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Review

Exosome membrane-coated nanosystems: Exploring biomedical applications in cancer diagnosis and therapy

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SUMMARY

Bio-mimicking principles have recently been proposed for the surface functionalization of nanoparticles (NPs). Such a strategy is based on camouflaging the NP surface with functional biomembranes to render superior biocompatibility, interfacial features, immune evasion, and active targeting properties to nanomaterials. In this area of research, cell membranes derived from a plethora of highly optimized cells, such as red blood cells, immune cells, platelets, stem cells, cancer cells, and others, have been the pioneers as coating materials. This biomimetic concept has then been applied to subcellular structures, namely extracellular vesicles and intracellular organelles. Exosomes are a nanosized extracellular vesicle subtype secreted by most cells. These phospholipid bilayer nanovesicles are surface enriched with proteins accounting for their dynamic and prominent roles in immune escape, cell-cell communication, and specific cell uptake. Their intrinsic stability, biocompatibility, reduced immunogenicity and toxicity, and specific cell-targeting features denote an optimal biological nanocarrier for biomedical applications. This review highlights the current clinical applications of exosome membrane-coated nanosystems in cancer diagnosis and therapy. These biomimetic nanosystems have emerged as a promising avenue to provide effective, highly specific, and safer cancer-targeted applications. Finally, challenges hindering their clinical application will be mentioned.

INTRODUCTION

Cancer, one of the most serious and life-threatening disease groups, accounts for millions of deaths worldwide.[1–5] Surgery, radiotherapy, immunotherapy, and chemotherapy are the currently used cancer therapeutic regimes.[6,7] Although chemotherapy constitutes the standard strategy for several cancer types, it is associated with severe toxicity, emergence of multidrug-resistant tumor cells, and unsatisfactory clinical outcomes.[5,7–9] Nanomedicine, an exciting field that brings together the nanometer scale and medicine, has revolutionized cancer management by enabling a more precise, safe, and targeted diagnosis and therapy.[3,4,10] By capitalizing on the enhanced permeability and retention effect of tumorous tissues, nanoparticles (NPs) can passively reach these highly vascularized areas.[3,11] This contributes to boost therapeutic efficacy, and reduce non-specific drug accumulation and toxicity of traditional modalities.

PROGRESS AND POTENTIAL

Driven by the limitations of conventional nanoparticle-based delivery systems, emerging insights in the rational design of nanomaterials are applying bioinspired principles to optimize their performance *in vivo*. Cell-membrane-coated nanoparticles, designed to mimic cellular biofunctions, were the first to be explored. However, this biomimetic approach has recently focused on other biomembranes, such as those derived from naturally cell-secreted exosomes. Exosome membrane-coating nanotechnology, a nature-inspired approach that operates via functionalizing nanomaterials with bioactive and multifunctional exosome membranes, is presumed to improve the biocompatibility, blood circulation half-life, and biodistribution of nanomaterials at targeted tumorous tissues. In this review, the recent advances in exosome membrane-coated nanosystems toward cancer clinical diagnosis and therapy and the challenges to successful clinical translation are discussed and summarized.

Despite the obvious advantages of harnessing NPs for oncology applications, concerns related to their performance *in vivo* are hampering translation into clinical settings.[10,12] Inspired by biological events and cellular behaviors, a recent biomimetic concept based on the use of biological membranes as NP cloaking materials successfully enhanced biocompatibility, immune evasion, blood circulation time, and site-specific targeting features.[3,8,12–14] The idea of biomimicry first appeared with cell membranes, but soon expanded to other subcellular structures, including extracellular vesicles[15–17] and intracellular organelles.[18–20] As nanosized cell-derived vesicles, exosomes constitute an optimal alternative to artificial cell membranes on account of their endogenous nature, immunocompatibility, optimized nanometer size, and ability to transfer their cargo to surrounding and distant cells.[21,22] This review focuses on the clinical applications of exosome membrane-coated NPs for cancer diagnosis and therapy, as well as the challenges hindering their successful clinical application.

EXOSOME MEMBRANES VERSUS OTHER COATING MATERIALS

Current efforts in nanomedicines design have been applying biomimetic and nature-inspired principles to address critical shortcomings of conventional NPs.[8,13,23] These include rapid clearance from blood circulation, poor biocompatibility, and restricted ability to cross biological barriers (such as the blood-brain barrier).[3,24–26] This top-down strategy aims at designing biomembrane surface-engineered nanodevices with augmented biocompatibility, immune evasion, specific active cell-targeting features, and enhanced bio-interfacing.[24,27–29]

Numerous types of biomembranes have been explored to coat various types of nanosized materials. The most reported ones range from natural cell membranes to cell-secreted vesicles, especially the membrane of exosomes (Figure 1).[30–32] Cell membrane-coating nanotechnology harnesses the intrinsic biofunctionality of cell membranes to design bioinspired nanosystems with more cell-like functions and improved interfacial features.[33–36] Exosome membrane-coating nanotechnology capitalizes on the biological superiorities of exosome membranes to confer superior biocompatibility, immune evasion, and tissue-homing features to NPs.[16,17]

FABRICATION PROCESS OF EXOSOME MEMBRANE-COATED NANOSYSTEMS

Typically, exosome membrane-coated NPs are prepared through a three-step biomimetic technology. This include: (1) exosome isolation and membrane extraction; (2) selection and preparation of the NP inner core; and (3) coating NPs with exosome membranes (Figure 2).[16,37]

For exosomes isolation and membrane extraction, cell-secreted exosomes are first isolated by ultracentrifugation from the cell supernatant, followed by hypotonic treatment to remove the intra-exosomal cargo and extract the emptied exosome membranes.[16,37] Despite several isolating techniques having been documented, ultracentrifugation constitutes the most commonly used and gold standard approach for exosome isolation.[38] This process should be performed as carefully as possible to ensure the integrity of the exosomal protein markers and the biofunctionality of the nanosized exosomal membranes.

The next step involves the proper selection and preparation of NP inner cores. According to the intended application, both organic- and inorganic-based nanomaterials can be selected as the inner cores for subsequent exosome membrane

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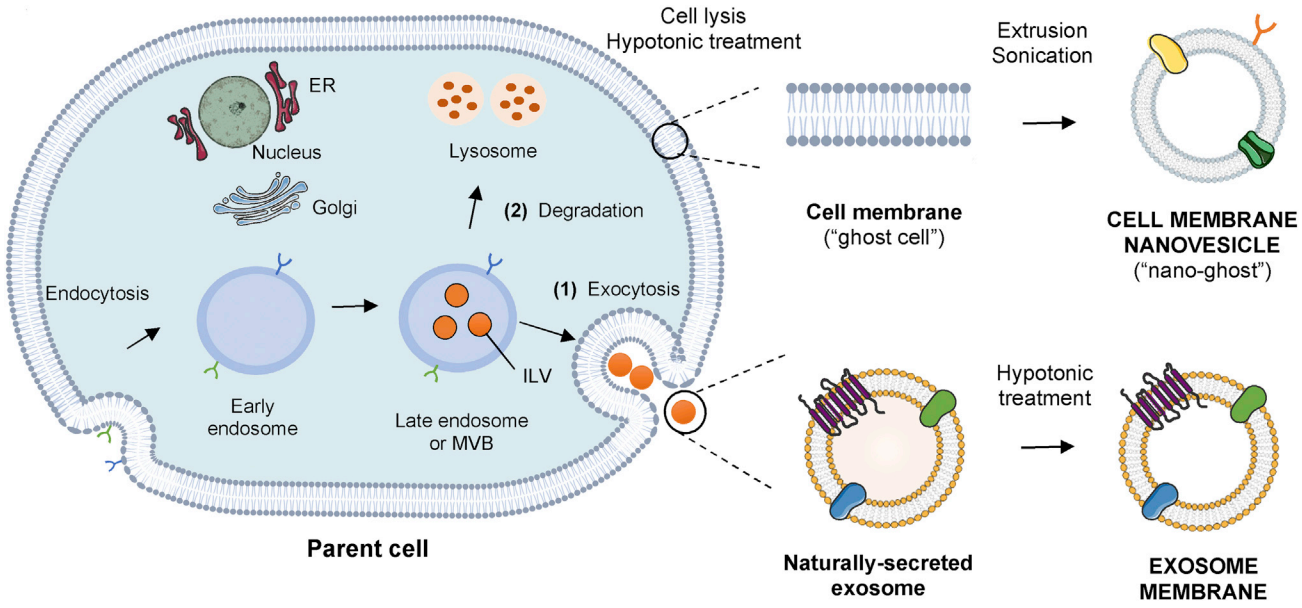

Figure 1. Exosome membranes versus natural cell membranes as biomimetic coatings for NP surface functionalization

Comparative illustration of the manufacturing process for obtaining cell membrane nanovesicles and exosome membranes for subsequent NP coatings. ER, endoplasmic reticulum; ILV, intraluminal vesicle; MVB, multivesicular body; NP, nanoparticle.

coating.[15] Apart from their fundamental role in mediating cargo delivery and protection, the NP cores can also possess intrinsic diagnostic imaging and/or therapeutic features to provide a multifunctional platform.

The final step regards the cloaking process, in which the synthesized NP inner cores are surrounded by exosomal membranes.[15–17] To date, various coating techniques have been proposed for preparing exosome membrane-coated NPs. These include: (1) physical co-extrusion through porous membranes; (2) sonication; (3) direct incubation of NPs with living cells (allowing them to secrete NP-containing exosomes by leveraging the exosomal biogenesis pathway); (4) direct incubation of NPs with cell-secreted exosomes; (5) use of microfluidic sonication-based coating techniques; and (6) electroporation to open transient pores in exosome membrane for NPs to enter. Table 1 describes the main principle of these coating techniques.

Since the first reported study on exosome membrane-coated NPs, the development process of these biomimetic nanosystems has significantly evolved, and major technological discoveries have been developed in this field over the past few years (Figure 3). Primary exosome membrane-coating methods were mainly focused on direct incubation of selected NPs with living cells or cell-secreted exosomes. Then, other coating techniques such as co-extrusion and sonication (often employed for cell membrane coatings) were introduced to this field, with the requirement of prior extraction of the exosome membrane via hypotonic treatment. More recently, the employment of microfluidic sonication- and electroporation-based coating techniques has been investigated and proven efficient for exosome membrane coatings.

A novel and still rarely explored strategy to enhance tumor targeting is to functionalize the exosome membrane with a specific binding domain of a molecule overexpressed on the membrane of target tumor cells.[39,41,42] Accordingly, a biomimetic system with high tumor-targeting efficiency was developed by coating

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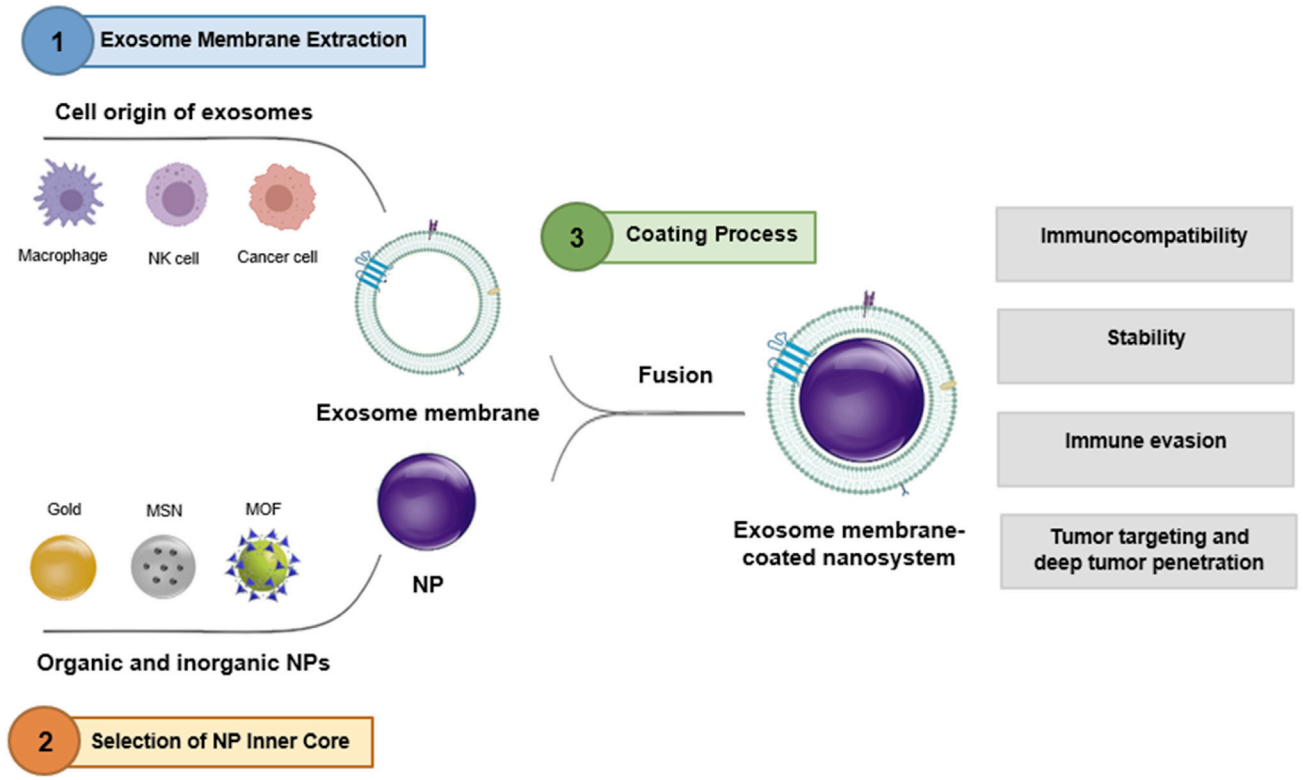

Figure 2. Schematic illustration of the three-step preparation process of exosome membrane-coated nanosystems

(1) Exosome membrane extraction via hypotonic treatment.

(2) Selection and preparation of NP inner cores.

(3) Coating NPs with exosome membranes.

MOF, metal organic framework; MSN, mesoporous silica NP; NP, nanoparticle; NK, natural killer.

poly(lactic-co-glycolic acid) (PLGA) NPs with breast cancer cell-derived exosome membranes decorated with the AS1411 aptamers.[39] The exosome membrane coating could prolong the blood circulation time of the nanosystem due to the expression of surface proteins on the exosome membrane, especially CD47, CD55, and CD59, providing an escape from the immune system. The AS1411 aptamer, an easily synthesized oligonucleotide with high stability and specificity, allows efficient tumor targeting and retention in the target tumor cells by specific binding to the nucleolin, which is overexpressed in the tumor cell membrane. The rapid assembly of the nanosystem was divided into two parts, namely microfluidic sonication for coating the PLGA NPs with the exosome membrane and vortexing for conjugation of aptamers through hydrophobic interactions. These AS1411 aptamer-decorated exosome membrane-coated biomimetic NPs showed efficient tumor targeting and prolonged systemic circulation time *in vivo*, which was not affected by surface modification of aptamer. Hence, functionalization of exosome membranes with surface proteins that interact with specific membrane receptors overexpressed by tumor cells is a promising strategy for efficient targeted drug delivery.[39]

FUNCTIONALIZATION BENEFIT OF EXOSOME MEMBRANE-COATED NANOSYSTEMS

Exosome membrane-coating nanotechnology combines the physicochemical benefits of NPs with the biological advantages of exosomes.[16,37] In the following sections, we discuss the potential benefits of exosome membrane functionalization in terms of

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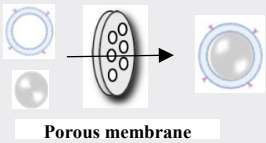
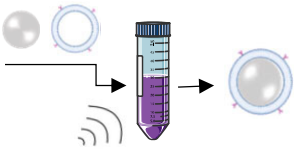
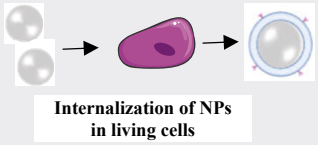
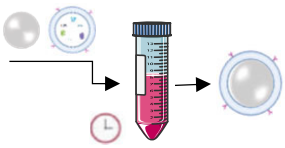
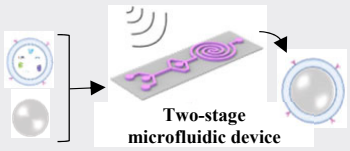
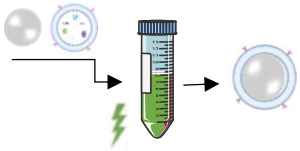
Table 1. Common coating techniques used for preparing exosome membrane-coated nanosystems

Coating technique	Schematic depicting	Mechanistic principle	Key features	Reference
Physical extrusion or co-extrusion[a]		mechanical extrusion through porous membranes disrupts exosome membrane structure, allowing it to reassemble around NP cores	• possible disruption of exosome membrane structure and integrity • time-consuming and labor-intensive	Wang et al.,[12] Fathi et al.,[15] Lu and Huang[16]
Sonication[a]		spontaneous reassembly of exosome membrane around NP cores induced by ultrasonic energy	• possible disruption of exosome membrane structure and integrity • time-consuming and labor-intensive	Wang et al.,[12] Fathi et al.,[15] Lu and Huang[16]
Direct incubation of NPs with living cells		direct incubation of NPs with living cells, allowing them to secrete exosomes containing exogenous NPs (exosomal biogenesis pathway)	• non-disruptive coating technique • negligible impact on exosome proteins and functionalities	Fathi et al.,[15] Lu and Huang[16]
Direct incubation of NPs with exosomes		preparation of exosome membrane-coated nanosystems by incubating cell-secreted exosomes with NPs	• non-disruptive coating technique • negligible impact on exosome proteins and functionalities	Fathi et al.[15]
Microfluidic sonication method		use of external ultrasonic forces coupled to a two-stage microfluidic device for coating NPs with exosome membranes	• overcome the laborious and time-consuming limitations of co-extrusion and sonication • continuous and one-step production of exosome membrane-coated NPs	Fathi et al.,[15] Liu et al.,[21] Han et al.[39]
Electroporation		use of an external electric field to open transient pores on exosome membrane for NPs entry	• not suitable for larger nanomaterials	Pan et al.[40]

NP, nanoparticle.
[a]The two most frequently used coating techniques for preparing exosome membrane-coated nanosystems.

cell-cell communication, protein corona impedance, immune evasion, biocompatibility, and manufacturing process.

Cell-cell communication and tumor-targeting ability

Exosomes, a small group of extracellular vesicles naturally released by cells, possess a size usually ranging from 30 to 150 nm.[30,43,44] These nanovesicles are recognized as important messengers for cell-cell communication.[45–47] The discovery of the key role mediated by exosomes in the transport of biomolecules and biological signals between surrounding cells is capturing attention in the contemporary biomedical field.[48]

Exosomes are composed of a phospholipid bilayer membrane structure enriched with lipids, proteins, and genetic material (RNA [e.g., miRNA and mRNA] and DNA), as well as other biomolecules derived from the cells from which they are

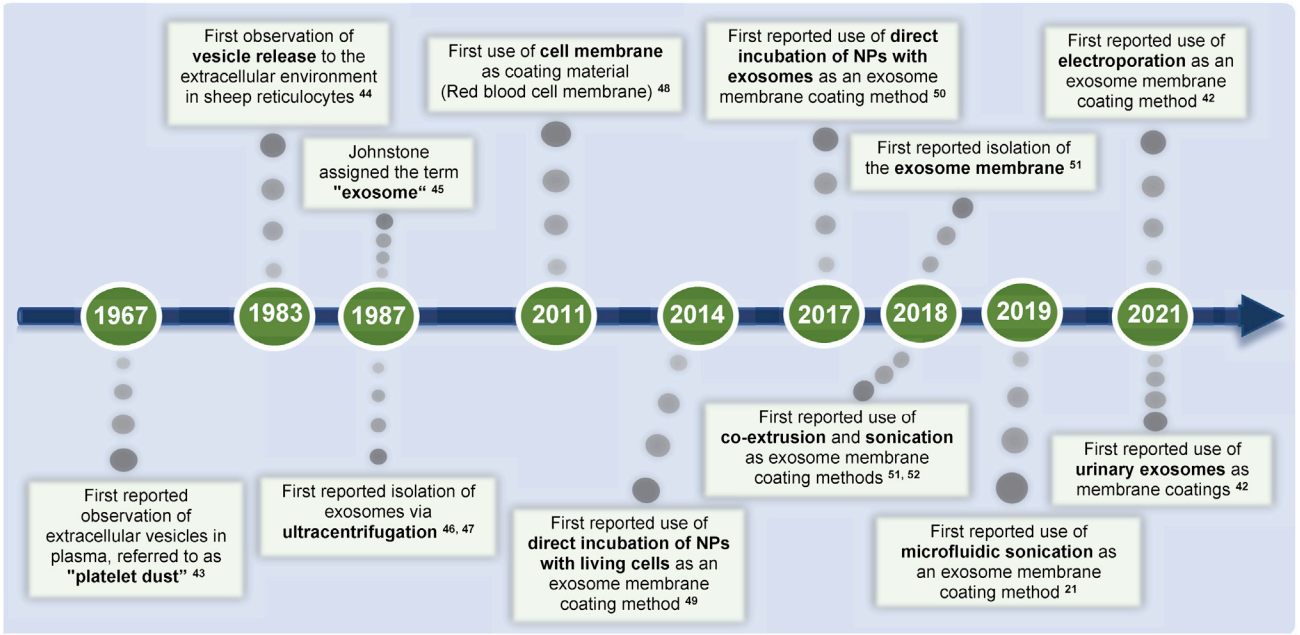


Figure 3. Timeline of exosomes and their applications

Timeline illustrating the development process and the major technological discoveries related to exosome membrane-coated nanosystems preparation.

originated.[49] Thus, the exosomal content is highly influenced by the pathological and physiological status of the source cell.[50] Cell-cell communication is essential for homeostasis and can occur via a variety of signaling systems, most notably exosomes, which are released by almost all healthy and diseased cells and serve as critical mediators for intercellular communication, since the encapsulated biomolecules can be transferred to neighboring and distant cells.[46,51,52]

When multivesicular bodies fuse with the plasma membrane, exosomes are released into the extracellular space, which can then be taken up by the recipient cells and dictate changes in cellular phenotypes and behaviors.[53–55] This is due to their ability to activate/inhibit certain signaling pathways, or trigger changes in gene expression or protein translation. There are three different ways that exosomes potentially enter cells: directly fusing with the cell membrane, interacting with cell surface receptors (ligand-receptor interactions), and uptake of exosomes through endocytosis, which includes caveolin-mediated endocytosis, clathrin-mediated endocytosis, lipid-raft-mediated endocytosis, phagocytosis, and macropinocytosis.[56,57]

Cell-secreted exosomes are promising biological nanocarriers.[16,58] The superiorities of exosomes over synthetic nanomaterials include their excellent biocompatibility and safety, intrinsic stability, immune evasion, and biological barrier-crossing abilities, as well as their intrinsic cell-specific targetability.[16,17,45,51] As nanovesicles produced by invagination of cell membranes, natural exosomes can retain the membrane repertoire and the biofunctionality of donor cells. In this way, exosomes are surface enriched with specific donor cell-related membrane proteins, which confer them with a higher cell-specific targeting ability.[15,16,43]

This is particularly relevant in the field of cancer.[17,51] Cancer cell-derived exosomes can preserve the surface proteins of donor cancerous cell membranes, as well as

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their homotypic tumor-homing features. Thus, cancer cell-derived exosomes can be selectively taken up by the cancer cells that released them.[15,21,49] This well-established mechanism underlying the tumor tropism of cancer cell-derived exosomes has been receiving increasing attention to improve specificity and efficacy of cancer clinical interventions.[15] The exosomes secreted by immune cells have also shown striking results in this arena,[59] mostly due to their cancer immunomodulatory effects and tropism to inflammatory/tumorous tissues.[15,35] Macrophage-derived exosomes exert key immunostimulatory effects, being responsible for activating immunological and inflammatory responses to suppress cancer development and progression.[35,60] Natural killer cell-derived exosomes can recognize abnormal cells (e.g., cancer cells) and activate important cytotoxic pathways to induce cell death due to the presence of donor cell killer proteins (e.g., FAS ligand and perforin).[61,62] Dendritic cell-derived exosomes are enriched with molecules derived from donor cells (such as the major histocompatibility complex proteins), which confer them with potent antigen-presenting and T cell-activating activities to promote an immune-enhancing environment.[63,64] B cell-derived exosomes are nanovesicles specialized not only in secreting immunoglobulins but also in inducing the anti-tumor activity of T cells.[59] T cell-derived exosomes carry T cell killer proteins, such as the T cell receptor, which specifically recognize and interact with tumor antigens to induce tumor cell death by releasing cytotoxic exosomal components (e.g., granzyme and perforin).[65] A comprehensive discussion of the various types of cell-secreted exosomes with respect to the advantages and limitations of their use, as well as their main applications in cancer therapy, is summarized in Table 2.

In vivo interaction: Protein corona

In the design of systemically administrated nanosystems, some hurdles must be addressed, namely the accelerated clearance and protein corona.[68–70] After entering the bloodstream, synthetic NPs encounter a highly complex biological medium containing a plethora of active biomolecules.[69,71,72] Depending on the particular physicochemical attributes of NPs, the biological conditions, and the residence time in such environments, a diverse set of biomolecules are dynamically absorbed onto the NP surface.[73,74] This results in the formation of an NP-protein surface layer referred to as protein corona.[71,75] Protein binding on the NP surface can be either irreversible (hard corona) or easily removable (soft corona) based on the binding affinity of proteins to NPs.[69,71,73]

The protein corona may render a novel biological prolife to NPs, and govern their blood circulation, biodistribution, toxicity, and ability to interact with target cell membranes.[73,75] Such a protein coating may "target" the NPs for immune clearance, augmenting their recognition by immune cells and removal from the bloodstream.[69,72] For instance, a buildup of opsonin proteins, such as fibrinogen and immunoglobulin G, on NP surfaces improves macrophages' ability to recognize and ingest them, which leads to quick removal from the bloodstream. In contrast, a protein corona made of dysopsonin proteins, namely, albumin and apolipoproteins, improves the systemic circulation of NPs.[76,77] In addition, protein adsorption on the outer NP surface can negatively influence its targeting ability via blocking the interaction of specific ligands with their corresponding cell-expressing receptors.[69]

After being exposed to the biological environment, the amount of protein that can be adsorbed to the surface of coated NPs is much lower than the amount that can be adsorbed to the surface of uncoated NPs. In addition, protein corona analysis revealed a unique composition, with certain proteins shared by both uncoated and coated NPs, as well as other proteins found only in one or the other. Coated NPs

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Table 2. The type of cell-secreted exosomes often employed for cancer-targeted applications (i.e., cancer-cell- and immune-cell-derived exosomes), their advantages and limitations, and current cancer applications

Cell origin of exosomes		Advantages	Limitations	Applications in cancer therapy	Reference
Cancer cells[a]		(1) intrinsic homing features to homologous tumor tissues (attributed to the cancer cell homotypic proteins) (2) good biocompatibility and stability (3) immune evasion potential (4) efficient in overcoming biological barriers (e.g., blood vasculature)	(1) high heterogeneity in exosomal size and composition (both are highly influenced by the cells of origin) (2) limited control of intra-exosomal content (3) incomplete knowledge about the mechanisms underlying the cell-cell communication mediated by exosomes (4) the cellular uptake of exosomes still require in-depth investigation (5) exosomal biomarkers need further research	attractive carriers of various molecules (e.g., proteins, chemotherapeutics, genetic material) to tumor tissues. The lipid bilayer structure ensures cargo integrity and protection during delivery	Fathi et al.,[15] Shao et al.[49]
Immune cells	macrophage	(1) good tumor targetability inherited from macrophage surface proteins (e.g., integrins, selectins) (2) extended blood circulation time (3) strong inducer of anti-tumor immune responses, contributing to suppress tumor progression and metastasis		cancer immunotherapy (cancer vaccines) and tumor-targeted chemotherapy	Zhao et al.,[59] Hong and Kim[62]
	NK cell	(1) immune scaping behavior (2) negligible immunogenicity in comparison to NK cells (3) high efficiency in eliminating tumor cells without requiring previous MHC activation or antigen recognition		cancer eradication by exploiting the intrinsic anti-tumor potential of NK-derived exosomes	Zhao et al.,[59] Hazrati et al.,[66] Zhang et al.[67]
	dendritic cell	(1) potent antigen-presenting activity and T cell-activating features (2) strong inducer of both innate and adaptive immunological responses to prevent tumor development and recurrence		cancer vaccines	Zhao et al.,[59] Hong and Kim[62]
	B cell	(1) high specialized secretion of immunoglobulins upon antigen exposure (2) strong immunological inducer of T cell anti-tumor activity		cancer immunotherapy based on stimulating T cell proliferation and anti-tumor activity	Zhao et al.,[59] Hazrati et al.[66]
	T cell	(1) potent and selective cytotoxicity against targeted tumor cells via the TCR/tumor antigen binding pathway (2) good immunocompatibility and stability in biological medium			Zhao et al.,[59] Hong and Kim,[62] Hazrati et al.[66]

MHC, major histocompatibility complex; NK, natural killer; TCR, T cell receptor.
[a]The most commonly used exosome type for cancer applications.

are able to avoid detection by the immune system and display reduced cytotoxicity because of the quantitative and qualitative differences in their protein corona compared with those of uncoated NPs. Consequently, the biomembrane serves as an advantageous layer around the NP, enhancing its safety and efficiency.[78–80]

In this way, the NP surface functionalization with biomembranes (such as those derived from naturally cell-secreted exosomes) can circumvent these challenges

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by reducing NP immunogenicity and enhancing both immunocompatibility and cell-specific targeting ability.

Escaping immune clearance and prolonged blood circulation

Accelerated immune recognition and elimination of NPs from systemic circulation, both attributed to their foreign nature and immunogenicity, remain one of the most challenging issues that dampens their clinical application.[3,25,26,81,82] To confer stealth properties, the bottom-up approach based on functionalizing the NP surface with hydrophilic polymers (usually polyethylene glycol [PEG]) has been extensively studied over the last years.[18,33,83] Presently, contemporary strategies leverage the intrinsic immune p behavior of cells or cell-derived nanovesicles to maximize immunocompatibility and extend blood half-life.[81,84]

Numerous biomolecules located on the exosome surface have been identified as crucial immunomodulators. These cannot only protect exosomes from macrophage-mediated immune clearance (e.g., CD47) but also from complement attack (e.g., glycosylphosphatidylinositol-anchored complement regulatory proteins CD55 and CD59), contributing to increase the stability and systemic circulation of exosomes.[85] The "self-marker" CD47 is a "self-recognition" protein ubiquitously expressed in healthy cell membranes.[27,29,86] CD47 is responsible for impairing immune clearance via interacting with signal-regulatory protein alpha surface expressed on the membrane of phagocytes (e.g., macrophages), producing a "don't eat me" signal that suppresses macrophage-mediated phagocytosis.[87,88] As exosomes inherit the complete protein profile from their parent cells, some subsets of exosomes can surface express CD47.[21,89] This effectively makes them invisible for the immune system, protecting them from macrophage-mediated phagocytosis.[85] Thus, coating CD47-expressing exosome membranes onto the NP surface has the potential to significantly enhance not only the safety and pharmacokinetic profiles of NPs but also biocompatibility and stability.[21,89]

Besides, exosomes can also harbor proteins responsible for escaping complement-mediated lysis.[90] The complement system is a key element of innate immunity, referred to as the first line of defense against invaders.[91] The complement cascade can be activated through the classical, alternative, or lectin pathways. Complement activation results in the generation of C3/C5 convertase enzyme for subsequent formation of a membrane attack complex that triggers cell lysis.[91] CD55 and CD59 expression on exosome membranes can offer protection against complement-mediated lysis.[92] These membrane-bound proteins are potent inhibitors of the complement system, increasing the stability and systemic circulation time of exosomes.[85]

Biocompatibility, biomimetic profile, and manufacturing properties

Exosomes, as naturally occurring nanovesicles produced by cells, are presumed to have good biocompatibility and safety, as well as negligible immunogenicity.[16,93–95]

Regarding manufacturing protocols, exosome membrane-coated NP preparation is usually less complex than that of cell membrane-coated NPs. In terms of biomembrane isolation, cell membranes can be more easily isolated than naturally cell-secreted exosomes. This is caused by current lack of standardized protocols for exosome isolation and purification.[96–99] Nevertheless, although nanovesicles derivation is crucial in cell membrane-coated NP preparation, this step is usually not required for exosome-mimicking nanosystems.[18,22] As exosomes already exhibit an ideal nanosize, moderately aggressive techniques often employed to tailor cell membrane vesicles to the nanometer size, such as extrusion or sonication, are not

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Table 3. Comparative analysis between exosome membrane-, natural cell membrane-, and hybrid cell membrane-coated nanosystems

End-product features and manufacturing properties	Exosome membrane-coated nanoparticles	Cell membrane-coated nanoparticles	Hybrid membrane-coated nanoparticles	Reference
Cell-cell biointeraction	++[a]	++	+	Huang et al.,[100] Scully et al.[101]
Escaping immune clearance	+	+	++[b]	Dabbagh Moghaddam and Romana Bertani,[8] Zhang et al.,[89] Patra and Rengan[102]
Protein corona	–[c]	–	–	Han et al.,[68] Shen et al.[103]
Subcellular and cellular structures isolation complexity*[j]	++[d]	0	+	Ai et al.,[97] Yakubovich et al.,[98] Chen et al.,[99] Kimiz-Gebologlu and Oncel[104]
Membrane extraction complexity	0	+	++[e]	Lu and Huang,[16] Chen et al.[105]
Fabrication complexity*[k]	0	+	++[f]	Zhang et al.,[83] Zhang et al.,[106] Zeng et al.[107]
Biomimetic profile	++[g]	+	+	Wang et al.,[30] Song et al.,[51] Kimiz-Gebologlu and Oncel[104]
Production yield	–[h]	+	0	He et al.,[96] Zeng et al.[107]
Industrial scale up	–[i]	0	0	Zhang et al.,[83] He et al.,[96] Ai et al.,[97] Kimiz-Gebologlu and Oncel[104]

Label map:	Highly positive	Positive	Neutral	Negative	Highly negative
	+++	++	0	–	–

[a]Cell-secreted exosomes are nanosized messengers optimized for intercellular communication and interaction.
[b]Biomimetic coatings can prevent immune clearance and prolong systemic circulation due to the CD47/SIRPα interaction. Hybrid membranes combine the functionalities of various cell membranes to maximize immune evasion.
[c]NP surface functionalization with exosome or cell membranes can reduce protein absorption on NP surface (protein corona).
[d]Exosome isolation complexity is attributed to the lack of standardized protocols for exosome isolation and purification.
[e]Disruptive techniques (such as co-extrusion and sonication) are usually not employed for exosome membrane extraction. On the contrary, after cell membrane extraction, these aggressive techniques are required for tailoring cell membrane vesicles to the nanosize.
[f]Hybrid cell membranes are obtained by fusing two (or more) different cell types, which complicates the preparation process.
[g]Exosomes are naturally produced by cells and already possess an optimal nanoscale size. Therefore, exosome membrane-coated NPs are more biomimetic than cell membrane-coated NPs.
[h]The reduced number of exosomes naturally secreted by most cells is the contributing factor to the low production yield.
[i]Similar to natural exosomes, clinical-scale production is a major challenge toward the clinical translation of exosome membrane-coated NPs.
[j]This topic regards the isolation complexity of naturally secreted exosomes and cells.
[k]Including membrane extraction and NP coating.

required.[22] This helps preserving the wholeness of the surface repertoire and membrane co-localization. For this reason, exosome membrane-coated NPs comprise a more biomimetic counterpart when compared with synthetic cell membrane-coated NPs. Table 3 presents a comparative analysis of the biocompatibility, biomimetic profile, and manufacturing challenges between exosome membrane-, natural cell membrane-, and hybrid cell membrane-coated nanosystems.

CANCER DIAGNOSIS AND THERAPY

Cancer, as one of the most serious ailments, is one of the leading causes of death worldwide.[5,108–112] Exosome membrane-coated nanocarriers are promising tools for cancer diagnosis and therapy, by delivering both imaging agents and therapeutic molecules to tumorous tissues. These biomimetic nanocarriers have been experimentally used for cancer bioimaging and theranostic, chemotherapeutics delivery, protein delivery, gene delivery and gene silencing, anti-metastatic therapy, phototherapy, chemodynamic therapy, radiotherapy, and cancer immunotherapy (Figure 4). A summary of the studies employing exosome membrane-coated NPs for cancer applications is presented in Table 4.

Cancer bioimaging and theranostic applications

Apart from their experimental use as drug delivery systems, exosome membrane-coated NPs have also been used experimentally for tumor imaging. Imaging is widely used for the early detection of cancer and to monitor tumor progression. Magnetic resonance imaging (MRI) and near-infrared (NIR) fluorescence imaging

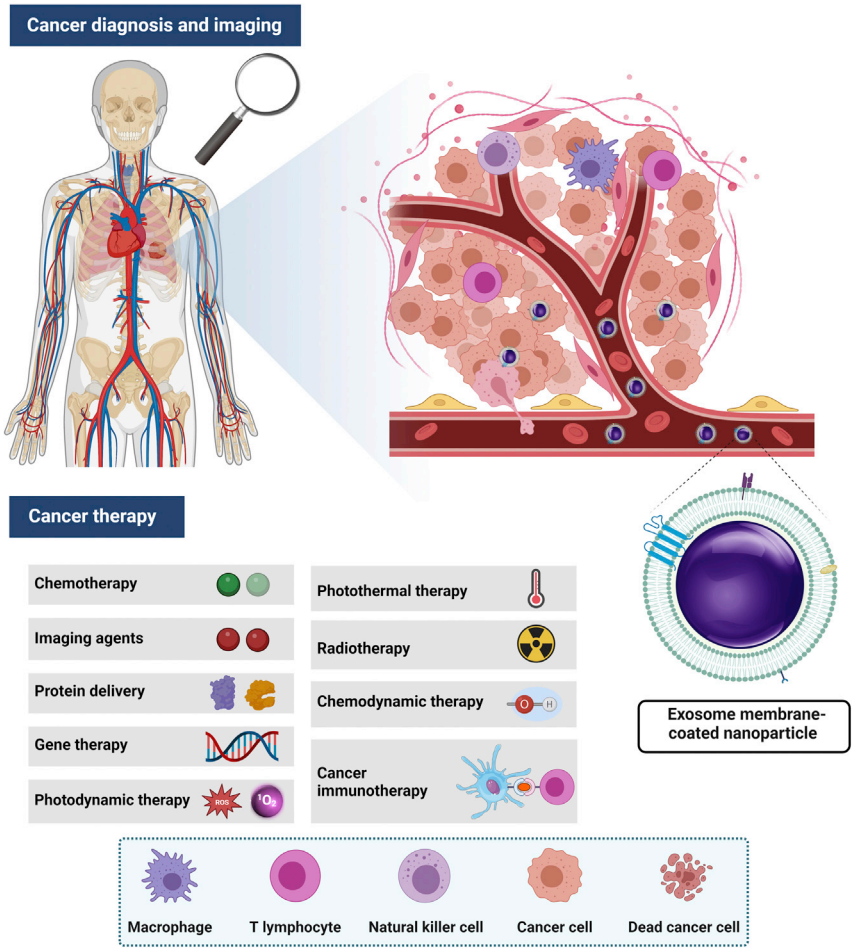

Figure 4. Schematic illustration on the potential of exosome membrane-coated nanosystems carrying imaging agents and anti-cancer therapeutics to the tumor site for efficient cancer diagnosis and therapy

Exosomes have considerable potential in cancer therapy; however, employing natural exosomes is challenging and rarely results in the intended therapeutic response. Engineered exosomes transporting specific chemicals, proteins, or RNAs, on the other hand, have been proven to have a promising prospect for cancer treatment.

are useful cancer imaging tools.[131–133] In recent years, theranostic nanoplatforms, which combine both therapeutic and diagnostic features into a single nanoplatform, have gained considerable attention for cancer management.[131] Exosome membrane-coated NPs have been identified as auspicious theranostic tools for simultaneous cancer imaging and therapy by delivering both therapeutic molecules and imaging agents to targeted tumor sites.

Different types of NPs have been investigated for theranostic applications, including gold (Au)-iron oxide NPs, which have unique properties for both imaging applications and photothermal therapy (PTT). This is because iron oxide acts as a contrasting agent for MRI, while the AuNP functions as a photothermal agent for converting NIR radiation into cytotoxic heat for thermal ablation of tumor cells through hyperthermia.[113] In a study, Au-iron oxide NPs were coated with breast cancer cell-derived exosome membranes for tumor-targeted delivery of anti-sense miRNA that is designed to target microRNA-21 (anti-miR-21), photothermal ablation of tumor cells,

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Table 4. Overview of some of the studies employing exosome membrane-coated nanosystems in cancer imaging and therapy

Application	Exosome membrane source	Inner core	Drug(s)	Coating method	Size/zeta potential	*In vivo* mouse model	Outcomes	Reference
Cancer bioimaging and theranostic	4T1 murine breast cancer cell-derived exosome membrane	gold (Au)-iron oxide NP	anti-sense miRNA targeting miRNA-21 (anti-miR-21)	co-extrusion through 100 nm porous membranes	97.0 nm – 29.2 mV	syngeneic subcutaneous 4T1 tumor-bearing mouse model	• homotypic tumor-targeting ability • ↑ accumulation in 4T1 cells • ↑ photothermal therapy (PTT) efficiency *in vitro* • good magnetic resonance imaging (MRI) properties • targeted delivery of anti-miR-21 to tumor sites • ↓ doxorubicin resistance • 3-fold higher cell killing efficiency of anti-miR-21 plus doxorubicin compared with doxorubicin alone	Bose et al.[113]
Delivery of chemotherapeutics	H22, Bel7402, and B16-F10 cell-derived exosome membranes	luminescent porous silicon nanoparticle (PSiNP)	doxorubicin	direct incubation of target cells with NPs (exosome biogenesis pathway)	260.0 nm – 11.0 mV	subcutaneous H22 tumor-bearing mouse, orthotopic 4T1 tumor-bearing mouse, and lung metastasis B16-F10 melanoma-bearing mouse model	• ↑ uptake in cancer cells and cancer stem cells (CSCs) • ↓ tumor size • ↓ number of CSCs • ↑ overall survival time of tumor-bearing mice • cross-reactivity between different cancer cell types	Yong et al.[114]
	HeLa cervical cancer cell-derived exosome membrane	MIL-88A metal-organic framework (MOF) NP	suberoyl bis-hydroxamic acid	incubation of exosomes with MOF NPs	–	–	• specific uptake by homotypic HeLa cells *in vitro* • tumor-targeted drug delivery • minimal premature leakage of the therapeutic payload	Illes et al.[115]
	HT1080 cell-derived exosome membrane	liposome	doxorubicin	co-extrusion through 200 nm porous membranes	–	subcutaneous HT1080 tumor-bearing nude mouse model	• homotypic tumor-targeting ability • ↑ uptake by HT1080 cells • 2.3-fold increase of drug accumulation in tumor sites compared with non-coated Doxil • ↑ anti-cancer effects • tumor growth suppression to practically undetectable levels • ↓ cardiotoxicity	Qiao et al.[116]
	macrophage-derived exosome membrane	poly(lactic-co-glycolic acid) (PLGA) NP	doxorubicin	co-extrusion through 100 nm porous membranes	137.0 nm – 30.6 mV	orthotopic MDA-MB-231 tumor-bearing nude mouse model	• ↑ systemic circulation time • ↑ tumor-targeting ability provided by the c-Met binding peptide • tumor-targeted drug delivery • ↑ anti-tumor effects • ↓ triple-negative breast cancer growth	Li et al.[117]

(*Continued on next page*)

Table 4. *Continued*

Application	Exosome membrane source	Inner core	Drug(s)	Coating method	Size/zeta potential	*In vivo* mouse model	Outcomes	Reference
	urinary exosome membrane (isolated from the urine of breast cancer patients)	poly(2-ethyl-2-oxazoline)-poly (D,L-lactide) (PEOz-PLA) NP	doxorubicin	co-extrusion through porous membranes	61.5 nm – 15.0 mV	orthotropic MCF-7 tumor-bearing mouse model	• ↓ macrophage-mediated phagocytosis (immune evasion) • ↑ systemic circulation time • homotypic tumor-targeting ability • ↑ anti-tumor efficacy • ↓ tumor growth *in vivo* (inhibition rate of 87.6%)	Ni et al.[118]
Protein delivery	human breast adenocarcinoma MDA-MB-231 cell-derived exosome membrane	ZIF-8 MOF NP	therapeutic proteins (gelonin)	sonication and extrusion	–	orthotopic MDA-MB-231 tumor-bearing mouse model	• 97% coating efficiency • protection from protease degradation • ↑ immune evasion ability • ↑ systemic circulation time • homotypic tumor-targeting ability • specific uptake by tumor cells • ↑ transduction efficiency of protein gelonin • 14-fold increase in anti-tumor efficacy	Cheng et al.[119]
Gene delivery and silencing	PC-3 prostate cancer cell-derived exosome membrane	spherical nucleic acids (SNAs)	anti-miR-21	direct incubation of target cells with NPs (exosome biogenesis pathway)	–	–	• < 1% of SNAs were sorted in exosomes by leveraging exosomal biogenesis pathway • downregulation of miRNA-21 expression with a knockdown efficiency of 50%	Alhasan et al.[120]
	natural killer cell-derived exosome membrane	tyrosine-coupled dendrimers	Let-7-a miRNA	incubation of purified exosomes with tyrosine-coupled dendrimers (24 h, 4°C)	–	neuroblastoma CHLA-255 tumor-bearing mouse model	• tumor-targeting ability • ↑ accumulation at tumor sites *in vivo* and *in vitro* • efficient delivery of Let-7-a miRNA to target tumor cells • synergistic anti-tumor effects of the therapeutic Let-7-a miRNA and natural killer cell-derived exosomes • ↓ tumor growth	Wang et al.[121]
Anti-metastatic therapy	murine RAW 264.7 cell-derived exosome membrane	laurate-functionalized platinum (Pt (IV) prodrug human serum albumin (HSA) NP	Pt (IV)	sonication	128.6 nm – 13.28 mV	Balb 4T1tumor-bearing mouse model with lung metastasis	• ↑ systemic circulation time • ↑ biocompatibility • ↑ accumulation in both orthotopic breast tumors and lung metastatic nodules • efficient anti-tumor and anti-metastatic effects • ↓ hepatotoxicity and nephrotoxicity	Xiong et al.[122]
	autologous breast cancer cell-derived exosome membrane	cationic bovine serum albumin NP	S100A4 siRNA (siS100A4)	co-extrusion through 200 and 100 nm porous membranes (100 times)	263.71 nm – 28.63 mV	postoperative lung metastasis mouse model	• efficient delivery of siS100A4 to pre-metastatic niches in the lungs • downregulation of S100A4 metastasis-related protein expression • gene-silencing effects • ↓ postoperative breast cancer lung metastasis	Zhao et al.[123]

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Table 4. *Continued*

Application	Exosome membrane source	Inner core	Drug(s)	Coating method	Size/zeta potential	*In vivo* mouse model	Outcomes	Reference
	human breast adenocarcinoma MDA-MB-231 cell-derived exosome membrane	PEGylated-poly (ε-caprolactone) NP	paclitaxel-linoleic acid prodrug and cucurbitacin B	co-extrusion through 220 nm porous membranes	–	orthotopic and xenograft MDA-MB-231 tumor-bearing mouse model	• ↑ immune evasion ability • ↑ systemic circulation time • homotypic targeting ability • efficient anti-tumor effects and tumor growth inhibition • ↑ circulating tumor cells capture ability and cancer metastasis suppression • ↓ number of metastatic nodules in the lungs	Wang et al.[124]
Photothermal therapy	4T1 breast cancer cell-derived exosome membrane	mesoporous silica NP (MSN)	indocyanine green and doxorubicin	co-extrusion through porous membranes	−28.9 mV	4T1 tumor-bearing mouse model	• homotypic tumor-targeting ability • selective accumulation at homotypic 4T1 tumor sites • effective near-infrared (NIR) light absorbance and targeted photothermal effects • synergistic anti-tumor effects of chemotherapy and PTT	Tian et al.[125]
	B16-F10 murine melanoma cell-derived exosome membrane	PEGylated-hollow AuNP (PEG-HGN)	–	direct incubation of target cells with PEG-HGNs (exosome biogenesis pathway)	–	–	• ↑ encapsulation efficiency (50%) by taking advantage of exosome biogenesis pathway • selective accumulation at homotypic B16-F10 cells • strong absorbance at NIR region • ↑ PTT efficiency *in vitro*	Sancho-Albero et al.[126]
Photodynamic therapy	U87 glioblastoma cell-derived exosome membrane	hollow zinc sulfide (ZnS) NP	hydroxy-chloroquine	co-extrusion through 200 nm porous membranes	99.0 nm – 15.0 mV	intracranial Luc-U87 glioblastoma-bearing mouse model	• homotypic tumor-targeting ability • ↓ autophagic activity • synergistic anti-tumor effects • ↑ anti-tumor efficiency of photodynamic therapy (PDT) • ↓ tumor growth • ↑ survival time of mice with glioblastoma (up to 73 days)	Mo et al.[127]
Chemodynamic therapy	urinary exosome membrane (isolated from the urine of prostate cancer patients)	Fe_3O_4-HSA NP	doxorubicin	electroporation (250 V)	89.0 nm – 25.9 mV	DU145 tumor-bearing BALB/C nude mouse model	• homotypic tumor-targeting ability • ↑ uptake by prostate cancer cells • synergistic chemo/chemodynamic effects and inhibition of EGFR/AKT/NF-κB IkB pathway • ↓ tumor growth	Pan et al.[40]
Radiotherapy (boron neutron capture therapy)	macrophage-derived exosome membrane	carbon dots	nonradioactive isotope boron-10 (^{10}B)	incubation of purified exosomes with ^{10}B boron-containing carbon dots (37°C, 2 h)	96.9 nm – 15.1 mV	orthotopic U-87-MG glioma tumor-bearing mouse model	• ↑ ability to cross the blood-brain barrier • selective accumulation at glioma tumor cells *in vivo* • ↓ tumor growth • ↑ survival time of glioma-bearing mice (100% at day 30)	Li et al.[128]

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Table 4. *Continued*

Application	Exosome membrane source	Inner core	Drug(s)	Coating method	Size/zeta potential	*In vivo* mouse model	Outcomes	Reference
Immunotherapy	bEnd.3 cell-derived exosome membrane	PEGylated-poly-lactic acid NP	doxorubicin	co-extrusion through 100 nm porous membranes	–	orthotopic glioblastoma xenograft-bearing mouse model	• ↑ accumulation in homotypic bEnd.3 cells *in vivo* and *in vitro* • maturation of dendritic cells and infiltration of cytotoxic $CD8^+$ T lymphocytes in tumor tissues • immunogenic chemotherapy of glioblastoma • ↓ tumor growth • ↑ survival time of glioblastoma-bearing mice	Zhang et al.[129]
	exosome membranes derived from hyperthermia-treated tumor-bearing mice	black phosphorus quantum dots	–	sonication	–	subcutaneous lung tumor-bearing B6 mouse model	• ↑ accumulation at tumor tissues • synergistic anti-tumor effects of PTT and immunotherapy • ↑ PTT efficiency upon NIR irradiation • maturation of dendritic cells and infiltration of cytotoxic $CD8^+$ T lymphocytes in tumor tissues • ↑ survival of tumor-bearing mice	Liu et al.[130]

↑ indicates enhancement; ↓ indicates reduction.

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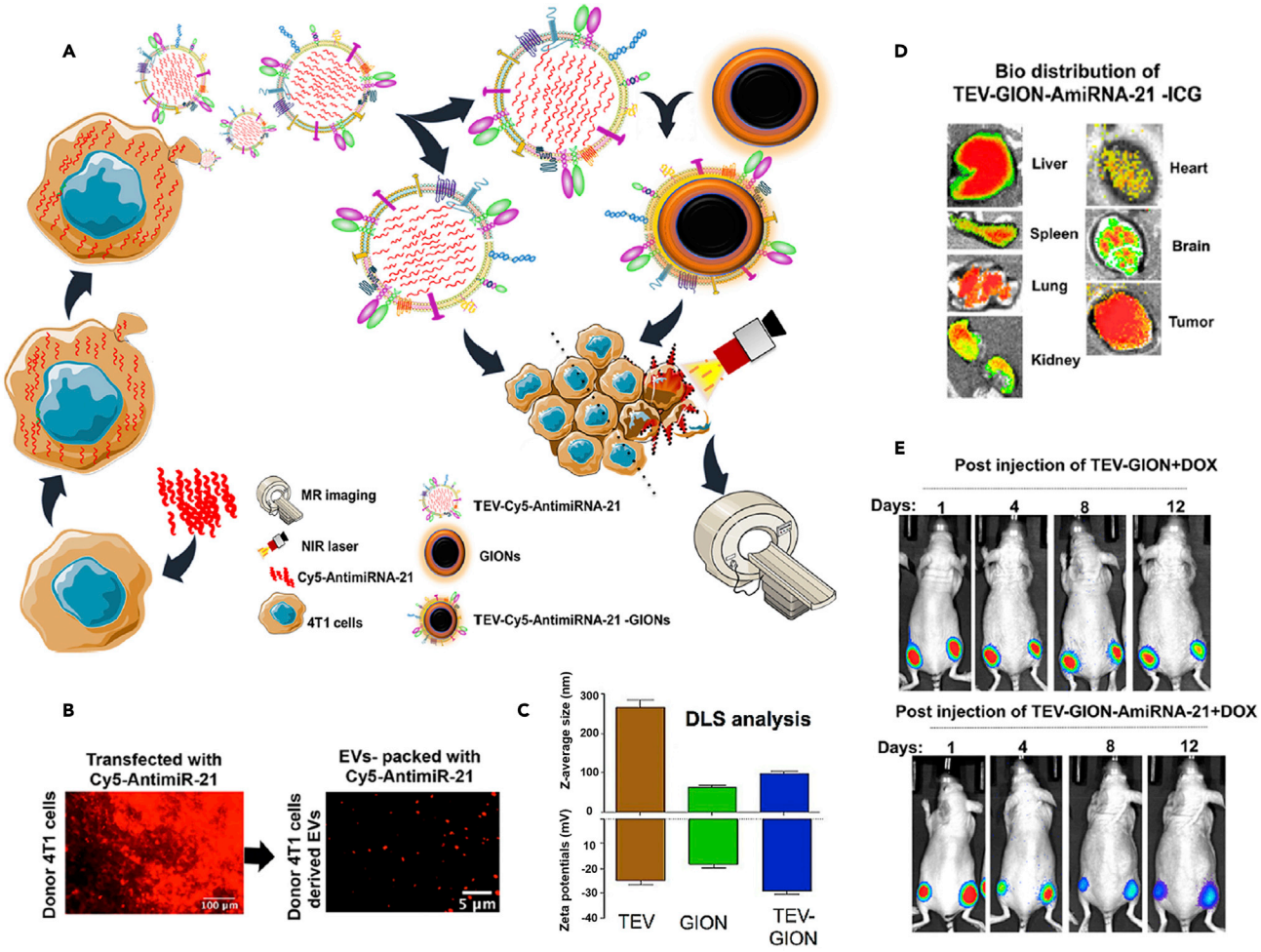

Figure 5. Exosome-coated nanoparticles for photothermal ablation of tumor cells and MRI imaging

(A) Preparation of TEV-GION-anti-miR-21 for tumor-targeted delivery of anti-miR-21, photothermal ablation of tumor cells, and MRI imaging.

(B) Anti-miR-21 transfection into donor 4T1 cells.

(C) Zeta potential (surface charge) and size analysis of the biomimetic nanosystem by dynamic light scattering.

(D) Biodistribution of TEV-GION-anti-miR-21 in major organs, indicating their accumulation in tumor tissue.

(E) Comparative analysis of tumor growth in mice treated with TEV-GION + DOX (up) or TEV-GION-anti-miR-21 + DOX (down).

Reproduced with permission from Bose et al.[113] Copyright American Chemical Society (2018). Anti-miR-21, anti-sense miRNA targeting miRNA-21; DLS, dynamic light scattering; DOX, doxorubicin; GION, gold-iron oxide nanoparticle; MRI, magnetic resonance imaging; NIR, near-infrared; TEV, tumor cell-derived extracellular vesicle; TEV-GION-anti-miR-21, GION coated with the membrane of anti-miR-21 loaded TEV; TEV-GION, extracellular vesicle membrane-coated GION.

and MRI of cancer.[113] The anti-miR-21-loaded exosomes were generated by direct transfection of 4T1 cells with anti-miR-21. The exosome membranes of anti-miR-21-loaded exosomes were employed to coat the Au-iron oxide NPs (Figures 5A–5C). The multifunctional system showed efficient photothermal effects upon NIR radiation *in vitro* and demonstrated promising results as an MRI contrasting agent. These properties were attributed to the Au-iron oxide core. These NPs specifically targeted and accumulated within homotypic 4T1 tumor cells *in vivo*. This enabled targeted delivery of anti-miR-21 to the tumor sites, with efficient anti-tumor effects when combined with doxorubicin (Figure 5D). The co-delivery of anti-miR-21 and doxorubicin reduced chemotherapy resistance in breast cancer cells, resulting in excellent anti-tumor efficacy and suppression of tumor growth. The use of anti-miR-21 silenced the expression of the oncogene miR-21 (Figure 5E). This study

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provides a multifunctional theranostic nanoplatform that incorporates both imaging and photothermal agents for simultaneous tumor imaging, photothermal ablation of tumor cells, and chemo-sensitization of anti-miR-21.[113]

Delivery of chemotherapeutics

Chemotherapy is one of the most extensively used therapeutic measures for cancer eradication. However, the clinical outcome of this strategy is limited because of the low tumor specificity of chemotherapeutics. This results in severe side effects and off-target toxicity in healthy cells.[5,34,111,134,135] Encapsulation of NPs with exosome membranes has been used to circumvent the limitations of chemotherapy via targeted delivery of chemotherapeutics to specific tumor sites. This markedly reduces the side effects and off-target toxicity of chemotherapy in healthy cells and increases therapeutic efficacy and safety.

Cancer-cell-derived exosomes are the most frequently used exosomes for coating NPs. Exosomes derived from cancer cells can maintain the surface antigens from their progenitor cells. Thus, they are used as effective NP coatings to target homologous cancer cells.[15,136]

Cancer-cell-derived exosome membrane-coated NPs have been developed for targeted delivery of chemotherapeutics to tumor sites without damaging the protein integrity of the exosome membrane.[114] Luminescent porous silicon NPs (PSiNPs) containing doxorubicin (DOX@PSiNPs) were camouflaged with exosome membranes derived from different cancer cell lines.[114] The exosomes were secreted by the cancer cells by exocytosis via the exosome biogenesis pathway and used to generate exosome membrane-coated DOX@E-PSiNPs for delivering doxorubicin, a chemotherapeutic agent. After intravenous injection in subcutaneous, orthotopic, and metastatic tumor-bearing mice models, the DOX@E-PSiNPs showed better extravasation as well as enhanced accumulation and penetration into tumor tissues. The DOX@E-PSiNPs were efficiently internalized by both cancer cells and cancer stem cells (CSCs). The CSCs are a small population of cells responsible for cancer proliferation and metastasis (Figure 6A). The biomimetic nanosystem showed efficient anti-tumor and CSC-killing activities *in vivo*, suppressing tumor growth in the subcutaneous, orthotopic, and metastatic tumor-bearing mice models (Figures 6B–6D). The DOX@E-PSiNPs also demonstrated cross-reactivity among different cancer cell types; those coated with H22 cancer-cell-derived exosome membranes demonstrated increased uptake in B16-F10 cancer cells and vice versa. This study provided an innovative coating technique based on exocytosis from tumor cells to synthesize exosome membrane-coated NPs. The nanocarriers delivered anti-cancer drugs to tumor sites without damaging the surface protein integrity of the exosome membranes.[114]

Metal-organic framework (MOF) MIL-88A NPs are desirable drug nanocarriers because of their optimal biocompatibility, controlled drug release capability, and high loading efficacy. The MIL-88A NPs were camouflaged with exosome membrane derived from HeLa cells for targeted delivery of suberoyl bis-hydroxamic acid, a histone inhibitor, and chemotherapeutic drug to homotypic HeLa cells.[115,137] The exosome membrane-coated MIL-88A NPs were selectively taken up by homotypic HeLa cells *in vitro* because of the homotypic tumor-targeting ability of the exosome membrane coating. This enabled targeted delivery of the chemotherapeutic without premature leakage of the therapeutic payload. This is a promising strategy for markedly reducing chemotherapy side effects and off-target toxicity.[115]

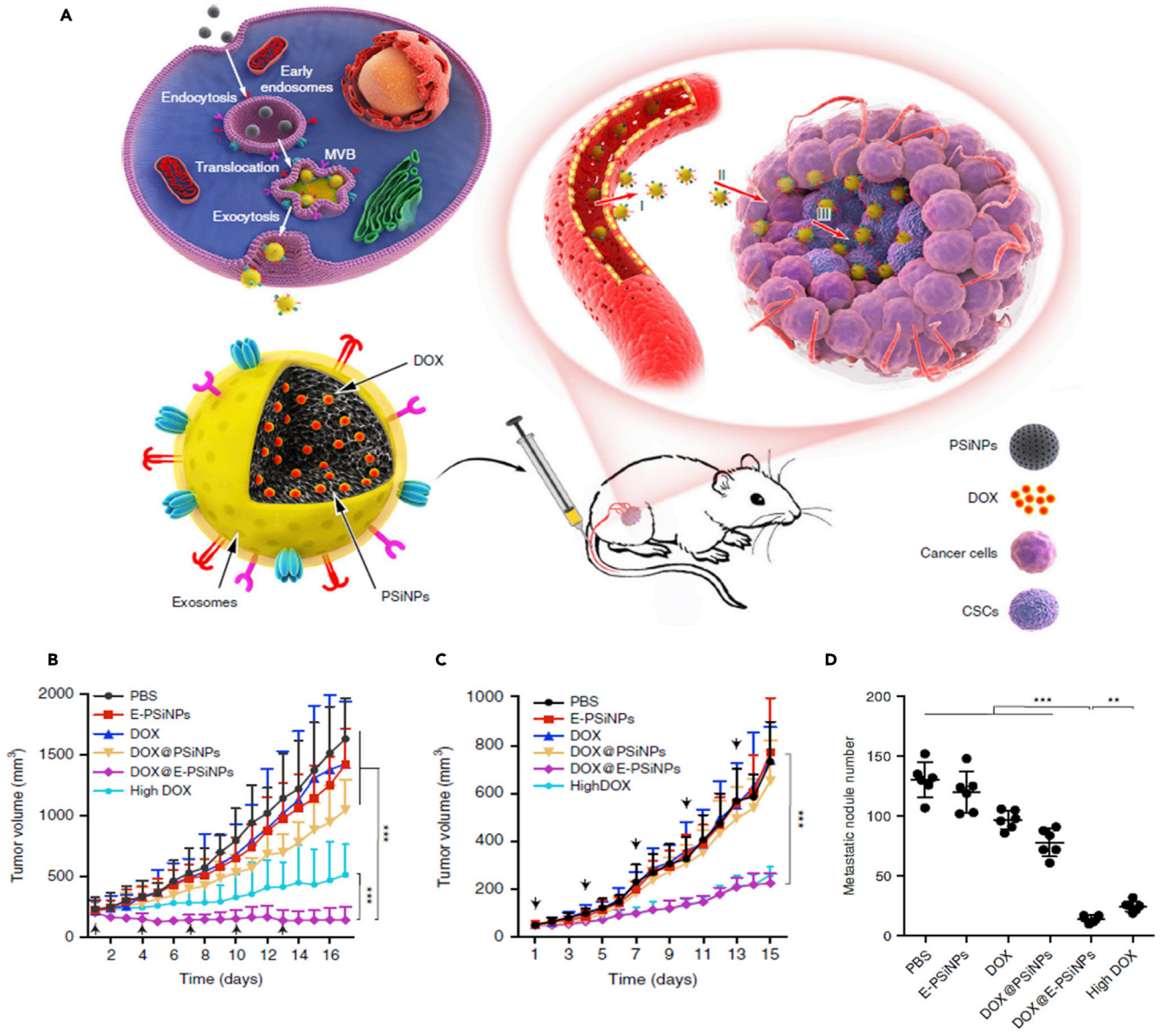

Figure 6. Exosome-coated nanoparticles for drug delivery

(A) Preparation of DOX@E-PSiNPs by coating DOX@PSiNPs with exosome membranes derived from different cancer cell lines by exocytosis from tumor cells.

(B) Tumor growth curves of H22 tumor-bearing mice after intravenous injection with different treatments.

(C) Tumor growth curves of 4T1 tumor-bearing mice after intravenous injection with different treatments.

(D) Number of metastatic lung nodules of B16-F10 tumor-bearing mice after intravenous injection with different treatments.

Reproduced with permission from Yong et al.[114] Copyright Springer Nature (2019). CSCs, cancer stem cells; DOX, doxorubicin; DOX@E-PSiNPs, exosome membrane-coated DOX@PSiNPs; DOX@PSiNPs, DOX-loaded PSiNPs; MVB, multivesicular body; PSiNPs, luminescent porous silicon nanoparticles.

In another study, Doxil, a chemotherapeutic drug that encapsulates doxorubicin within liposomes, was camouflaged with exosome membranes derived from HT1080 tumor cells.[116] These camouflaged NPs effectively delivered doxorubicin to HT1080 tumors *in vivo* to inhibit tumor growth. The HT1080 cell-derived exosomes homed to their source cells more efficiently *in vivo* than HeLa cell-derived exosomes, with enhanced accumulation in homotypic HT1080 tumor cells. These results indicate the innate tropism of HT1080 cell-derived exosomes to accumulate in

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homotypic HT1080 tumor cells. Doxil encapsulation in exosomes induced significantly less doxorubicin-induced cardiotoxicity compared with free Doxil. This is likely to be the result of increased accumulation of doxorubicin in the tumor cells and reduced accumulation in the heart.[116]

Apart from using cancer cell-derived exosome membranes for coating NPs, exosome membranes derived from non-cancerous cells have also been used experimentally for tumor-targeted delivery of chemotherapeutics.[117] For example, doxorubicin-loaded PLGA NPs were coated with exosome membranes derived from macrophages for targeted delivery of doxorubicin to triple-negative breast cancer (TNBC) cells, an aggressive subtype of breast cancer known for its high proliferation rate and poor overall survival.[117] To further enhance tumor targeting, a c-Met targeting peptide was decorated on the surface of the exosome membrane-coated PLGA NPs to increase their ability to target mesenchymal epithelial transition factor (c-Met), which is highly expressed by TNBC cells. The exosome membrane-coated PLGA NPs had superior accumulation at targeted tumor sites *in vivo*. The pH-sensitive doxorubicin was released under the acidic conditions of the lysosomes.[117] The exosome membrane-coated doxorubicin-loaded PLGA NPs decorated with c-Met binding peptide demonstrated immune evasion capability, prolonged systemic circulation, and enhanced tumor targeting. This resulted in superior anti-tumor efficacy and greater suppression of tumor growth *in vivo*. No pathological manifestations were observed in the major organs, confirming the biocompatibility and safety of this biomimetic nanosystem.[117]

For the design of exosome-mimicking NPs, cell-secreted exosomes are usually isolated from *in vitro* cell culture supernatants. However, the production yield of exosomes by most cells is often very low and considered insufficient for therapeutic applications.[118] Thus, urinary exosomes have been studied as a non-invasive alternative exosomeś source for NP coatings. Patients' own urinary exosomes can improve therapeutic efficacy and safety by inducing less immunogenicity, providing a highly individualized nanomedicine.[118] Inspired by this, the membranes of urinary exosomes (isolated from the urine of breast cancer patients) were recently employed to coat doxorubicin-loaded poly(2-ethyl-2-oxazoline)-poly(D,L-lactide) (PEOz-PLA) NPs (PP-D NPs) for targeted delivery of chemotherapeutics to breast cancer cells (Figures 7A and 7B).[118] CD47-surface expressed exosome membrane-coated PP-D NPs (UEPP-D NPs) could efficiently avoid macrophage-mediated phagocytosis, exhibiting prolonged blood circulation *in vivo* (Figure 7C). Besides, pronounced accumulation at homotypic MCF-7 breast tumors was observed after intravenous injection (Figure 7D), markedly improving the tumor growth inhibitory effects of doxorubicin. Superior anti-tumor efficacy and greater suppression of tumor growth *in vivo* were observed with these urinary exosome membrane-mimicking NPs (Figures 7E and 7F).[118]

Protein delivery

Intracellular delivery of therapeutic proteins via systemic administration is challenging because of the susceptibility of proteins to degradation and denaturing *in vivo* and their low transduction efficiency.[119] These limitations, in turn, compromise the therapeutic efficacy of those protein molecules. Exosome membrane-coated NPs have been employed to protect the loaded proteins from degradation by proteases *in vivo*, avoid phagocytic clearance, and selectively target homotypic tumor sites. Such a strategy increases cell-specific uptake and enhances intracellular protein delivery.[119]

A protein-loaded ZIF-8 MOF inner core (MP) was camouflaged with an exosome membrane derived from MDA-MB-231 cells for intracellular delivery of functional

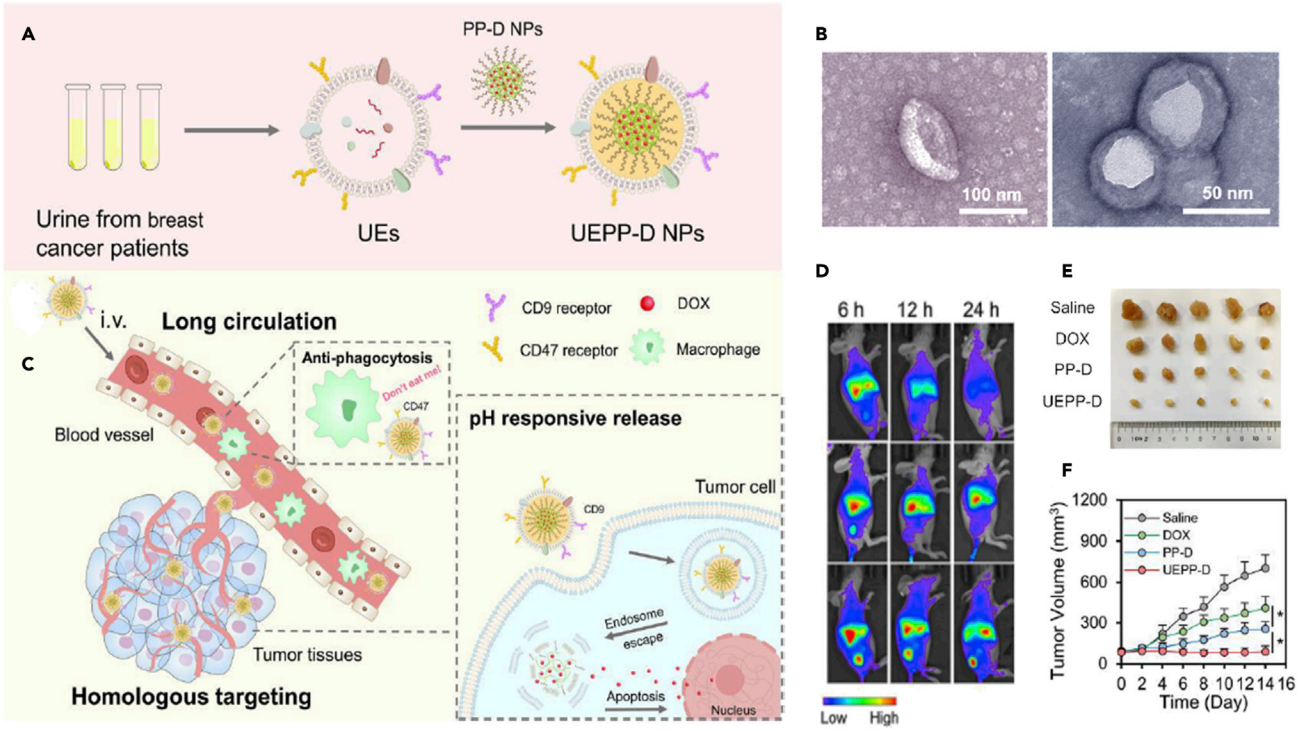

Figure 7. Preparation of UEPP-D NPs by coating PP-D NPs with the patients own urinary exosome membranes (isolated from the urine of breast cancer patients)

(A) Fabrication and mechanism of UEPP-D NPs by coating PP-D NPs.

(B) TEM images of urinary exosomes (left) and UEPP-D NPs (right, in which a core-shell nanostructure can be seen).

(C) Depicting of the immune evasion, prolonged systemic circulation, homologous tumor-targeting and pH-responsive release features of UEPP-D NPs *in vivo*.

(D) Distribution of free DiR (upper), PP-DiR NPs (middle), and UEPP-DiR NPs (lower) 6, 12, and 24 h after administration.

(E) Photographs of MCF-7 breast tumors after different treatments.

(F) Tumor volume changes of MCF-7 tumor-bearing mice receiving different treatments.

Reproduced with permission from Ni et al.[118] Copyright MDPI AG (2022). DOX, doxorubicin; NP, nanoparticle; PP-D NPs, doxorubicin-loaded poly(2-ethyl-2-oxazoline)-poly(D,L-lactide) (PEOz-PLA) NPs; TEM, transmission electron microscopy; UE, urinary exosome; UEPP-D NPs, urinary exosome membrane-coated PP-D NPs.

proteins to human breast adenocarcinoma MDA-MB-231 cells (Figure 8A).[119] The exosome membrane-coated MP (EMP) possessed immune evasion capability and prolonged systemic circulation. The EMPs also protected the loaded proteins from degradation by protease *in vivo*. The therapeutic cargoes were only released in the acidic conditions of the tumor microenvironment. Because of their homotypic tumor-targeting ability, the EMPs were preferentially taken up by homologous MDA-MB-231 cells. This finding confirms the intrinsic ability of tumor cell-derived exosomes to target homotypic tumor cells from which the exosomes were derived (Figures 8B and 8C). Compared with uncoated NPs, there was augmented accumulation of the EMPs at tumor sites *in vivo*. This resulted in improved transduction efficiency of gelonin, a protein that induces cell apoptosis by disturbing protein synthesis. The EMPs exhibited superior anti-tumor efficacy (Figures 8D–8F).[119]

Gene delivery and gene silencing

Gene therapy delivers therapeutic nucleic acids (mRNA, miRNA, and siRNA) to target tumor cells to correct abnormal gene expression and suppress tumor growth.[138–140] Because of the intrinsic ability of exosomes to transport nucleic acids between neighboring cells, exosome membrane-coated NPs are promising gene

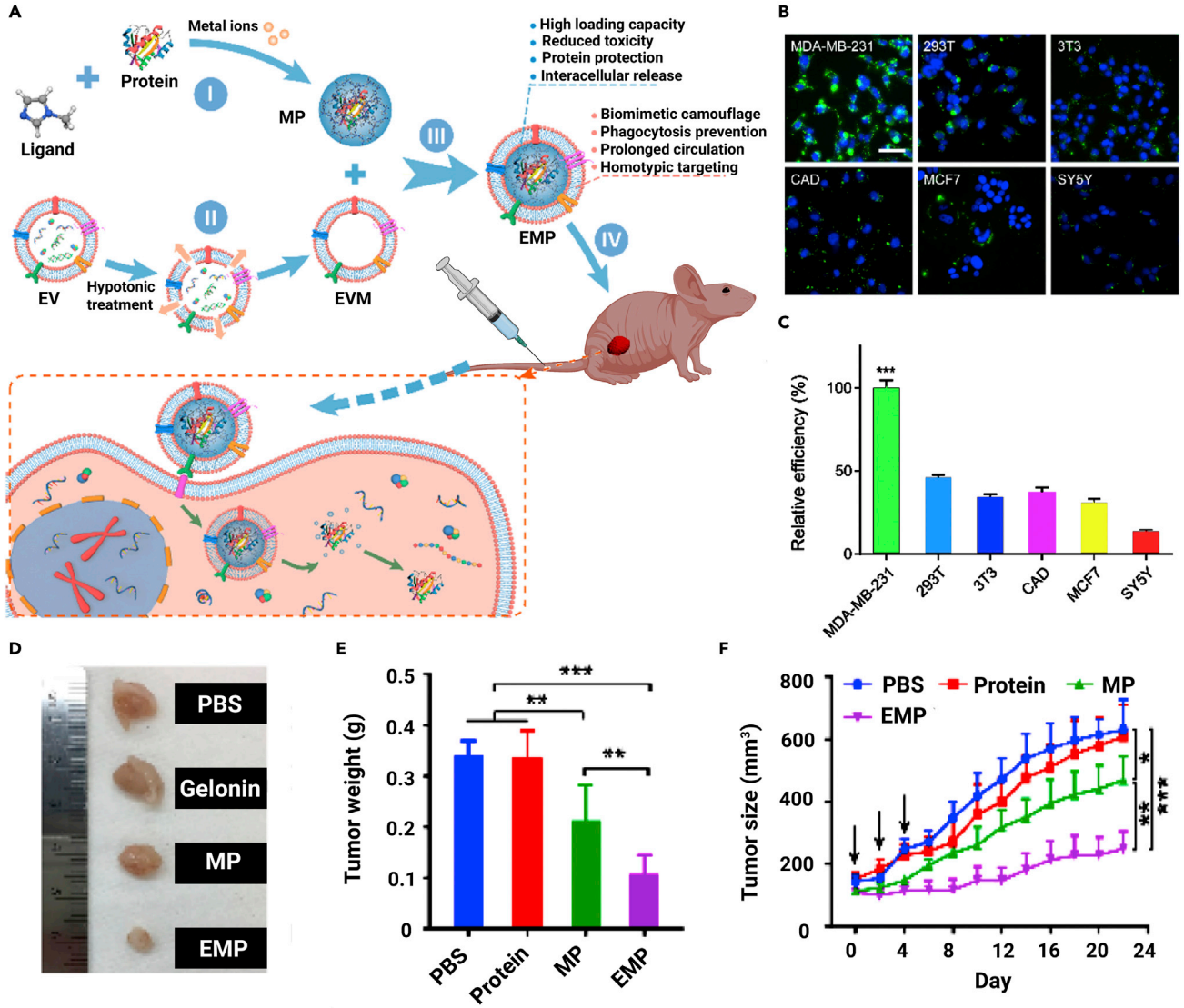

Figure 8. Exosome-coated materials for intracellular delivery of functional proteins

(A) Preparation of EMP by coating MP with exosome membranes derived from human breast adenocarcinoma MDA-MB-231 cells.

(B and C) Cellular uptake of EMP in MDA-MB-231 cells, 293T human embryonic kidney cells, 3T3 mouse embryo fibroblasts, CAD mouse central nervous system-derived cells, MCF7 human breast adenocarcinoma cells, and SH-SY5Y human neuroblastoma cells.

(D) Photographs of MDA-MB-231 breast tumors after different treatments.

(E) Tumor weight changes after intravenous injection of MDA-MB-231 tumor-bearing mice with different treatments.

(F) Tumor size curves after intravenous injection of MDA-MB-231 tumor-bearing mice with different treatments.

Reproduced with permission from Cheng et al.[119] Copyright American Chemical Society (2018). EMP, exosome membrane-coated MP; EV, extracellular vesicle; MP, protein-loaded metal-organic framework nanoparticle.

delivery vehicles for the targeted delivery of therapeutic nucleic acids to tumor sites.[132]

Spherical nucleic acids (SNAs) consist of a gold core and a dense shell of oriented oligonucleotides.[120] The SNAs were loaded with anti-miR-21, and subsequently coated with exosome membranes derived from PC-3 prostate cancer cells using the exosome biogenesis pathway.[120] The exosome membrane-coated loaded SNAs efficiently delivered the anti-miR-21 to PC-3 prostate cancer cells, resulting

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in significant downregulation of oncogenic miR-21 expression. The miR-21 is significantly overexpressed in tumor tissues and is involved in cancer proliferation and metastasis.[120]

Exosomes secreted by specific types of cells may exhibit direct anti-tumor properties.[16] Natural killer cells release exosomes that are capable of accumulating at specific tumor sites to exert potent anti-tumor activity. This is attributed to the presence of killer proteins, such as FAS ligand, granzymes, and perforin on the exosomes surface.[17,141] Natural killer cell-derived exosomes have potential use in cancer therapy because they can improve tumor targeting by guiding therapeutics to specific tumor sites. These exosomes also behave as direct anti-tumor agents because of their natural anti-tumor properties.[121]

Inspired by the aforementioned concept, a biomimetic core-shell nanosystem was developed by loading tyrosine-coupled dendrimers with therapeutic Let-7a miRNA. The loaded dendrimers were coated with natural killer cell-derived exosome membranes.[121] The exosomes were isolated from natural killer cell culture supernatants by differential centrifugation. The tumor-targeting capability of the natural killer cell-derived exosome membrane coating is due to specific binding of the C-X-C chemokine receptor type 4 (CXCR4) expressed on natural killer cell-derived exosomes to stromal cell-derived factor-1 released by the tumor cells. The CXCR4 is a chemokine receptor involved in leukocyte trafficking. The assembly accumulated specifically at tumor sites, enabling the targeted delivery of the therapeutic Let-7a miRNA to neuroblastoma CHLA-255 cells. The exosome membrane-coated, loaded dendrimers demonstrated superior anti-tumor effects and suppressed tumor growth *in vitro* and *in vivo*. These favorable experimental outcomes were attributed to the synergistic anti-tumor effects of the Let-7a miRNA and the intrinsic anti-tumor properties of natural killer cell-derived exosomes.[121]

Anti-metastatic therapy

Apart from targeting primary tumor sites, exosome membrane-coated core-shell NPs are also capable of targeting metastatic tumor sites to suppress metastatic tumors.[17] Inspired by the ability of macrophages to be efficiently recruited to inflamed/tumor sites, a biomimetic core-shell structure was developed by constructing a human serum albumin (HSA) core consisting of a laurate-functionalized platinum (Pt (IV)) prodrug (Pt (IV) HSA NPs). The core was coated with exosome membrane derived from murine RAW264.1 cells (Rex) to generate Rex-coated Pt (IV) HSA NPs (NPs/Rex).[122] The assembly was used for targeted delivery of Pt (IV) to orthotopic breast tumors and lung metastatic nodules (Figures 9A and 9B). After internalization of the assemblies by tumor cells, Pt (IV) was reduced to cisplatin, a well-known chemotherapeutic agent that causes DNA damage and induces death of the breast cancer cells by triggering apoptotic signals. After intravenous injection in a tumor-bearing mouse model, the NPs/Rex exhibited longer systemic circulation and enhanced biocompatibility. The NPs/Rex were specifically recruited to orthotopic breast tumors and metastatic lung nodules, with remarkable anti-tumor and anti-metastatic effects *in vivo* (Figures 9C–9F). Because the NPs/Rex were preferentially taken up by orthotopic breast tumors and metastatic lung nodules, they were taken up to a lesser extent by the liver and kidneys. This resulted in considerably less hepatotoxicity and nephrotoxicity, which are common side effects of free cisplatin.[122]

The high incidence of lung metastasis of TNBC after surgery is the most significant cause of death related to breast cancer.[123] To suppress post-surgical lung

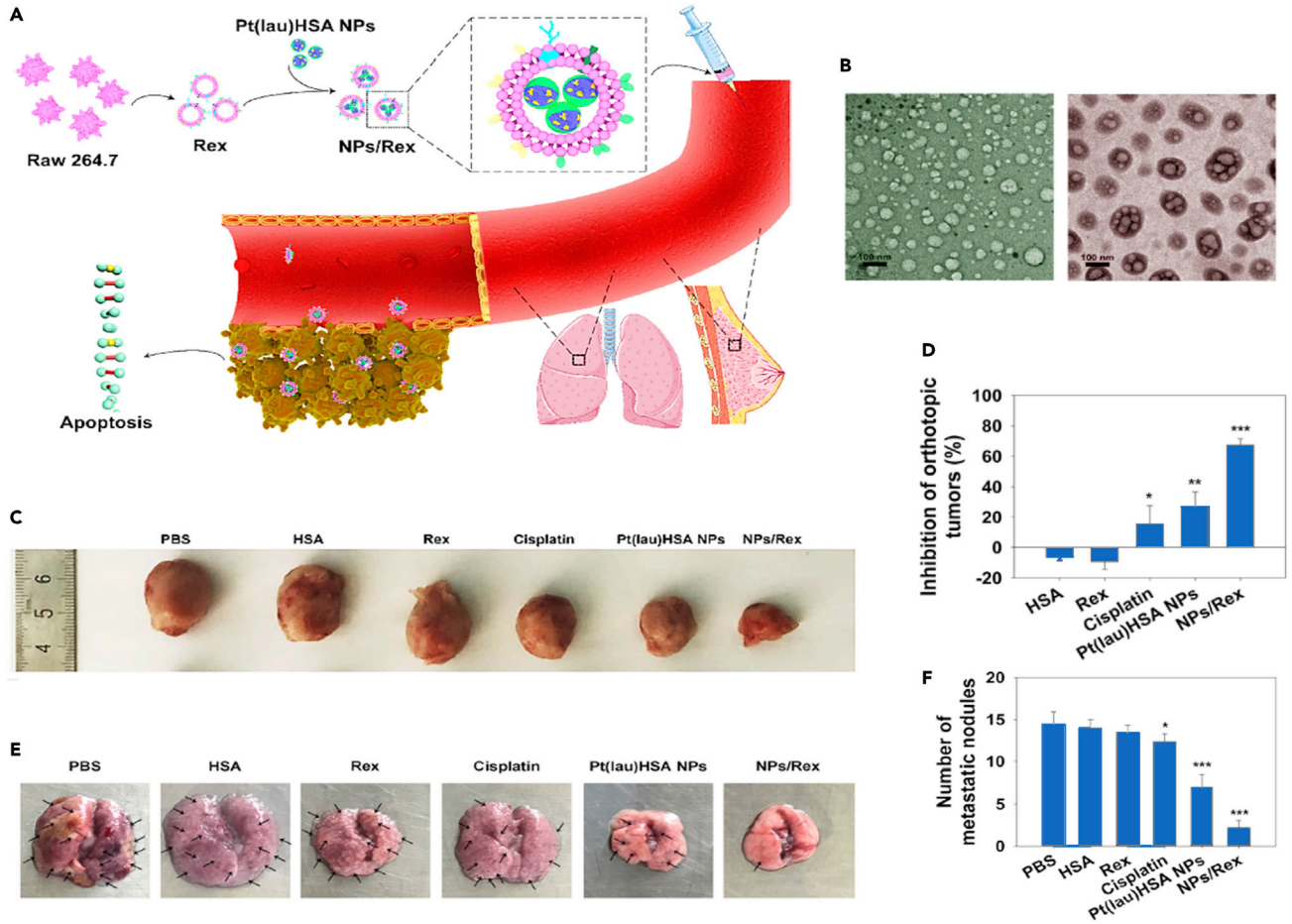

Figure 9. Application of exosome-coated nanoparticles in cancer therapy

(A) Preparation of NPs/Rex by coating Pt (IV) HSA NPs with exosome membranes derived from Raw 264.7 cells for targeted delivery of Pt (IV) to orthotopic breast tumors and lung metastatic nodules.

(B) TEM imaging of Pt (IV) HSA NPs (left) and NPs/Rex (right).

(C) Photographs of orthotopic tumors after different treatments.

(D) Inhibition rate of 4T1 orthotopic tumors after different treatments.

(E) Photographs of lung tissues with visible metastatic nodules after different treatments (black arrows indicate metastatic lungs nodules).

(F) Number of metastatic lung nodules after different treatments.

Reproduced with permission from Xiong et al.[122] Copyright American Chemical Society (2019). HSA, human serum albumin; NPs/Rex, Rex-coated Pt (IV) HSA NPs; Pt (IV) HSA NP, HSA inner core composed of a laurate-functionalized platinum (Pt (IV)) prodrug; Rex, exosomes derived from murine RAW264.1 cells; TEM, transmission electron microscopy.

metastasis through modulation of the lung pre-metastatic niche microenvironment, a biomimetic core-shell nanoplatform was designed by coating a cationic bovine serum albumin core conjugated with S100A4 siRNA (siS100A4), with an exosome membrane derived from autologous breast cancer cells.[123] The assemblies exhibited superior biocompatibility and efficiently protected the loaded siS100A4 from degradation. This helped to improve the delivery efficacy of the therapeutic siS100A4 to pre-metastatic niches in the lungs. This targeted gene-silencing approach resulted in efficient suppression of postoperative breast cancer lung metastasis by downregulating the expression of the S100A4 metastasis-related protein.[123]

Cancer metastasis is dependent on the activity of circulating tumor cells (CTCs). These cells play a critical role in tumor genesis, development, progression, and

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metastasis. The CTCs travel and invade distant tissues. For effective prevention of the development of metastatic nodules, the CTCs in blood have to be successfully identified and captured to prevent them from spreading and colonizing distant tissues.[142]

To date, the efficacy of anti-metastatic therapy is unsatisfactory. This is mainly attributed to the difficulty in recognizing and capturing CTCs from the blood of the affected subject.[124] To address this challenge, a biomimetic nanoplatform was developed for breast cancer metastasis inhibition by preparing PEGylated-PCL NPs that were co-loaded with reactive oxygen species (ROS)-sensitive, thioether-linked, paclitaxel-linoleic acid prodrug, and cucurbitacin B (named PCNPs).[124] The PCNPs were coated with exosome membranes derived from human breast adenocarcinoma MDA-MB-231 cells. Adhesion molecules such as CD44 are abundantly expressed on both the cancer cell membrane and the surface of the exosome membrane-coated PCNPs. The CD44 is responsible for mediating homotypic cancer binding. The core-shell nanostructure effectively targeted both primary tumor cells and blood circulating CTCs. Cucurbitacin B was released first after cellular internalization. This suppressed tumor metastasis through downregulation of the FAK/MMP signaling pathway and increased the intracellular levels of ROS within tumor cells, which induced the release of paclitaxel from the nanosystem (Figure 10A). The nanoplatform possessed immune evasion ability and prolonged systemic circulation, with enhanced tumor accumulation. This resulted in improved anti-tumor efficacy and greater suppression of tumor growth (Figures 10B and 10C). Due to its ability to recognize and capture blood CTCs through CD44-mediated interaction, anti-metastasis was effectively achieved, with a significant reduction of the metastatic lung nodules (Figures 10D–10F).[124]

Phototherapy

Phototherapy is a non-invasive and effective strategy to selectively destroy cancer cells without damaging healthy cells. This treatment strategy reduces the side effects and increases therapeutic efficacy compared with traditional anti-cancer therapies. Because of its advantages, including non-invasiveness, specific tumor targeting, and low systemic toxicity, this approach has been recognized as a promising strategy for cancer treatment.[143–145]

The major types of phototherapy include photothermal therapy (PTT) and photodynamic therapy (PDT). These are light-activated approaches that require tumor irradiation with external light to destroy cancer cells via thermal ablation and generation of ROS, respectively.[132,146,147]

PTT

In PTT, photothermal agents with light-absorbing properties are delivered to target tumor sites. The photothermal agents are then irradiated with NIR light to produce heat that is capable of destroying cancer cells.[144,148,149] This is possible due to the ability of the photothermal agents to absorb light energy and convert it into cytotoxic heat capable of killing cancer cells through hyperthermia.[143,150] PTT is a promising and minimally invasive modality for cancer therapy because of the lower susceptibility of healthy cells to heat compared with cancer cells.[113]

Exosome membrane-coated NPs have recently been used for PTT. These biomimetic core-shell NPs enhance the delivery efficacy of photothermal agents to targeted tumor sites. The PTT approach may be combined with other anti-cancer approaches such as chemotherapy to produce synergistic anti-cancer effects.[125]

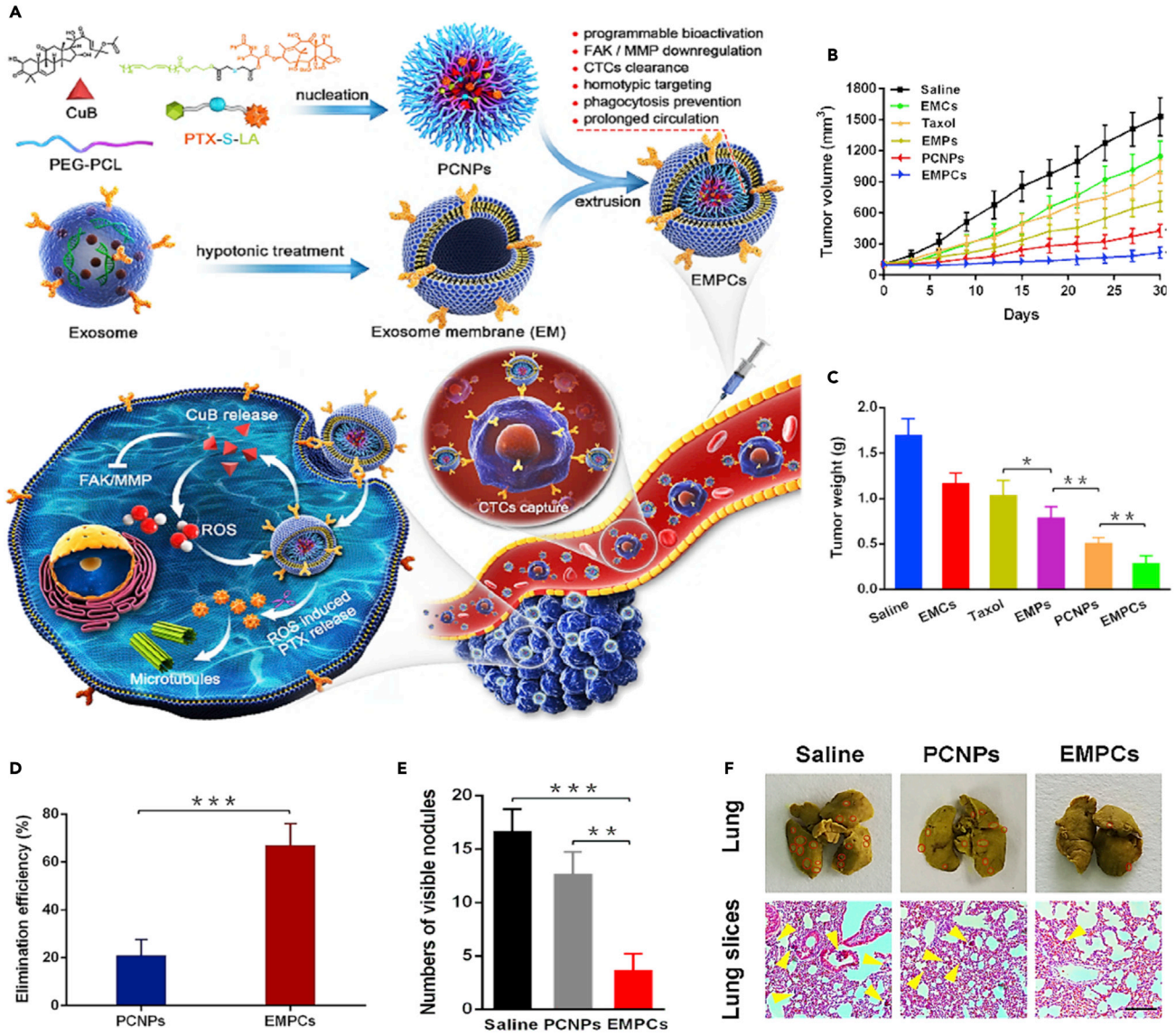

Figure 10. Exosome-coated polymeric nanoparticles

(A) Preparation of EMPCs by coating PCNPs with the exosome membranes derived from human breast adenocarcinoma MDA-MB-231 cells for suppression of breast cancer metastasis.

(B) Tumor volume curves after intravenous injection in orthotopic MDA-MB-231 tumor-bearing mice.

(C) Tumor weight changes after intravenous injection in orthotopic MDA-MB-231 tumor-bearing mice.

(D) CTC elimination efficiency of PCNPs and EMPCs.

(E) Numbers of visible metastatic lung nodules after intravenous injection.

(F) Photographs of mice lungs (top) and hematoxylin and eosin staining of lung slices (down) after different treatments (red circles represent visible metastatic lung nodules).

Reproduced with permission from Wang et al.[124] Copyright Elsevier (2020). CTC, circulating tumor cell; CuB, cucurbitacin B; EMPCs, exosome membrane-coated PCNPs; PCNPs, PEG-PCL nanoparticles co-loaded with CuB and PTX-S-LA; PEG-PCL, PEGylated-poly(ε-caprolactone) nanoparticle; PTX, paclitaxel; PTX-S-LA, paclitaxel-linoleic acid prodrug; ROS, reactive oxygen species.

A combined chemotherapy-PTT approach was used against 4T1 breast cancer cells by co-loading mesoporous silica NPs (MSNs) with indocyanine green and doxorubicin (ID@MSNs). The ID@MSNs were camouflaged with 4T1 breast cancer cell-derived exosome membranes to generate ID@E-MSNs (Figure 11A).[125] After intravenous injection into tumor-bearing mice, the ID@E-MSNs demonstrated

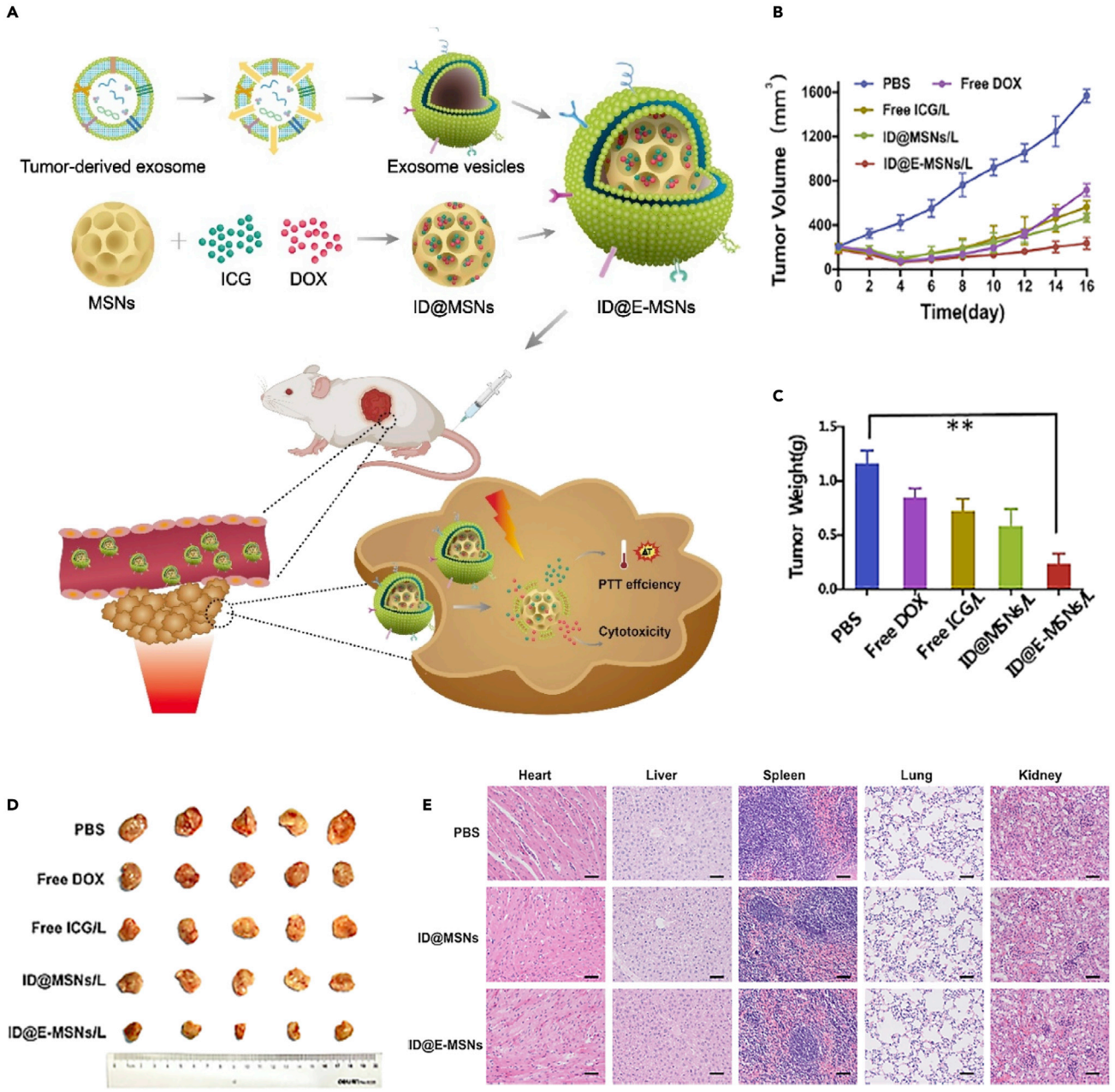

Figure 11. Exosome-coated nanoparticles for combination therapy

(A) Preparation of ID@E-MSNPs by coating ID@MSNPs with exosome membranes derived from 4T1 breast cancer cells for combined chemotherapy-PTT against 4T1 breast cancer cells.

(B) Tumor volume curves after intravenous injection to 4T1 tumor-bearing mice after 16 days of treatment.

(C) Tumor weight changes after intravenous injection of different treatment agents to 4T1 tumor-bearing mice.

(D) Comparative images of 4T1 tumors after different treatments.

(E) Histologic sections from major organs (heart, liver, spleen, lung, and kidney) after different treatments.

Reproduced with permission from Tian et al.[125] Copyright Frontiers Media S.A. (2020). DOX, doxorubicin; ICG, indocyanine green; ID@MSNs, mesoporous silica nanoparticles co-loaded with ICG and DOX; ID@E-MSNs, exosome membrane-coated ID@MSNs; MSNs, mesoporous silica nanoparticles; PTT, photothermal therapy.

enhanced uptake by homotypic 4T1 breast cancer cells, with better accumulation in the tumor tissue and greater suppression of tumor growth *in vivo* (Figures 11B–11D). After NIR irradiation, indocyanine green efficiently converted light into cytotoxic

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heat to produce hyperthermia to kill cancer cells. The hyperthermia also disrupted the ID@E-MSN structure to release doxorubicin for chemotherapy, resulting in synergistic effects. There was no pathological malformation on major organs, confirming the biosafety of this biomimetic nanoplatform (Figure 11E).[125]

Another exosome-mimicking nanosystem for tumor-targeted PTT was fabricated using PEGylated-hollow AuNPs (PEG-HGNs).[126] In this system, the NP core was coated with an exosome membrane derived from B16-F10 murine melanoma cells by direct incubation of PEG-HGNs with tumor cells via the exosome biogenesis pathway. The exosome membrane-coated PEG-HGNs were effectively taken up by homotypic B16-F10 murine melanoma cells *in vitro* and showed promising results as photothermal agents for thermal ablation of cancer cells upon NIR radiation. This was attributed to the ability of the exosome membrane-coated PEG-HGNs to convert the NIR radiation into cytotoxic heat for the thermal damaging of the cancer cells. In addition, the authors utilized the intrinsic reflective optical properties of the exosome membrane-coated PEG-HGNs to monitor their accumulation in tumor tissues and validate the tumor-targeting ability of the multifunctional theranostic nanoplatform.[126]

PDT

PDT is a non-invasive approach that requires photosensitizer agents. These agents are delivered to the tumor sites and activated through irradiation with a specific wavelength of light energy. Laser irradiation is usually employed.[144,151] This causes the photosensitizer agents to transfer energy to the surrounding oxygen molecules to produce a large amount of ROS, particularly singlet oxygen ($^1O_2$). ROS are capable of damaging tumor cells.[143,152,153] Consequently, elevated oxygen levels in the tumor microenvironment are crucial to increase ROS production upon laser irradiation and ensure the efficiency of PDT. The effectiveness of this approach is compromised in hypoxic solid tumors due to the lack of oxygen.[154]

Apart from the oxygen levels within the tumor microenvironment, another barrier that compromises the efficacy of PDT is the high autophagic activity of cancer cells. The augmented autophagic activity causes the cancer cells to eliminate the damaged organelles generated by ROS.[127] To increase the efficacy of PDT against glioblastoma, a strategy based on suppression of the autophagic activity in glioblastoma cells was recently reported. In this strategy, hollow zinc sulfide (ZnS) NPs were loaded with hydroxychloroquine, an autophagic inhibitor drug. The loaded ZnS NPs were coated with U-87 glioblastoma cell-derived exosome membranes and further decorated with iRGD-modified phosphatidylserine.[127] The ZnS NPs functioned as photosensitizers to produce ROS under light irradiation to induce cancer cell damage. The loaded hydroxychloroquine inhibited autophagic flux, resulting in the accumulation of damaged organelles within the cancer cells, thereby increasing the efficiency of PDT. The loaded core-shell assembly crossed the blood-brain barrier effectively and preferentially accumulated in glioblastoma cells *in vivo*. Because of the homotypic glioblastoma cell-targeting ability of the exosome membrane and the ability of the iRGD peptide to target αvβ3 integrins and neuropilin-1 receptors expressed by glioblastoma cells, there was greater suppression of tumor growth and extended survival of the glioblastoma-bearing mice. This study provides an efficient strategy based on the suppression of autophagy within cancer cells to increase the anti-cancer efficacy of PDT.[127]

Chemodynamic therapy

Chemodynamic therapy employs the Fenton reaction to convert hydrogen peroxide (H_2O_2) into cytotoxic hydroxyl radicals (·OH) that are capable of killing cancer cells.[40]

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An experimental chemo/chemodynamic therapeutic approach was recently reported for the treatment of prostate cancer by coating doxorubicin-loaded Fe_3O_4-HSA cores (PMA/Fe-HSA@DOX) with urinary exosome membranes (isolated from the urine of prostate cancer patients), producing exosome membrane-coated PMA/Fe-HSA@DOX (Exo-PMA/Fe-HSA@DOX).[40] A novel electroporation-based coating technique was used to camouflage the NPs with exosome membranes. This technique employed an external electric field to open pores in the exosome membranes through which the NPs can pass. After being internalized by tumor cells, the Fe_3O_4 core decomposed H_2O_2 under the acidic conditions of the tumor microenvironment, producing ·OH to synergistically augment the anti-cancer effect of doxorubicin (Figure 12A). The high intracellular levels of ·OH and doxorubicin within the cancer cells resulted in increased inhibition of epidermal growth factor receptor and its AKT/NF-κB/IkB signaling pathway that is responsible for tumor growth and proliferation. Because of the tumor-targeting ability of the urinary exosome membranes, there was enhanced uptake of the Exo-PMA/Fe-HSA@DOX by prostate cancer cells. This resulted in a more profuse accumulation of the Exo-PMA/Fe-HSA@DOX at the tumor sites. The amplified chemo/chemodynamic effects resulted in efficacious suppression of tumor growth *in vivo* (Figures 12B and 12C).[40]

Radiotherapy

Boron neutron capture therapy (BNCT) is a non-invasive and targeted radiation therapy that is capable of selectively destroying boron-accumulating tumor cells without damaging neighboring healthy tissues. This form of radiotherapy is based on the ability of the nonradioactive isotope boron-10 (^{10}B) to capture thermal neutrons and release highly energetic particles, namely helium-4 (^{4}He) and lithium-7 (^{7}Li) nuclei, after irradiation with a precise dose of neutron radiation. The BNCT approach comprises two key steps. First, ^{10}B boron-containing compounds are delivered to accumulate at tumor sites selectively. This is followed by neutron irradiation to destroy tumor cells.[128,155,156]

A core-shell system based on exosome membrane-coated, ^{10}B boron-containing carbon dots (BCDs) was recently developed with the aim of using the BNCT approach to treat brain glioma *in vivo*.[128] The BCDs consisted of boron phenylalanine, a boron-containing compound, and D-glucose. They were coated with macrophage-derived exosome membranes to produce exosome membrane-coated BCDs (BCD-Exos) (Figures 13A and 13B).[128] Compared with non-coated BCDs, the BCD-Exos efficiently cross the blood-brain barrier *in vivo*, with superior accumulation within the tumor 4 h after intravenous administration (Figure 13C). The tumor-bearing mice were irradiated with a precise dose of thermal neutrons. Those mice that were treated with BCD-Exos had greater suppression of tumor growth and extended survival (Figure 13D). No pathological malformation was observed in the mouse brain and major organs, which was indicative of a desirable biosafety profile (Figures 13E and 13F). These findings demonstrate the potential of BCD-Exos as a promising boron delivery system to improve the efficacy of BNCT to treat brain glioma *in vivo*.[128]

Immunotherapy

Immunotherapy is a rapidly developing and very promising facet of anti-cancer therapy that may be used for cancer treatment as well as for preventive cancer vaccination.[106,157] The principle of cancer immunotherapy is to stimulate the patients own immune system to suppress tumor progression and destroy malignant cells.[84,158] In recent years, naturally secreted extracellular vesicles have been used to improve the efficacy of cancer immunotherapy. The use of extracellular vesicles offers the possibility of more targeted and site-specific therapy.[159–161]

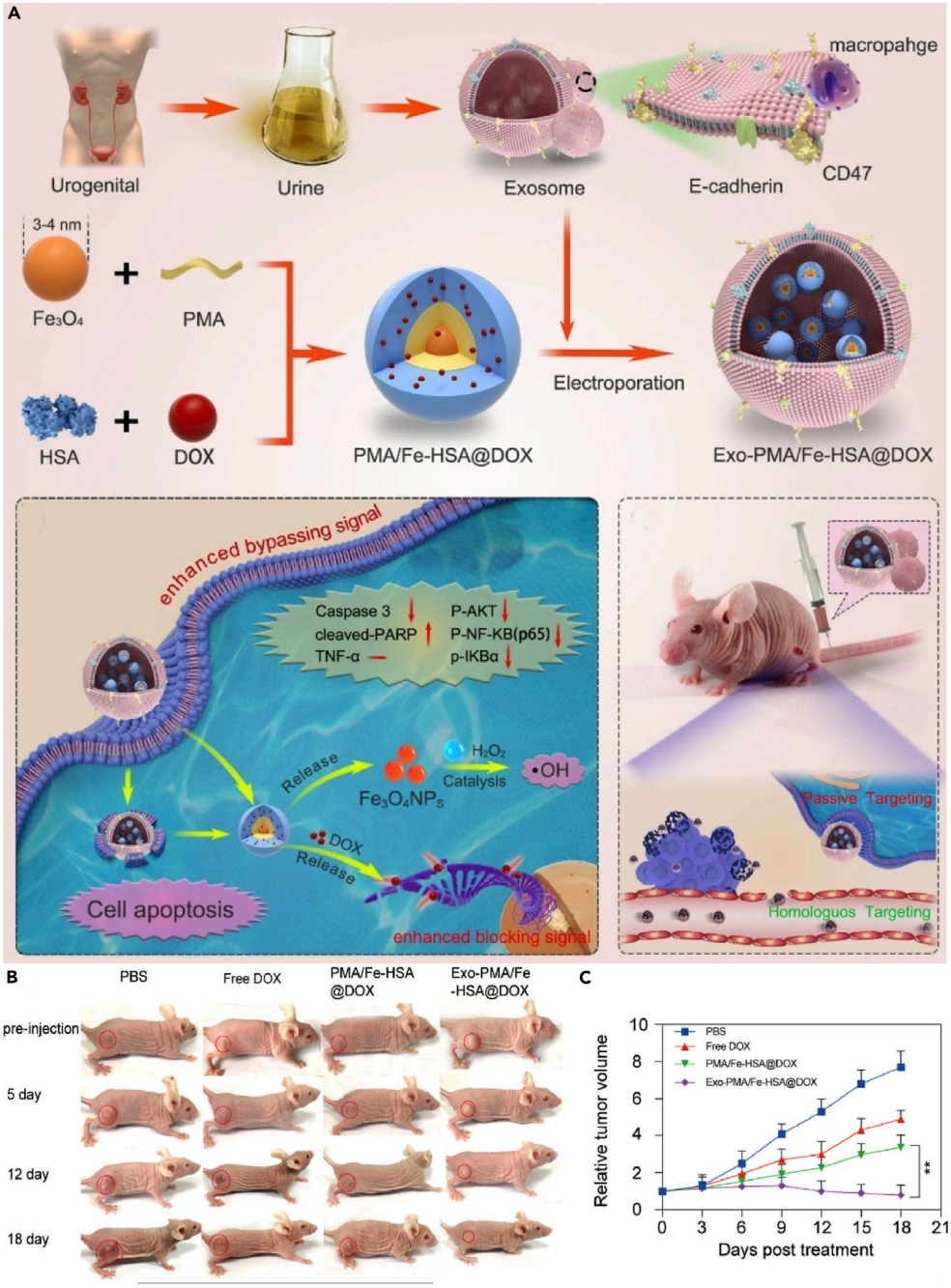

Figure 12. Exosome-coated nanoparticles for treatment of prostate cancer

(A) Preparation of Exo-PMA/Fe-HSA@DOX by coating PMA/Fe-HSA@DOX with urinary exosome membranes for synergistic chemo/chemodynamic therapy against prostate cancer.

(B) Photographs of mouse tumors at pre-injection and 5, 12, and 18 days after intravenous injection with different treatments.

(C) Tumor volume curves after different treatments.

Reproduced with permission from Pan et al.[40] Copyright Elsevier (2021). DOX, doxorubicin; EGFR, epidermal growth factor receptor; Exo-PMA/Fe-HSA@DOX, exosome membrane-coated PMA/Fe-HSA@DOX; HSA, human serum albumin; PMA/Fe-HSA@DOX, DOX-loaded Fe_3O_4-HSA nanoparticle core.

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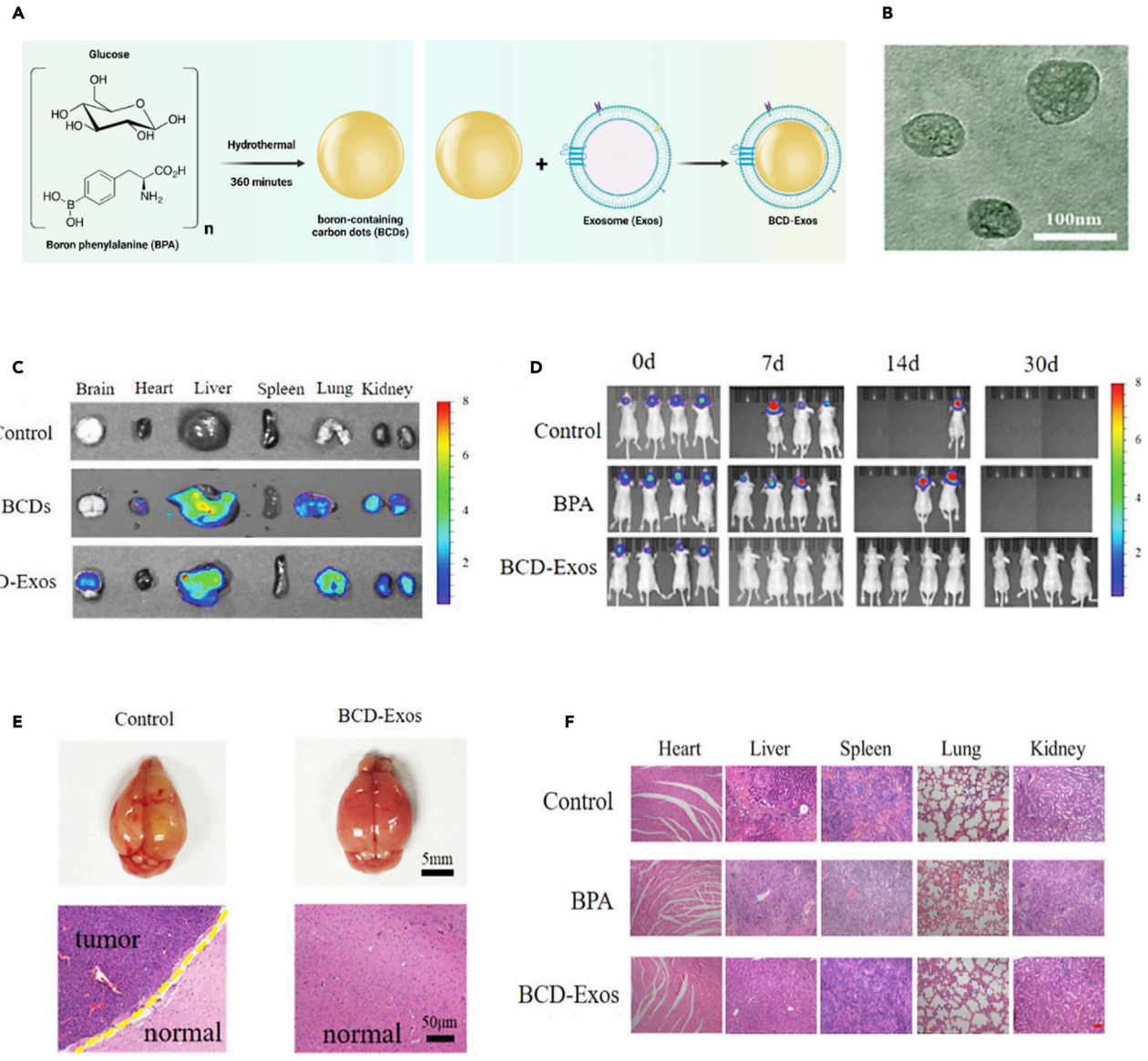

Figure 13. Exosome-coated nanoparticles for treatment of brain glioma

(A) Preparation of BCD-Exos by coating BCDs consisted of boron phenylalanine (BPA) and D-glucose with macrophage-derived exosome membranes for BNCT against brain glioma.

(B) TEM of BCD-Exos revealed a 100 nm core-shell nanostructure.

(C) Distribution of BCDs and BCD-Exos in the brain, heart, liver, spleen, lung, and kidney at 4 h after intravenous administration.

(D) Overall survival rate of mice treated with control, BPA, and BCD-Exos at 0, 7, 14, and 30 days after administration.

(E) Macroscopic (top) and microscopic (down) histologic evaluation of the mouse brain tissues after different treatments.

(F) Histologic sections from major organs (heart, liver, spleen, lung, and kidney) after different treatments.

(B–F) Reproduced with permission from Bose et al.[128] Copyright Wiley-VCH Verlag (2021). BCD-Exos, exosome membrane-coated BCDs; BCDs, ^{10}B boron-containing carbon dots; BNCT, boron neutron capture therapy; BPA, boron phenylalanine; TEM, transmission electron microscopy.

Glioblastoma is one of the most common brain tumors. Effective treatment is not readily available because of the ability of the blood-brain barrier to block the penetration of anti-cancer drugs into glioblastoma cells.[162] To increase the penetration ability across the blood-brain barrier and develop an efficient treatment for glioblastoma, doxorubicin-loaded PEGylated-poly-lactic acid (PEG-PLA) NPs were coated with exosome membranes derived from bEnd.3 cells, a murine brain endothelial cell line, for

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immunogenic chemotherapy of glioblastoma cells.[129] Such a strategy relies on the ability of some chemotherapeutic drugs to simultaneously induce apoptosis and immunogenic cell death (ICD) of tumor cells. ICD is a particular form of cell death that triggers a potent anti-tumor immune response by stimulating the maturation of antigen-presenting cells and the infiltration of cytotoxic $CD8^+$ T lymphocytes into tumor sites. The core-shell NPs were efficiently taken up by bEnd.3 cells *in vitro* and *in vivo*. An *in vitro* model of the blood-brain barrier confirmed that the exosome membrane coating powerfully promotes an efficient penetration and intense accumulation of doxorubicin in glioma GL261 cells compared with the uncoated NPs and the drug alone group. One possible understanding for the efficient drug delivery across the blood-brain barrier is the interaction between the ligands preserved in the membrane of brain endothelial cell-derived exosomes and the endothelial cell receptors of the blood-brain barrier.[129,163] In addition to inducing tumor cell apoptosis, doxorubicin is also a potent ICD inducer. It is capable of triggering a potent anti-tumor immune response by stimulating the maturation of dendritic cells and the infiltration of cytotoxic $CD8^+$ T lymphocytes into tumor sites. After intravenous injection in a glioblastoma-bearing mouse model, the resulting exosome membrane-coated PEG-PLA NPs significantly enhanced drug delivery to glioma cells. This resulted in better tumor growth inhibition and extended survival of the glioblastoma-bearing mice. These findings demonstrate the potential of the biomimetic nanosystem as a new avenue for immunogenic chemotherapy against cancer.[129]

The combination of immunotherapy and PTT has also been investigated.[130] A cancer vaccine against lung cancer was developed by coating black phosphorus quantum dots (BPQDs) with exosome membranes derived from hyperthermia-treated tumor-bearing mice. Those exosome membranes contained tumor-specific antigens capable of inducing strong anti-tumor immune responses.[130] The cancer vaccine appeared to be a promising approach for photothermal cancer immunotherapy because of its combined PTT-immunotherapy effects. The BPQDs acted as a photothermal agent that triggered the release of tumor-associated antigens upon NIR irradiation. This helped to amplify the immune stimulatory effects of the tumor antigens expressed on the exosome membranes. A strong anti-tumor immune response was produced by stimulating the maturation and differentiation of dendritic cells and the infiltration of cytotoxic $CD8^+$ T lymphocytes into the tumor sites. There was a profuse accumulation of the exosome membrane-coated BPQDs in the tumor tissues *in vivo*. The exosome membrane-coated BPQDs demonstrated enhanced biocompatibility, superior PTT efficiency upon NIR irradiation, and elicited potent anti-tumor immune responses. This ultimately resulted in greater suppression of tumor growth and extended survival of the tumor-bearing mice treated with the vaccine in combination with PTT. The experimental photo-vaccine appears to be effective against lung cancer because of its combined immune-stimulatory and photothermal effects.[130]

CHALLENGES AND HURDLES FOR CLINICAL TRANSLATION

Therapeutic delivery systems can benefit from the application of exosome coatings, a bioinspired strategy that overcomes the obstacles of NP-based delivery and optimizes the delivery of drugs and diagnostic chemicals to the target tissue and may thereby improve clinical outcomes attained with NP-based systems.[16,17,164,165] By cloaking the NPs with functionalized and intact exosome membranes obtained from different cells, the generated core-shell NPs can acquire the complex protein profile of cell membranes, which gives them advantages such as increased biocompatibility, sustained release, enhanced cellular contact, and improved ability to detect, bind, and phagocytose malignant cells.[15–17]

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Cell-secreted exosomes have proven to possess a good prospect in cancer diagnosis and therapy; however, employing natural exosomes is very challenging and rarely results in the intended therapeutic response. Exosome membrane-coated NPs constitute a promising alternative carrier of several compounds for improved cancer applications.[32] These include imaging agents, chemotherapeutic drugs (e.g., doxorubicin,[40,114,116–118,125,129] paclitaxel,[124] suberoyl bis-hydroxamic acid,[115] platinum[122]), therapeutic proteins (e.g., gelonin[119]), genetic material (e.g., anti-miR-21,[113,120] Let-7-a miRNA,[121] siS100A4[123]), photosensitizers and photothermal agents (e.g., indocyanin green[125]) for cancer phototherapy, and nonradioactive ^{10}B-containing compounds for BNCT.[128] After reaching the target tumor cell, the disruption of the outer membrane layer and subsequent cargo release from exosome membrane-coated NPs can be dictated by several triggering mechanisms, including (among others) the acidic pH conditions that prevail in the tumor microenvironment,[117–119] and the PTT-induced hyperthermia that disrupts membrane structure and enables cargo release.[125]

Despite the promising results indicating enhanced therapeutic efficiency and decreased toxicity *in vivo*, the translation of exosome membrane-coated nanosystems from benchtop to bedside has been hindered due to several hurdles. Consequently, considering the immense potential of these biomimetic nanosystems, these hurdles must be overcome before successfully implementing these approaches in clinical practice (Figure 14).

A substantial hurdle to the widescale employment of exosome coating as a simple targeting strategy for NPs is the low production and isolation yields of naturally cell-secreted exosomes. Due to the reduced number of cell-derived exosomes and isolation hurdles, the scalability of this technology is a major challenge toward clinical translation.[15–17,166] A simple, efficient, and standardized methodology is needed to make it possible to manufacture exosome membrane-coated NPs on an industrial scale.[16] Extrusion through membrane filters or slicing over specialized microfluidic devices to generate cell-derived exosome-like nanovesicles has shown to be an efficient and straightforward approach for scaling up the production of exosomes.[16,167]

Another issue that needs to be solved prior to clinical translation is the possibility of coating techniques to modify the biological functionality and safety of exosome membranes. Extrusion and sonication—although the most commonly used coating methods—can disrupt membrane structure and damage the protein integrity of exosomes.[16] Thus, new innocuous coating procedures with negligible impact on exosome proteins and functionalities are highly desired.[16,17] The widespread disagreement within this field indicates that the optimal encapsulation approach may differ depending on the NP type and cell.[168,169] Therefore, in-depth research evaluating various NP types and cell lines should be carried out to provide a thorough insight into the criteria that render each encapsulation approach optimal in certain instances.[15]

Furthermore, investigations are required on the precise absorption of exosome membrane-coated nanosystems into the target cell lineages.[15] In contrast with the findings of targeted uptake to the exosome origin cells, observations of cross-targeting between various cell types appear to create inconsistency. This is attributable to the similarities between various exosome origin cell types, such as several cancer cell lines, allowing for cross-reactivity. These features must be thoroughly investigated, and defined criteria between cross-reactivity and selective uptake must be established.[15]

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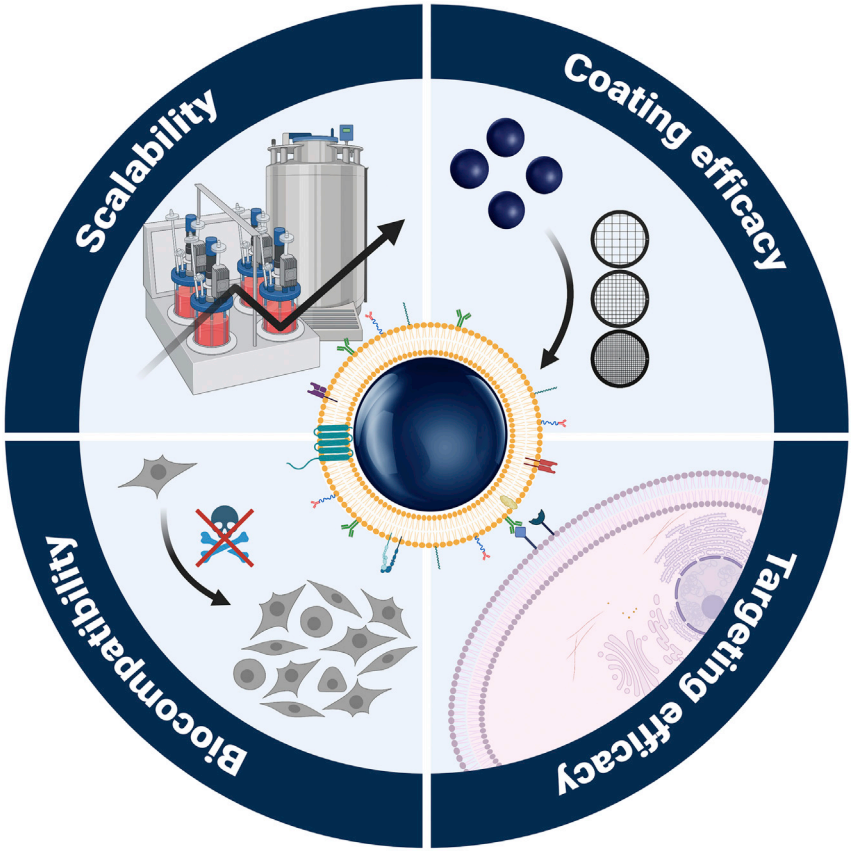

Figure 14. The main advantages of bioengineered exosome membrane-coated nanosystems and challenges for successful clinical translation

The benefits are mainly related to the biocompatibility and non-immunogenicity of natural exosomes, as well as their immune evasion, long blood circulation, and specific tissue-homing features. This can result in a targeted and more precise nanomedicine. The hurdles in clinical translation are attributed to the low production and isolation yields of naturally cell-secreted exosomes, the difficulty of clinical-scale production, as well as the high risk of the coating methods to disrupt exosome membrane structure. This can compromise their bioactivity and safety.

Orienting and coating exosomes on NPs are crucial in preserving exosome proteins and functionalities.[15–17] The coating integrity significantly regulates the cellular uptake of these bioinspired nanostructures. Individualized cellular uptake of nanosystems occurs in high coating degrees (≥50%), whereas in low coating degrees (<50%), nanosystems infiltrate cancer cells via a cooperation process based on proper NP aggregation.[170] Consequently, a detailed investigation is requisite to improve internalization by the tumor cells.

Finally, as these bioinspired nanosystems carry biological materials, the potential *in vivo* side effects of exosome membrane-coated NPs should be carefully investigated.[16,17] The immunogenicity and adverse side effects of exosome membrane-coated nanosystems should be investigated by means of long-term *in vivo* studies. This can ensure that long-term retention of these biomimetic NPs within human body has no negative implications.[15]

In conclusion, even though they are cutting-edge, exosome membrane-coated biomimetic NPs are not yet fully developed. An improved understanding of the

above-mentioned issues is likely to pave the way for the development of exosome membrane-coated nanosystems for cancer clinical diagnosis and treatment.

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DECLARATION OF INTERESTS

J.C. is a co-founder and shareholder of TargTex S.A. Targeted Therapeutics for Glioblastoma Multiforme.

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