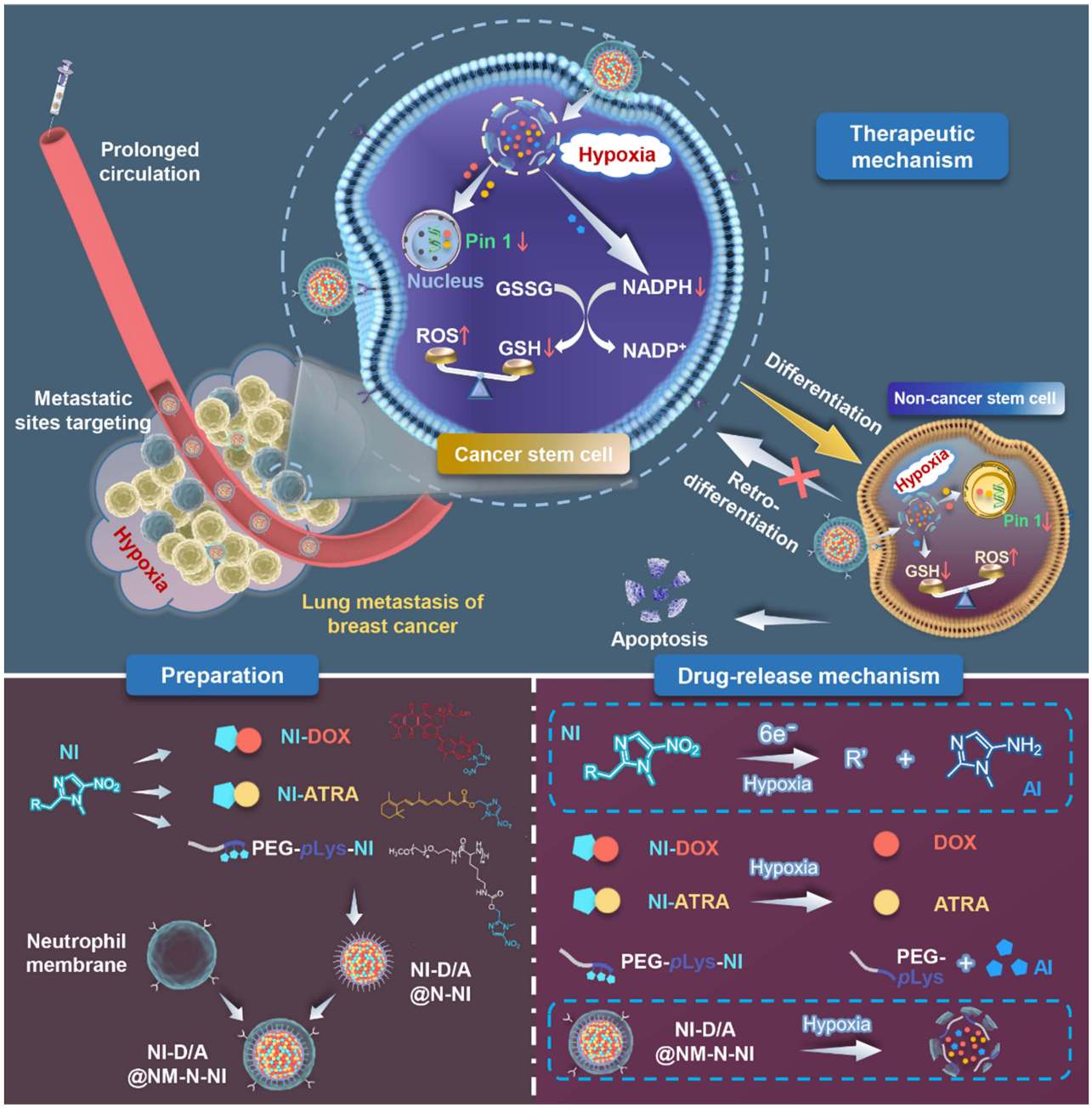

Figure 2 Schematic illustration of neutrophil-biomimic platform for eradicating metastatic breast cancer stem-like cells by redox microenvironment modulation and hypoxia-triggered differentiation therapy. Reproduced from Chu Y, Luo Y, Su B, et al. A neutrophil-biomimic platform for eradicating metastatic breast cancer stem-like cells by redox microenvironment modulation and hypoxia-triggered differentiation therapy. Acta pharmaceutica Sinica B. 2023;13(1):298–314. Copyright 2023, with permission from Elsevier.[92]

T Cell-Mediated Nanodrug Delivery

T cells are the second most abundant subset of WBCs in the human body.[95] As integral components of the adaptive immune system, they are capable of recognizing antigens with remarkable specificity, with each T cell responding to only a single antigen. This specificity positions T cells as highly effective targeting cells for therapeutic purposes.[96] Upon encountering their specific antigens, T cell receptors initiate a signaling cascade that alters the cell surface potential, leading to the secretion of proteins that induce apoptosis in antigen-presenting cells.[97] These two key properties (specific antigen recognition and the ability to trigger apoptosis) highlight the considerable potential of T cells in drug delivery and

cancer therapy.[98] Chimeric antigen receptor (CAR) T cells have garnered considerable attention in cancer research, especially for their applications in breast cancer therapy. Stephan et al demonstrated that the combination of nanoparticles loaded with immune adjuvants and adoptive T cell therapy could substantially enhance tumor eradication, showcasing the potential of T cells as effective vehicles for targeted drug delivery.[99] Additionally, Liu et al explored the efficacy of a cuproptosis-immunotherapy system using PD-1 overexpressing T cell membrane-coated nanosheets for the treatment of TNBC.[100] This multifaceted approach simultaneously induced cuproptosis, PTT, and immunotherapy in a murine model, demonstrating a promising combination strategy for cancer treatment. In a similar context, a PD-1 receptor-presenting PTX prodrug nanoparticle system has shown significant promise in chemotherapeutic immunotherapy for TNBC. These biomimetic PTX nanoparticles not only exhibit superior cytotoxicity against TNBC cells but also disrupt the PD-L1/PD-1 axis, which is crucial in immune evasion by tumors. By selectively targeting PD-L1 ligands on breast cancer cells, these nanoparticles enhance the delivery of the chemotherapeutic agent directly to the tumor site. In vivo studies have revealed that PD-1@PTX2 nanoparticles achieve a remarkable 71.3% tumor growth inhibition in 4T1 xenograft models and significantly prolong survival in these models. Furthermore, treatment with these nanoparticles leads to a 3.2-fold increase in CD8 T cell infiltration within the tumor and a 73.7% depletion of regulatory T cells (Tregs), fostering a potent antitumor immune response.[101] Together, these findings highlight the growing potential of immune checkpoint receptor-targeted nanoparticles in combination with chemotherapy, providing an innovative approach to enhance cancer treatment. The combination of increased cytotoxicity, immune modulation, and prolonged survival underscores the clinical promise of this strategy in overcoming current limitations in cancer therapy.

Macrophage-Mediated Nanodrug Delivery

Macrophages are the largest type of WBCs and serve as the primary phagocytic cells of the innate immune system. Depending on their location and the specific requirements of the host, macrophages can display distinct phenotypic and functional characteristics, which are modulated by the surrounding microenvironment, thus exhibiting remarkable functional plasticity.[102] They can be polarized into different functional phenotypes under various stimuli, typically categorized as M1 and M2 types. M1 macrophages are capable of capturing, engulfing, and lysing tumor cells, while also secreting a range of immune-stimulating cytokines. In contrast, M2 macrophages act as immunosuppressors within the tumor microenvironment by expressing anti-inflammatory molecules.[103] Due to their excellent biocompatibility, abundant surface receptors, chemotactic properties that enable efficient tumor localization, and their ability to extend drug circulation, enhance stability, and reduce immunogenicity in vivo, macrophages hold immense promise in the delivery of therapeutic drugs for breast cancer.[104,105]

Macrophage-targeted drug delivery systems using nano-carriers can be broadly classified into two types: passive targeting, which is primarily driven by the mononuclear phagocytic system rich in macrophages, and active targeting, which is primarily driven by ligand-receptor interactions.[106] The tumor microenvironment is typically characterized by low pH and hypoxic conditions, which attract macrophages to accumulate in hypoxic regions of the tumor vasculature.[107] Quijia et al utilized macrophage membrane-modified nanostructures to enhance immune evasion capabilities.[108] They proposed an innovative approach with promising potential for breast cancer therapy, wherein metal-organic frameworks (MOFs) encapsulating piperine (PIP) were coated with macrophage membrane, demonstrating enhanced cytotoxicity compared to free PIP. Similarly, nano-sized dendritic alkaloids coated with macrophage membranes, as well as PTX-loaded nanoparticles with mannose-decorated/macrophage membrane coatings (UCNP@mSiO_2-PFC/Ce6@RAW-Man/PTX), effectively suppressed breast cancer growth and metastatic burden without inducing systemic toxicity.[109] Tumor-associated macrophages in the tumor microenvironment play a crucial role in enhancing or mediating the anti-tumor effects of cytotoxins and checkpoint inhibitors, contributing significantly to cancer progression, metastasis, and relapse. In a study focused on the postoperative recurrence of TNBC, Qiu et al used macrophages as carriers, incorporating PTX and resveratrol into R8-modified pegylated liposomes. This strategy facilitated macrophage uptake, resulting in cell-mediated carriers with high drug loading and a targeted response to inflammation and tumors, thereby improving therapy for postoperative tumor recurrence.[110] Nevertheless, multimodal treatments that combine chemotherapy, PDT, and immunotherapy have demonstrated the most effective anti-tumor outcomes. A multifunctional biomimetic nanoplatform (mTSeIR) has been developed by researchers, incorporating selenium conjugates as an ultrasound sensitizer and tirapazamine (TPZ), encapsulated within M1 macrophage

membranes. This platform utilizes hypoxia-driven chemotherapy to enhance the therapeutic efficacy of sonodynamic therapy, while simultaneously boosting adaptive immunotherapy through the activation of innate immunity and remodeling the immunosuppressive tumor microenvironment. Notably, mTSeIR facilitates the repolarization of M2 macrophages toward the M1 phenotype, further augmenting the anti-tumor immune response.[111]

Despite significant improvements in tumor-localized drug concentration achieved by existing technologies such as macrophage membrane-modified MOFs and R8 liposomes through passive/active targeting strategies (eg, a 52% increase in PIP cytotoxicity in the Quijia study), their therapeutic efficacy remains limited by the complexity of macrophage phenotype dynamics. Future studies should employ multi-omics approaches (such as single-cell sequencing and spatial transcriptomics) to dissect the receptor expression profiles of macrophage subpopulations within the tumor microenvironment. This will aid in the design of precise targeting ligands, such as specific antibodies targeting TREM2+ tumor-associated macrophages. Furthermore, the development of cross-scale efficacy assessment models is essential, integrating organ-on-a-chip platforms (to simulate vascular leakage effects) with artificial intelligence-based predictions (for drug release kinetics), in order to optimize the spatiotemporal controlled-release properties of delivery systems.

Natural Killer Cell-Mediated Nanodrug Delivery

Natural killer cells are key components of the body's innate immune system and serve as primary defense cells against malignancies.[112] These cells can directly recognize and destroy tumor cells through the perforin/granzyme and Fas/FasL pathways, without the need for antigen pre-sensitization, distinguishing them from T and B lymphocytes.[113] Natural killer cell activity is regulated by a balance of activation and inhibitory receptors, enabling them to effectively target tumors while maintaining self-tolerance.[114] As effector cells, natural killer cells offer immense potential for adoption in immunotherapy for cancer. However, treatment outcomes may be influenced by immune suppression within the tumor microenvironment. Research is ongoing to develop innovative nanomedicines capable of modulating the interactions between tumor cells and immune cells.[115] Nanoparticles coated with natural killer cell membranes (NKCM-NPs) have demonstrated considerable promise in enhancing tumor-targeting capabilities within nanoparticle drug delivery systems (NDDS), benefiting from the inherent tumor-recognition efficiency of natural killer cells. For instance, Deng et al designed natural killer cell-mimicking nanoparticles to improve anti-tumor immunity and the efficacy of PDT.[56] This biomimetic NDDS mirrors the antigen profile of natural killer cells and induces the polarization of pro-inflammatory M1 macrophages, effectively suppressing and eliminating breast cancer tumors in animal models. Similarly, Du et al developed self-assembled NKCM-NPs that treated breast cancer through chemotherapeutic immunotherapy.[57] The natural killer cell membrane-mimicking modification of these NDDS effectively targets breast cancer cells and induces the polarization of tumor-inhibitory M1 macrophages, thereby initiating tumor-specific immune responses. Another promising approach utilizing natural killer cell membrane-coated NEM-NDDS demonstrated excellent biocompatibility and extended drug circulation times, further improving tumor-targeting efficiency.[58]

In recent years, natural killer cells have garnered significant attention as potential targets for immunotherapy, highlighting their growing importance in advancing cancer treatment strategies. Immunotherapy is rapidly gaining attention as a promising approach for the treatment of TNBC when combined with chemical agents and genetic engineering tools. Recent studies have demonstrated that lipid-based nanoparticles (LNPs) exhibit natural killer cell-like functionality, enabling targeted tumor-specific therapies and effectively inhibiting tumor growth. These nanoparticles facilitate the precise delivery of HIC1 plasmid DNA and modulate immune cell functions. The therapeutic genes delivered via LNPs can suppress metastasis in TNBC and induce apoptotic cell death, while also targeting macrophages to promote cytokine release. Moreover, LNPs can fuse with natural killer cell membrane proteins, allowing for the simultaneous delivery of both therapeutic chemicals and genes, thus offering significant potential for anti-cancer applications in treating a wide range of refractory cancers.[116] The modification of nanoparticles with natural killer cell membranes enhances their ability to target and engage with tumors more effectively, as evidenced by the successful animal trials and the polarization of macrophages toward a pro-inflammatory phenotype. However, further research is needed to optimize these strategies for clinical applications, particularly in terms of scalability and the long-term stability of these nanoparticles.

Cancer Cell Membrane-Derived Biomimetic Nanotherapeutics

Currently, cell-mediated drug delivery primarily relies on living cell carriers that leverage the tumor microenvironment and the intrinsic properties and functions of cells for cancer therapy. However, there is still a need to improve drug efficacy and targeting specificity. Challenges include potential alterations in cell characteristics and surface protein dynamics upon drug loading, which may affect cell viability and increase immunogenicity.[117] Furthermore, live cells used for targeted drug delivery and cancer therapy may lack homologous targeting compared to cancer cells loaded with therapeutic agents.[118] As a result, therapeutic dead cells, such as cancer cells in hypothermic shock, have emerged as a novel approach for breast cancer treatment (Table 2). Zeng et al developed a cancer cell membrane (CCM) biomimetic nanodrug delivery method to enhance breast cancer chemophotothermal synergy.[119] Cell membrane-coated nanoparticles inhibited macrophage internalization and enhanced 4T1 cell uptake through homologous targeting.

The ability of cancer cell-coated nanomedicines to selectively interact with cells of the same origin is known as homotypic targeting. This feature is valuable for targeting drug delivery to malignancies. Homotypic affinity among cancer cells is associated with interactions between galectin-3 and cancer embryonic antigens on cell surfaces.[130] Fang et al explored the homotypic targeting of MDA-MB-435 CCM-coated PLGA nanoparticles as drug delivery vehicles. The coated PLGA nanoparticles accumulated 20 times more in MDA-MB-435 cells than uncoated ones, but showed minimal accumulation in human foreskin fibroblast cells.[131] In contrast, PLGA nanoparticles coated with nonspecific RBCs exhibited lower binding to cancer cells, indicating that the CCM coating enhanced particle-cell adhesion.[131] Additionally, lipid vesicles disguised with 4T1 cell membrane fragments encapsulating IR1048 (MLI) exhibited the highest uptake by 4T1 cells during tumor therapy. MLI enabled precise PTT through homologous tumor targeting and dual-modal imaging using NIR-II.[132]

Table 2 The Application of Cancer Cell Membrane-Coated Nanoparticles in Breast Cancer Therapy

Cytomembrane	Core	Loaded Drug	Tumor Type	Application
CCM (Cancer cell membrane)	PLGA	ICG	Breast cancer	Homologous targeting dual-modal imaging and PTT.[120]
	PLGA	Artesunate	Breast cancer	Targeted and efficient drug delivery.[121]
	Ir-B-TiO_2	–	Cervical carcinoma; breast cancer	Hierarchical targeted synergistic photothermal and sonodynamic cancer imaging and therapy.[122]
	ZIF-8 NPs	EPI; GOX; hemin	4T1 cell line; RAW 264.7 cell line	Effectively inducing ICD to improve the therapeutic effect of anti-PD-L1 antibodies.[123]
	UCNP	PTD	Triple-negative breast cancer	Combining chemo-photodynamic therapy and CD73 blockade for metastatic cancer.[124]
	MOF (PCN-224)	GOX, catalase	Breast cancer	Cancer-targeted starvation and photodynamic therapy.[125]
	Iron oxide NPs	The TPP1 peptide; MMP2 substrate short peptide	Human lung cancer and breast cancer	Cancer immunotherapy and diagnosis.[126]
	Nanorods	Camptothecin	Metastatic breast cancer	Combining chemo- and photothermal therapies for metastatic cancer.[127]
	siRNA	Au/MnO_2	4T1 cell line	Combining targeted enhanced radiotherapy with immune activation.[128]
	Benchmarked MIL-100(Fe) NPs	Dox	MDA-MB-468 cells	Enhanced colloidal stability, cellular uptake, and cytotoxicity in MDA-MB-468 cells.[129]
	Gelatin nanoparticles	Mitoxantrone	Breast cancer	Personalized chemotherapy-photothermal combination therapy of metastatic breast cancer.[119]
	Hollow mesoporous silica nanoparticles	Polyenetaxel	Breast cancer	Homologous targeting and immune escape.[22]

Abbreviations: UCNP, upconverting nanoparticles; EPI, epirubicin; MMP2, metallomatrix protease 2.

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Sun et al used a similar approach to create 4T1 cell membrane-coated PTX polymeric core biomimetic DDS (CPPNs) for the treatment of breast cancer and its lung metastasis.[133] Unlike lung fibroblast WML2 cells or macrophage RAW264.7 cells, CPPNs coated with 4T1 cell membranes selectively targeted 4T1 tumor cells. These nanomedicines showed a 3.3-fold increase in accumulation at primary tumor sites and a 2.5-fold increase at lung metastatic sites compared to bare NPs. Furthermore, red blood cell-coated PPNs (RPPNs) and synthetic liposome vesicle-coated PPNs (LPPNs) showed lower uptake than CPPNs. This suggests that the improved internalization of CPPNs may be due to tumor cell membrane proteins specific to 4T1 tumor cells. During metastatic colonization, membrane proteins involved in adhesion, such as TF antigen and E-cadherin, also influence homotypic interactions among tumor cells.[134,135] Surface markers like CD44 and CD326 on 4T1 cells are significant, playing a major role in the distant adhesion of metastatic cells.[136,137]

The specific interaction capabilities of cancer cell-coated drug delivery systems for breast cancer treatment have been the subject of numerous exciting results in recent years.[123,138] Cell membrane-coated nanoparticles can also be used to create innovative bioengineered nanocarriers for vaccines, in addition to cancer-targeted drug delivery. Tumor cell membranes can stimulate the immune system to detect and eradicate malignant tumor cells by recognizing the expression of variant antigens, as many tumor antigens serve as surface markers.[139] Strategies relying on single tumor-associated antigens may be inadequate when dealing with highly heterogeneous cancer cells and high mutation rates. In contrast, the therapeutic efficacy may be compromised when intracellular housekeeping proteins obscure relevant antigens when cell lysates are used to activate the immune system in a multi-antigen-based strategy.[140] Cancer cell-coated nanoparticles offer a promising strategy by combining homotypic recognition of tumor cells with the active delivery of tumor-associated antigens to dendritic cells for immune processing. This mechanism enables the subsequent activation of T cells specific to tumor antigens. Ni et al created a multifunctional CCM-coated calcium carbonate (CC) nanoparticle (MC) capable of producing tumor-associated antigens (TAAs) for DC vaccination.[141] In order to cause immunogenic cell death (ICD), low-dose Dox can be encapsulated in the CC core of MC. In the interim, Ce6 is a frequently employed photosensitizer that generates reactive oxygen species (ROS) to facilitate the development of a vaccine (MC/Dox/Ce6). However, while homotypic targeting has shown great promise, the complexity of tumor heterogeneity and the presence of multiple cell subtypes within a tumor may complicate the universal applicability of this approach. Additionally, the challenge of achieving efficient immune activation via tumor cell-coated nanoparticles needs to be carefully managed, especially considering the potential for immune evasion by tumors. The combination of CCM-based targeting with immunotherapeutic strategies, such as dendritic cell vaccination, offers a promising avenue for improving both localized treatment effects and overall patient outcomes.

Hybrid Cell Membrane-Derived Biomimetic Nanotherapeutics

Nanocarriers derived from engineered cancer cells present a promising approach for the targeted delivery of chemotherapeutic agents to breast cancer or metastatic sites, helping to minimize undesirable side effects. Moreover, the incorporation of novel antigens, other active targeting moieties, or chemotherapeutic agents is facilitated by surface modifications of these carriers, achieved through metabolic or genetic engineering. Hybrid cell membrane-derived carriers, which are created by fusing membranes from different cell types, enable the combination of diverse biological properties. For example, the integration of erythrocyte membrane fragments into cancer cell membranes (CCMs) extends the circulation time of these cells, while incorporating platelet cell membrane components allows for the targeting of specific CTCs.[142] The fusion of membrane fragments from multiple cell types into CCMs provides hybrid membranes with multi-targeting capabilities, effectively addressing multi-organ metastases in breast cancer treatment.[143] Zhang et al developed a hybrid biomimetic coating called TRM, which combines membranes from murine-derived 4T1 breast cancer cells with RAW264.7 (RAW) cells.[144] This hybrid membrane-coated platform was then used to create Fe_3O_4 nanoparticles loaded with imiquimod (R837) and indocyanine green for combined breast cancer therapy. In vitro studies demonstrated that the RIFe@TRM nanoparticles exhibited superior cell-specific recognition of 4T1 cells compared to bare Fe_3O_4 nanoparticles. This resulted in an extended circulation time and improved in vivo targeting. The biomimetic RIFe@TRM nanoplatform induced tumor necrosis through the Fenton reaction and photothermal effects, while R837 promoted the uptake of tumor-associated antigens, activating CD8 cytotoxic T cells and enhancing antitumor immunotherapy.

Table 3 The Application of Nanoparticles Encapsulated Within Hybrid Cells for the Treatment of Breast Cancer

Source Cells	Core	Loaded Drug	Tumor Type	Application	Ref.
PLT; RBC (hybrid)	PLGA	–	Breast cancer	Tumor-targeted delivery	[145]
RBC; cancer cell (hybrid)	Melanin	ICG	Breast cancer	Enhancing PTT efficacy in tumors	[148]
	Chitosan	Dox	Breast cancer	Enhance the chemotherapy effect of breast cancer	[142]
	AuNCs	Dox	Breast cancer	Achieving efficient and safe photothermal/radiation/ chemotherapy combination therapy	[149]
PLT; WBC (hybrid)	Fe_3O_4 NPs	PTX	Breast cancer	Targeting CTCs	[146]
Macrophage; cancer cell (hybrid)	PLGA	Dox	Breast cancer	Tumor-targeted chemotherapy	[143]
DCs; cancer cell (hybrid)	MOF (PCN-224)	–	Breast cancer	Targeting homotypic tumors, enhancing immunity and photodynamic therapy	[150]
RBC; TAFs (hybrid)	PMNPs	SAB	TNBC	Immune escape and homologous targeting	[151]
Cancer cell; Macrophage (hybrid)	Micelles	TMP195	TNBC	Converting the tumor microenvironment from the "cold" into "hot"	[152]
OMV; breast cancer cell (hybrid)	PLGA	IR780	Breast cancer	Treating breast cancer bone metastasis	[153]
Macrophage; cancer cell (hybrid)	PLGA	Dox	Breast cancer	Improve breast cancer therapy after laser irradiation in murine models	[154]

Abbreviations: TAFs, Tumor-associated fibroblasts; PMNPs, Porous magnetic nanoparticles; SAB, Salvianolic acid B; OMV, Bacterial outer membrane vesicles.

In addition to cancer cell hybrid membrane biomimetic drug delivery systems, hybrid cell membrane nanoparticles (CM-NPs) designed for breast cancer treatment encompass RBC-PLT and PLT-WBC hybrid CM-coated NPs (Table 3). In 2017, the initial hybrid membrane encapsulation for nanodrug delivery systems in breast cancer therapy was established, utilizing a combination of RBC and PLT hybrid cell membranes.[145] Since that time, the application of hybrid CM for coating nanoparticles has been progressively documented in numerous studies. Rao et al demonstrated the fusion of platelet and white blood cell membranes, followed by the attachment of the PLT-WBC hybrid membrane to magnetic beads, which were further enhanced with specific antibodies.[146] The resulting PLT-WBC hybrid membrane-coated immunomagnetic beads (HM-IMB) showed improved capacity for binding cancer cells derived from platelets, reduced interactions with homologous white blood cells, and facilitated the precise isolation of CTCs. Additionally, HM-IMB successfully detected high-purity CTCs in 19 out of 20 clinical blood samples from breast cancer patients. Researchers have also integrated engineered membranes with natural cell membranes to enhance the functionality of biomedicine nanocarrier drug delivery systems. This approach imparts beneficial biological properties to nanoparticles by combining two types of natural cell membranes.[147] Studies using mouse models have shown the effectiveness of a HER2-targeted DNA-aptamer-modified DNA tetrahedron camouflaged with hybrid membranes, in conjunction with maytansine (DM1), for the treatment of HER2-positive breast cancer. Hybrid membrane vesicles demonstrated enhanced anti-tumor efficacy, further improving the specificity and effectiveness of the treatment while minimizing systemic side effects. However, one potential challenge is the complexity of manufacturing these hybrid systems at a large scale, which could limit their clinical application. Although these carriers show excellent targeting properties in preclinical models, further clinical validation is necessary to fully assess their effectiveness across diverse patient populations and tumor types. Additionally, the integration of natural cell membranes could be optimized to reduce immune responses or off-target effects that might arise from fusing multiple cell types.

Bacterial Outer Membrane Vesicle-Derived Biomimetic Nanotherapeutics

Pathogenic cells, along with mammalian cells, can serve as sources for nanoparticle coatings. Bacteria have been explored in various studies as an innovative delivery system for biomedical applications.[155] Unlike traditional NP-based vaccine strategies, which incorporate immune-stimulating ligands, bacterial membranes are inherently immunogenic. They contain potent ligands for pattern recognition receptors (PRRs), which are crucial for stimulating the innate

immune system and enhancing adaptive immune responses.[156] Encapsulating nanoparticles with these molecular patterns imparts intrinsic adjuvant properties.[157] As a result, these nanoparticles, when co-administered with antigens, are processed by antigen-presenting cells (APCs) in a manner similar to the source pathogenic cells. Cui's group demonstrated anti-breast cancer efficacy by encapsulating over-expressed pre-miRNA, using *Escherichia coli* as a model pathogen.[158] They utilized bacterial outer membrane vesicles (OMVs), also known as extracellular vesicles. OMVs are nanoscale lipid bilayer vesicles naturally produced by all Gram-negative bacteria, and they contain various immune-stimulatory components.[159] Research has shown that bacterial membrane vesicles (B-MVs) secreted by the Gram-positive bacterium *Bifidobacterium* can induce apoptosis in TNBC cells, thereby inhibiting tumor growth.[160] In a similar vein, Cui et al developed a highly effective miRNA nano-delivery system for breast cancer treatment by coating zeolitic imidazolate framework-8 with OMVs.[161] This system demonstrated precise tumor targeting and high miRNA delivery efficacy in a murine breast cancer model. Furthermore, the therapeutic effect was enhanced by the synergistic impact of the miR-34a payload within the carrier, which promoted OMV-PD1-induced immune activation and checkpoint inhibition. As a result, OMVs have emerged as promising nanoscale carriers with inherent adjuvant functions.

Combining OMVs with other therapeutic modalities holds great potential for enhancing anti-tumor outcomes. Tumors are known to recruit platelets, and leveraging this phenomenon, He et al have innovatively utilized platelets as "messengers" to improve the tumor-targeted delivery efficiency of OMVs and photothermal agents. Specifically, they designed nanoparticles (IR780-SLN@O-P) based on OMVs, incorporating platelet-binding capabilities. These "delivery" platelets use P-selectin to transport the IR780-SLN@O-P NP "cargo" to the tumor site, ensuring precise targeting.[162] Upon laser irradiation, the photothermal agent induces a significant photothermal effect, which, combined with the immune-stimulatory properties of OMVs, elicits a robust anti-tumor immune response. Moreover, transferring and functionalizing OMVs onto other nanoparticle types that encapsulate pharmaceuticals or antigens could lead to the creation of highly effective multifunctional carriers. Despite the growing body of research focused on developing these bionic systems, the molecular interactions at the biological interface (particularly those between these membrane coatings and cells) require further investigation. Additionally, understanding the mechanisms of intracellular delivery is critical, as the cargo often includes therapeutics that must be effectively transported to intracellular targets.

Cell-Derived Extracellular Vesicles as Nanocarriers for Targeted Drug Delivery

Exosomes are endogenous extracellular vesicles derived from cells and are the most common type of vesicle found in cell-derived biological products, making them extensively utilized for drug delivery (Figure 3A and B). With a diameter ranging from 40 to 100 nm, exosomes carry proteins, lipids, and other biological molecules (Figure 3C).[163] The lipid bilayer of exosomes plays a crucial role in safeguarding the proper transport of drugs, ensuring their circulation in body fluids with enhanced circulatory stability and long-term safety properties.[164] Due to the diverse signaling molecules carried by exosomes secreted by different cells, as well as their inherently small size, exosomes serve as natural nanocarriers capable of targeted delivery.[165] The primary sources of exosomes include stem cells, immune cells (such as T cells, natural killer cells, and macrophages), and exosomes derived from tumor cells.[166] Additionally, exosomes exhibit a "homing" ability, enabling them to target the cells from which they originated. In breast cancer treatment, exosomes can selectively deliver anti-cancer drugs to tumor cells through interactions between their surface membrane proteins and cell receptors. This drug delivery method can help overcome multidrug resistance associated with proteins like P-glycoprotein.[167]

Exosomes have been widely studied as carriers for small molecule drug delivery and are capable of transporting a variety of drugs, both hydrophilic and hydrophobic, such as Dox, dopamine, curcumin, and PTX.[168,169] The methods for loading drugs into exosomes are generally categorized into several main types: direct loading into donor cells via transfection or co-incubation, and post-exosomal formation methods such as electroporation and direct mixing (Figure 3D). Research has demonstrated the effectiveness of exosome-mediated drug delivery in various models, showing promising anti-breast cancer effects. Haney et al demonstrated the high anti-cancer effects of macrophage-derived extracellular vesicles loaded with PTX and Dox in a mouse model of lung metastasis. They also observed anti-tumor activity targeting TNBC in immune-active BALB/C mice and in situ T11 tumors in athymic nu/nu mice.[170]

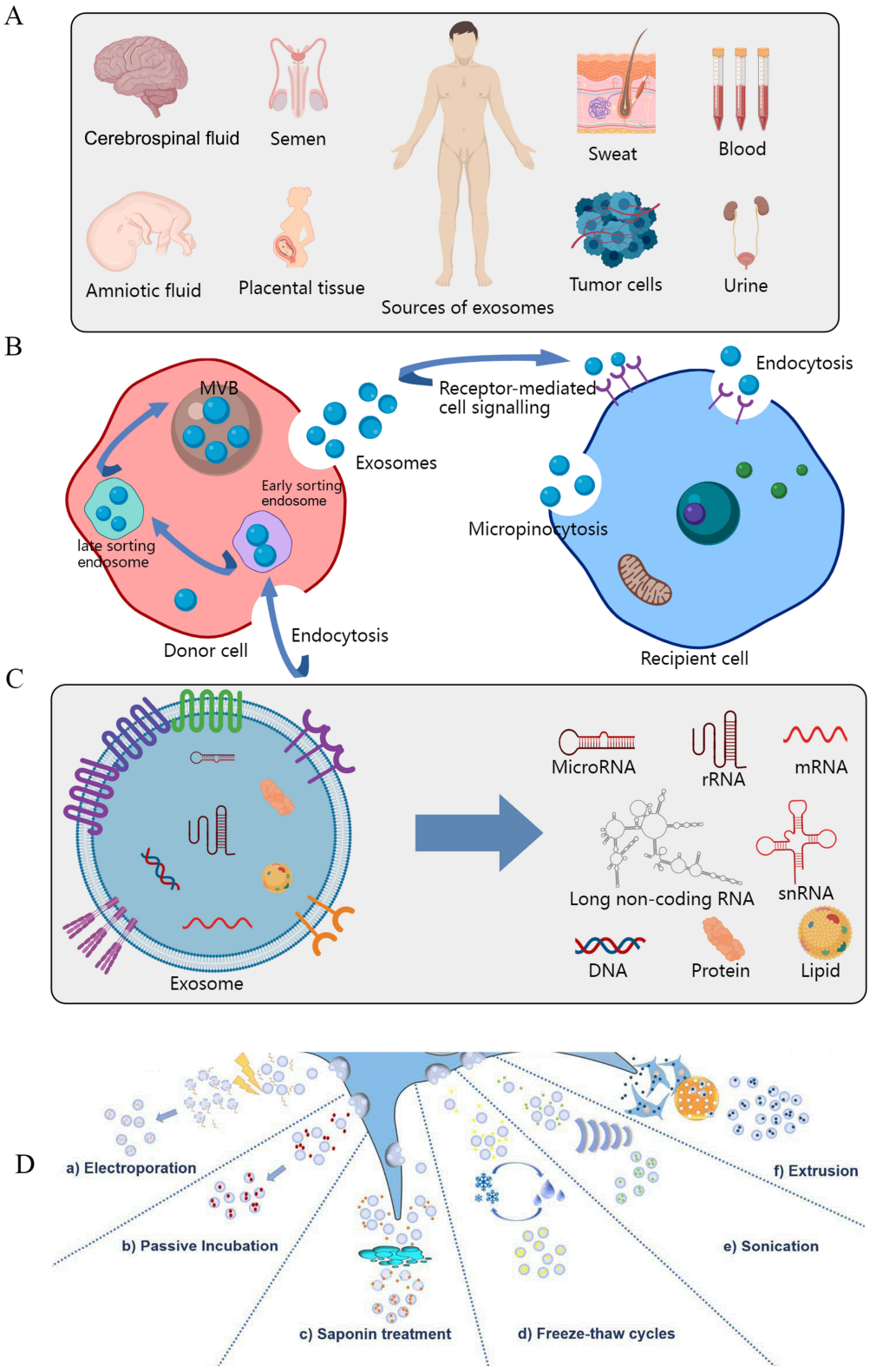

Figure 3 (**A**) Exosomes can be secreted by nearly all tissues and organs, making them detectable in a variety of bodily fluids, including blood, saliva, and sweat. (**B**) The process of exosome production involves the maturation of early endosomes, which invaginate and eventually transform into late endosomes or multivesicular bodies (MVBs). (**C**) Exosomes contain a diverse array of molecular constituents, including DNA, RNA, lipids, and proteins. (**D**) The methods by which exosomes load drugs.

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Table 4 Extracellular Vesicles Loading Different Contents and Effects in the Treatment of Breast Cancer

Type	Examples	Exosome Origin	Effect	Ref.
Nucleic acid	siRNATPD52	HEK 293T	Delays tumor development by down-regulatingTPD52	[173]
	miR-134	Triple-negative breast cancer cells (Hs578Ts(i)8cell)	Reduces triple-negative breast cancer aggression and increases drug sensitivity	[174]
	miR-381-3p	ADMSC	Inhibits triple negative breast cancer proliferation, migration, and invasion and promotes their apoptosis	[175]
	miR-424-5p	AT-MSC	Promotes apoptosis in MDA-MB-231 breast cancer cells	[176]
	LNA-antimiR-142-3p	MSC	Reduces the colony formation capability and the tumorigenicity of breast cancer stem cells	[177]
	miR-23b-3p, miR-126-3p, and the long ncRNA GAS5	Breast cancer cells treated with the multi-kinase inhibitor sorafenib	A remarkable reduction of xenograft tumor area, suppression of angiogenesis, and decreased number of micrometastasis in the tails	[178]
Protein	PTEN-CT	HEK293	Reduces tumor volume, inhibits cellular proliferation	[179]
Drug	Erastin	Human fetal lung fibroblasts (HFL-1)	Inhibits triple negative breast cancer proliferation, migration	[180]
	Taxol	MSC	Reduces of both primary tumor growth and the appearance of organ metastases	[181]
	PTX	Macrophages	Increases pro-inflammatory cytokines and enhances the anti-tumor activity	[182]
	Streptavidin	MSC	A versatile platform for targeted drug delivery	[183]
	PTX	MSC	Enhance the tropism of derived EVs/exosomes to tumors	[184]
	Methotrexate	Breast cancer cells	Improve the delivery efficacy of MTX directly to the cancerous cells	[185]
Nucleic acids and drugs	Cho-miR159, Dox	Macrophages	Demonstrate synergistic anti-tumor effects	[186]
	Docetaxel, miR-34a	Macrophages	Demonstrate synergistic anti-tumor effects	[187]

Abbreviations: ADMSC, Adipose-derived mesenchymal stem cells; AT-MSC, Adipose tissue-mesenchymal stromal cells.

Similarly, Sun et al loaded curcumin into extracellular vesicles derived from donor human adenocarcinoma cells and mouse breast tumor cells. Experimental data showed that curcumin delivered through extracellular vesicles was more stable in the blood at higher concentrations, enhancing its target specificity.[171] However, it is essential to package extracellular vesicles with therapeutic nucleic acids, proteins, or drugs for effective breast cancer treatment due to the content similarity between donor and recipient cells (Table 4). Additionally, since unmodified extracellular vesicles from most cell sources have limited targeting capabilities, there is a growing focus on surface modifications using strategies such as genetic engineering and chemical modification. These modifications aim to enhance targeting and improve the efficiency of delivering therapeutic small molecules for breast cancer treatment.[172]

While exosomes have been extensively investigated in preclinical studies for drug delivery in breast cancer, most clinical trials are currently in the early stages and potentially limited by low exosome yields and purification methods. Standard techniques like ultracentrifugation, ultrafiltration, precipitation, and immunoaffinity have been shown to compromise exosome structural integrity and functional properties.[172] Furthermore, exosome structure and composition are complex, influenced by precursor cell type, physiological conditions, and production methods.[172] Therefore, there is an urgent need to develop stable, effective and more scalable exosome-mimicking nanoparticles for advanced applications in drug delivery and breast cancer therapy.

Application of Other Membrane-Derived Biomimetic Nanotherapeutics

For the purpose of drug delivery, numerous specialized cell types have been developed. Tumor-associated fibroblasts (TAFs) are a critical element of the tumor microenvironment, which is characterized by their ability to secrete a variety of inflammatory and growth factors, as well as their ability to remodel the extracellular matrix. Li et al created semiconductor polymer NPs that absorb near-infrared light and are camouflaged with activated fibroblasts (AFs) for the purpose of combining photodynamic and PTT.[188] By facilitating the accumulation of NPs within the tumor, the cellular

membrane coating enhances the efficacy of photodiagnostics and phototherapy by providing homologous targeting to cancer-associated fibroblasts. Additionally, Zhang et al employed HEK293T cell membranes that express PD-1 to encapsulate a sinophoryrin sodium-binding human serum albumin-perfluorotributylamine nanoemulsion, with the objective of achieving synergistic photodynamic immunotherapy targeting hypoxic 4T1 breast tumors and their distant metastases.[189] Recently, there has been a growing interest in the concept of replicating natural viral intracellular infection mechanisms within the context of anti-tumor immunotherapy. Zhao et al created HSV-NP analogs aimed at cancer-targeted therapy, employing herpes simplex virus (HSV) to initiate innate immune responses as a mechanism of action.[190] This system involves the engineering of DNA enzyme-loaded Mn-ZIF-90 nanoparticles (ZM@TD) to mimic virus capsids containing genomes, while RBCMs are modified with RGD and HA2 functional peptides to imitate virus envelopes. This biomimetic platform effectively circumvents rapid clearance in the bloodstream while simultaneously mimicking several processes associated with HSV infection. Activation of the cGAS-STING pathway led to a significant stimulation of the innate immune system, achieving a 68% regression in primary tumors and extending median survival by 32 days in rodents bearing 4T1 tumors.

The Future Prospective

Personalized therapy is a primary goal for the future of breast cancer treatment. Cell-derived nanocarriers serve as versatile biomimetic nano-platforms for advanced personalized therapies, combining their intrinsic properties with established methods

Table 5 Advantages and Anti-Breast Cancer Applications of Different Drug-Loaded Cells

Cell Type	Advantages	Main Surface Markers
Mesenchymal stem cells	Tumor homing capability; Low immunogenicity; Long-term retention in tumor site	CD44, integrins
Red blood cells	Biocompatibility; High drug loading; Low immunogenicity	CD47
Platelets	High safety and reproducibility	CD47, membrane glycoproteins
Neutrophils	High specificity and mobility; Excellent targeting capability	L-Selectin, P-Selectin, Macrophage antigen-1, LFA-1, VLA-4
T cells	Highly specific, excellent targeting cells	LFA-1, CD11a
Macrophages	Biocompatibility; Enhanced drug stability; Reduced immunogenicity	CD86, CD80, MHC-II
Natural killer cells	Natural anti-tumor capability; Antigen-independent recognition; Rapid response; Low toxicity; Gene editing potential	CD56, CD16 (FcγRIIIa), NKG2D, NKp30, NKp44, NKp46, CD3-
Cancer cells	Homotypic tumor targeting; Immune evasion; Anti-cancer vaccines	Galectin-3, Cadherins, Integrins, CD326 (EpCAM), TF-antigen, CD44
Hybrid cells	Multifunctionality; Enhanced anti-tumor activity; Synergistic effects; Potential for personalized therapy	–
Bacteria	Stimulating innate immunity; Promoting adaptive immunity; Tumor targeting	Immunogenic antigens, Pathogen-associated molecular patterns (PAMPs)
Cell-derived extracellular vesicles	Strong blood circulation stability; Long-term safety	CD63, CD81, CD9, ALIX (PDCD6IP), TSG101, HSP70, LAMP1/2

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like phototherapy, immunotherapy, gene therapy, and chemotherapy (Table 5).[191] The tumor microenvironment is composed of various immune-related cells, including natural killer cells, macrophages, and dendritic cells. Recent studies have also highlighted the role of bacteria within the tumor microbiome.[192] By selecting appropriate cells (eg, immune cells, cancer cells, microbes), it is possible to replicate their natural characteristics and functions, thus facilitating breast cancer therapy. Most studies have focused on the in-vivo applications of cell-derived nanocarriers in murine models, which have demonstrated excellent biocompatibility and safety. However, understanding their cellular behavior is crucial for developing successful clinical applications. Fundamental research on cell-derived nanocarriers and their interactions within tissues and cells is still incomplete and requires more comprehensive and systematic analysis. On one hand, developing efficient nanocarriers for specific tissues necessitates identifying key motifs responsible for binding to surface markers and cell receptors. On the other hand, a deeper understanding of cellular internalization mechanisms opens new avenues for intracellular applications, particularly those requiring endosomal escape.

There is a need for more advanced and reliable 3D cell culture models, such as spheroids and organoids grown under flow conditions, to better mimic natural environments for investigating and predicting biomolecular mechanisms. These models enhance our understanding of the complex cellular behavior exhibited by cell-derived nanocarriers in vivo. As discussed in this review, cell membrane-derived nanocarriers show significant promise for improving drug delivery. However, several critical challenges must be addressed before advancing to clinical trials. Drug loading within cells can alter cell properties, affecting cell surface proteins and membrane fluidity, which may impact cell viability and increase immunogenicity.[193] For example, RBCs may affect biocompatibility when used as vectors, leading to potential drug exposure risks.[117] Certain cell types, such as macrophages, must maintain circulation in body fluids to enable migration and homeostasis when used as vectors and to release drugs in large quantities at tumor sites.[194] However, intracellular protective mechanisms may cause the excretion of free drugs, neutralizing their endocytotic effects and leading to premature drug release before reaching the tumor site. Furthermore, when cells are used for targeted drug delivery and breast cancer therapy, they may not possess the same homologous targeting properties as cancer cell-loaded drugs, which can reduce the efficacy of drug release at tumor sites. Currently, there is limited research on the delivery of therapeutic agents to dead cells, which introduces a degree of uncertainty. Further investigation is needed into the metabolism and safety of cancer cells in vivo, including the potential for tumor formation.

The large-scale production and standardization of manufacturing and characterization methods for these biomaterials present significant challenges. Various cell types require distinct culture conditions, and sample quantity and quality can be affected by factors such as cell type, cell cycle, lifespan, and channel number. This is critical not only for reducing inter-batch variability but also for achieving consistent biomimetic nanocarriers across different populations. Due to cell surface heterogeneity, nanocarriers with specific proteins or varied epitope sequences and densities can be generated within a single batch. Therefore, precise characterization tools are essential to analyze surface composition and biological performance. Ensuring the integrity of the cell surface, as well as the proper orientation, presence, and stability of key membrane proteins, is crucial following the assembly of cell membrane fragments. Targeting effectiveness may decrease due to protein loss or malfunction during membrane extraction, purification, or storage.

Data Sharing Statement

All data generated or analyzed during this study are included in this manuscript.

Consent for Publication

All authors have reviewed and approved the final version of the manuscript and have given their consent for the publication of this work.

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Disclosure

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