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Journal:	*The Innovation Drug Discovery*
Manuscript ID	TIDD-2026-0015.R3
Manuscript Type:	Review
Keywords:	Cancer cell membrane, Tumor extracellular vesicles, Exosomes, Subcellular organelle targeting, Biomimetic nanotechnology, Homotypic targeting

Cancer cell membranes, tumor extracellular vesicles, and subcellular organelle targeting as promising biomimetic drug delivery systems

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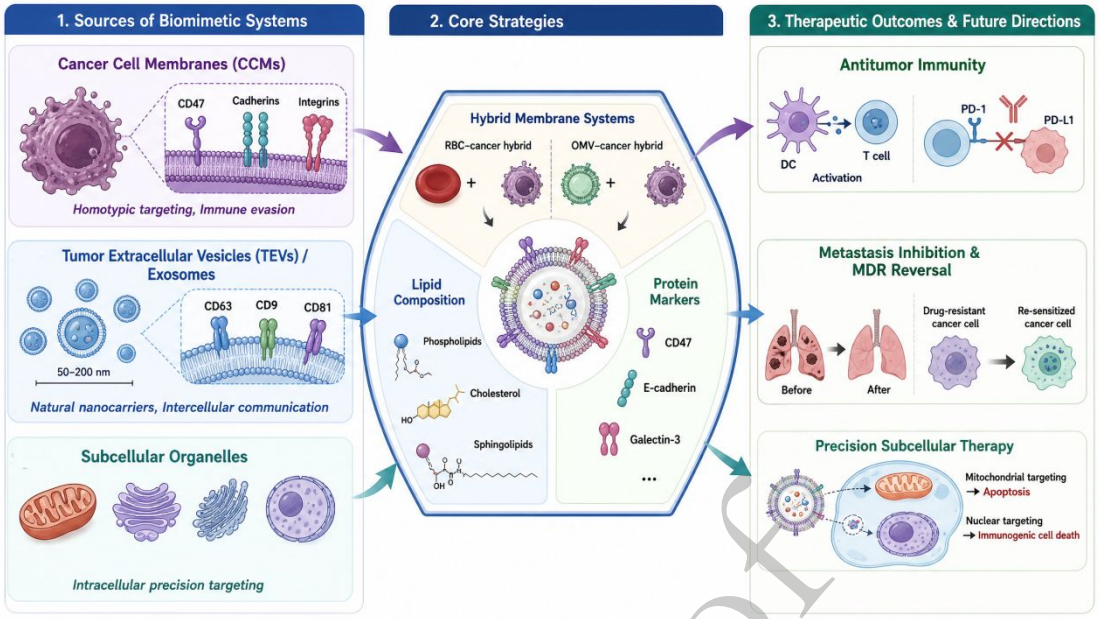
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

1. CCMs and TEVs provide biomimetic platforms with complementary advantages in tumor targeting and biocompatibility.
2. Hybrid membrane systems synergistically enhance circulation, immune evasion, and antitumor efficacy.
3. Subcellular organelle targeting integrated with membrane systems enables sequential precision delivery.

ABSTRACT

Conventional chemotherapy suffers from severe off-target toxicity and suboptimal efficacy. This review systematically summaries cancer cell membranes (CCMs), tumor extracellular vesicles (TEVs), and subcellular organelle targeting as biomimetic advanced drug delivery systems (ADDS) for precision cancer therapy. CCMs exhibit unique homotypic targeting, immune evasion, and enhanced tumor accumulation, while hybrid membrane systems further improve circulation and targeting specificity. TEVs, particularly exosomes, offer naturally occurring nanoscale carriers with inherent biocompatibility and intercellular communication capabilities. We critically compare the lipid and protein compositions between CCMs and TEVs, and explore emerging applications in metastasis inhibition, multidrug resistance reversal, and antitumor immunity. Beyond membrane-based strategies, we investigate mitochondria, Golgi apparatus, endoplasmic reticulum, and nucleus targeting for precise intracellular drug delivery. The review identifies critical gaps in standardized isolation protocols and lipid-mediated recognition mechanisms, proposing that hybrid systems integrating CCMs, TEVs, and organelle-targeting moieties represent the future direction for translating precision nanomedicine from bench to bedside.

KEYWORDS: Cancer cell membrane; Tumor extracellular vesicles; Exosomes; Subcellular organelle targeting; Biomimetic nanotechnology; Homotypic targeting

INTRODUCTION

Cancer is among the most serious diseases confronting human beings. Main treatment methods include surgery,[1] radiation therapy,[2] chemotherapy,[3] hormone therapy,[4], targeted therapy[5] and more recently immunotherapy.[6] Facing with different conditions of cancer patients, these treatments can be administered alone or in combination.[7, 8]. Chemotherapy is one of the most commonly employed therapeutic approaches, offering the advantage of ease of administration.[9] However, its critical role in cancer treatment, chemotherapy still faces several challenges.[10] The major drawback lies in side effects, as chemotherapeutic agents would kill cells in both normal and tumor tissue.[11] Another obstacle is the low therapeutic efficiency, which can be in some cases attributed to suboptimal drug delivery.[12]

The emergence of nanotechnology, which is based on passive or active targeting drug delivery systems, holds significant promise as a strategy for cancer therapy. This is attributed to the size and surface properties of nanomedicines, which can enhance the pharmacokinetics and pharmacodynamics of anticancer drugs intracellular delivery.[13] Indeed, the concept of tumor targeted chemotherapy was originally inspired by the "magic bullet" theory by Erlich's group,[14] wherein nanosized materials can be designed as tumor targeting drug carriers. This is obtained via the encapsulation of chemotherapeutic drugs, DNA, RNA, or proteins within nanosized vectors eventually equipped with tumor-homing ligands to achieve selective tumor target outcome, while preserving normal tissues from drug-induced toxic effects.[15] In the early stages of advanced drug delivery system (ADDS) design, the focus was primarily on strategies to prevent nanomedicine uptake by the reticuloendothelial system (RES),[16] prolong blood circulation time, and enhance the amount of ADDS accumulation around tumors via the enhanced permeability and retention (EPR) effect. [17] The most popular technology to prevent reticulo-endothelial sequestration consists on coating polyethylene glycol (PEG) to the surface of nanoparticulate ADDS, making them "stealth".[18] Popular pegoylated solid nanoparticles are composed of high molecular weight polymers, including poly(d,l-lactide-co-glycolide) (PLGA),[19] polycaprolactone (PCL),[20] poly(l-lactide-co-dl-lactide) (PLA),[21] amino-terminated poly(l-lactide)

(PLLA)[22] to which PEG chains of various molecular weights are grafted.[23] Although a single dose of PEG-coated ADDS exhibits a long-lasting blood circulation time, an accelerated clearance is observed upon the second administration.[24] The mechanism might be related to an immune response against PEG, as observed in rats.[25] Moreover, since stealth PEGylated nanoparticles lack specific targeting ability, this consequently increases the risk of drug accumulation in normal tissues and organs owing to their prolonged serum half-life.[26] The development of nanoscale preparation technology has made it possible to specifically target tumor tissues using a variety of ligand-receptor or antigen-antibody interactions.[27-29] However, the difficulty of selecting, purifying, and identifying the optimal tumor-specific ligand-receptors or antibody-antigens pairs still persists.[30] Moreover, the inter-individual variability among cancer patients cannot generally be predicted.[31] Because personalized antigen or cancer-associated receptor identification and vaccine manufacture would not be practical in large-scale therapeutic practice, these obstacles have rendered difficult for clinical application the strategies based on ligands or antigens active targeting.[32]

Cancer cells themselves are increasingly considered as tools for targeting tumor tissues through highly selective homogeneous recognition ability. Recently, cancer cell-based drug delivery systems have brought hope due to their natural biomimetic activity. By utilizing cell-based camouflage technology, cancer cell membranes derived ADDS have demonstrated the ability to overcome a cascade of physiological challenges, including blood circulation degradation, tumor penetration, tumor tissue accumulation, cell uptake and intracellular trafficking to targeted organelles.[33] The described tumor-cell derived ADDS exhibited not only homotypic recognition[34] and strong endocytosis efficiency,[35] but also improved immune escape ability.[36, 37] Recent advances in cancer immunology and targeted therapies have further underscored the potential of biomimetic systems to address these persistent clinical changes.[38] Cancer cell membranes (CCMs) or tumor extracellular vesicles (TEVs)/exosomes, which are naturally produced by tumor cells, can be used for ADDS applications. as depicted in Figure 1. Tumor exosomes are a specific type of extracellular vesicles that are released from tumor cells following the fusion of multivesicular bodies with the cell membrane.

Due to the multiple reported applications and abilities of tumor exosomes, we have focused on exploring their biochemical content differences between them and CCM, which suggest different specific ADDS applications.

This present review aims to provide an update on the utilization of cancer cell extracellular membrane and organelle-based nano-formulations as ADDS for precise cancer targeting and treatment, especially concerning CCM and tumor exosomes. In addition to CCM and tumor exosomes as ADDS carriers, we also discuss the potential of other organelle membranes, such as mitochondria, nuclear envelope, lysosomes and others. The present analysis suggests that the combination of biomimicry and nanotechnology has the potential to yield exceptional results in cancer therapy.

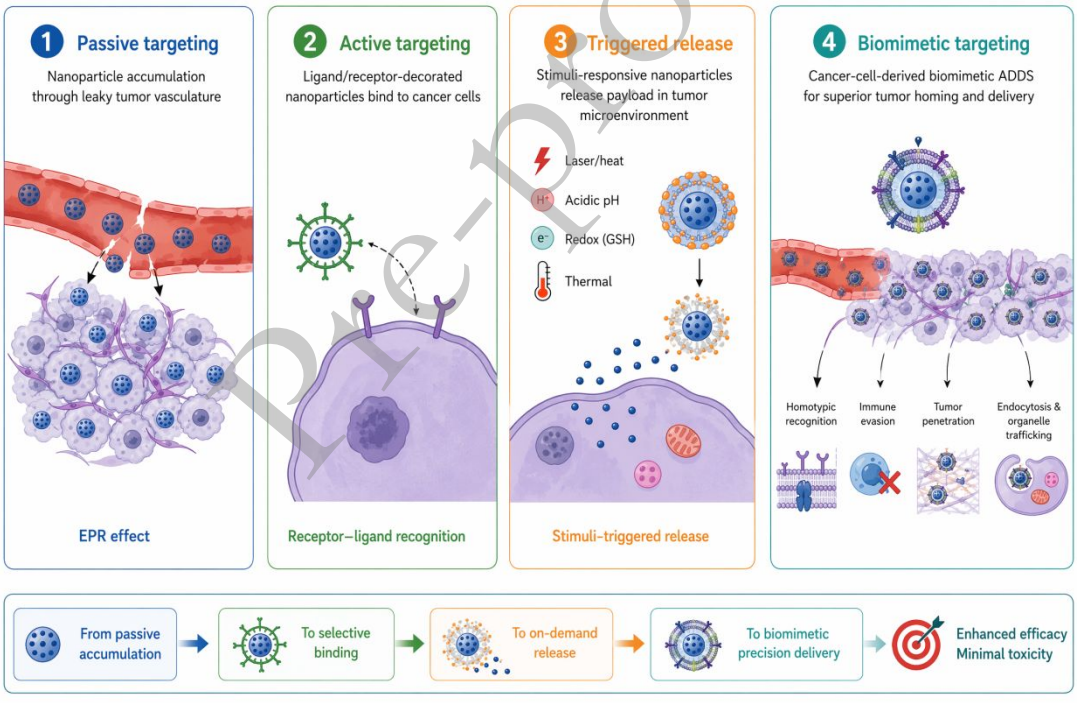


Figure 1. The development of ADDS. Schematic illustration from passive EPR accumulation to cancer cell-derived biomimetic homing, multi-modal targeting strategies in anticancer drug delivery for improved efficacy and reduced toxicity.

CANCER CELL-DERIVED BIOMIMETIC ADDS

Whole cells as ADDS for anti-tumor therapy

Recent findings have shown that cells have by themselves the potential to target the delivery of drugs such as RNA, chemotherapeutic drugs or viruses.[39] This approach is highly promising for delivering oncolytic viruses not only to the primary tumor site, but also to metastases. Unfortunately, there are currently no solid tumor-derived cancer cell carriers that exhibit tropism toward certain cancers such as glioma, thus limiting their usage.[40] Cancer cells used as a delivery carrier also require the expression of a self-destructive suicide gene after it reaches the target sites to prevent carrier-derived metastasis formation.[41] Tumor-associated cells contain mesenchymal stem cell, macrophages cell and T lymphocytes, called tumor-infiltrating lymphocytes (TILs). According to the intensive research, these cell types could serve as advanced drug delivery for cancer therapy.

Mesenchymal stem cells (MSCs) are multipotent cells capable of differentiating into a variety of cell types.[42] These cells have been evaluated as an additional potential vehicle for the delivery of antitumor therapy without any detectable neurotoxicity,[43] but with the capacity of self-renewal, migration toward and engraftment into tumor site.[44] As illustrated in Figure 2, bone-marrow-derived mesenchymal stem cells (BM-MSCs) and local tissue-associated MSCs would be affected by chemokine gradients, such as those formed by CXC-chemokine ligand 12 (CXCL12) or CXCL16.[45, 46] Subsequently, BM-MSCs migrate to the tumor microenvironment,[47] closely interacting with tumor cells, tumor endothelial cells, and tumor-infiltrating immune cells. On one hand, after the stimulation by cytokines such as tumor necrosis factor (TNF) and interleukin-1β (IL-1β), which are secreted by immune cells, BM-MSCs transform to tumor-associated MSCs (TA-MSCs) or cancer-associated fibroblasts (CAFs).[48, 49] On the other hand, exosomes derived from tumor cells also facilitate the transformation of BM-MSCs to CAFs.[50, 51] Till now, the molecular mechanism underlying the transformation of BM-MSCs into CAFs remains unknown. TA-MSCs and CAFs facilitate tumor cell growth,[52, 53] promote angiogenesis[54] and recruit monocytes,[55] macrophages[56] and myeloid-derived immune suppressor cells (MDSCs).[57] Preclinical studies that used MSCs as vehicles to improve the delivery of targeted agents for tumors have attracted

a lot of attention.[58] However, to our knowledge, only one most recent phase I/II clinical trial of MSC-based tumor therapy in advanced gastrointestinal tumors has been initiated so far.[59] This trial evaluated the safety, tolerability and efficacy of treatment with genetically modified autologous MSC transduced with the herpes thymidine kinase gene,[60] namely, MSC_apceth_101, in combination with ganciclovir. During Phase I, MSC_apceth_101 was given to six patients with advanced gastrointestinal adenocarcinoma at low (total dose of 1.5×10^6 cells/kg) or high doses (total dose of 3.0×10^6 cells/kg) followed by ganciclovir infusions. The results indicated favorable safety and tolerability, and resulted in the stabilization of the disease in four patients.

Macrophages as drug carriers

Macrophages, as a type of innate immune cells, exhibit a characteristic prolonged blood half-life and specific binding to tumor tissues.[61] Therefore, using macrophages for drug delivery can significantly prolong drug circulation time *in vivo* and enhance drug accumulation into tumors. Macrophages naturally capture foreign bodies, including viruses, bacteria, and drug-loaded nanoparticles, via phagocytosis, and subsequently deliver them to tumor tissues.[62] In the most frequent use, drug nanoparticles are incubated with liver macrophages.[63] Qiu et al[64] developed octaarginine (R8)-modified liposomes co-loaded with paclitaxel (PTX) and resveratrol (Res). These drug-loaded liposomes were then incubated with macrophages to treat metastatic 4T1 tumors. The high delivery rate of this system can be attributed to membrane fusion, which should be an important pattern leading to macrophages nanoparticle delivery into tumor cells. They also found that doxorubicin (DOX) did not have a significantly impact on macrophage targeting and viability. Guo et al found that DOX-loaded M1 macrophages can inhibit tumor invasion, while DOX-loaded liposomes alone lack this effect. In addition, they demonstrated that DOX-loaded macrophages can transfer drugs to ovarian carcinoma cells via a tunneling nanotube pathway.

CANCER CELLS MEMBRANES (CCMS) MIMETIC ADDS

Cancer cells membranes isolation and characterization

In order to produce CCM-based ADDS, cancer cell membrane is purified by emptying harvested cells of their intracellular contents using a combination of hypotonic lysis, mechanical membrane disruption, and lastly differential centrifugation. The overall procedure is illustrated in Figure 2, according to most of reported studies.[65, 66]

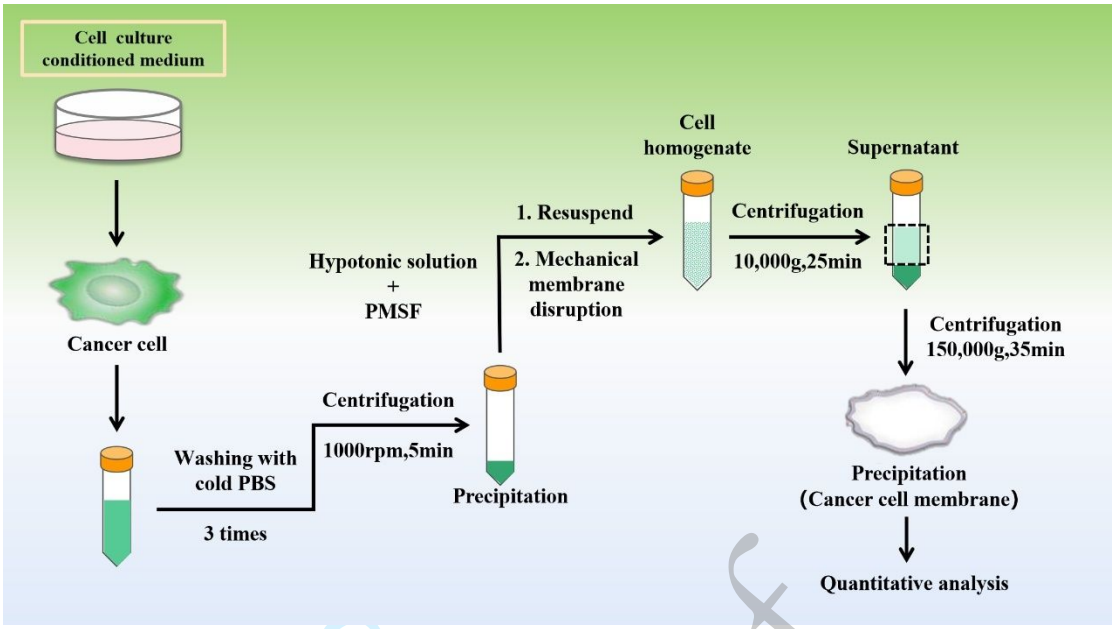


Figure 2. The brief process of CCM isolation. Cells derived from cancer cell culture supernatant are washed, resuspended in PMSF-containing hypotonic buffer, and mechanically disrupted. Following centrifugation, the supernatant is ultracentrifuged to yield a cell membrane pellet for quantitative quantification.

Dynamic light scattering (DLS),[65] transmission electron microscopy (TEM),[67] scanning electron microscope (SEM)[68] and atomic mechanics microscope (AFM)[66] are used to investigate particle size and shape. Stochastic optical reconstruction microscopy (STORM) images[69] supply a fluorescent labeled CCM image. CCM protein content is analyzed by SDS-PAGE or other proteomic techniques[70] assay, primarily through a comparison with the origin cancer cell. A similar protein profile indicates protein stability during the preparation steps.[66] The fluorescent lipophilic dye, 3-octadecyl-2-[3-(3-octadecyl-2(3H)-benzoxazolylidene)-1-perchlorate (DiO) is used to confirm the unbroken bilayer lipid structure.

Currently, a number of proteins are of pivotal importance for cellular interactions between cells and with the extracellular matrix, and might thus be of importance for CCM interaction with the targeted tumor cells. These include cadherins, such as E-cadherin, P-cadherin, and N-cadherin, which are essential for epithelial cell interactions,[71] as well as Galectin-3, a member of the lectin family taht is frequently up- or down-regulated in many types of cancer.[72] Extracellular galectin-3 binding to the

plasma membrane of T cells alters membrane organization and affects the formation of an immunological synapse;[25] thus, galectin-3 detection is crucial in immunotherapy. $Na^{+/}K^{+}$-ATPase,[73] an oligomeric enzyme that uses ATP chemical energy to translocate ions across cell plasma membrane, is commonly recommended as the specific cell membrane protein. Integrins not only bind to extracellular ligands, but also interact with cytoplasmic actors.[74] β-catenin, a 92 kDa protein, is frequently associated with cell-to-cell junctions and exhibits a high affinity for the transmembrane glycoprotein E-cadherin.[75]

The plasma membrane purity is also verified by assessing the absence of nuclear protein makers such as histone H3 or of the mitochondrial protein maker (COXIV). [76-78] Glycoprotein 100 is a widely reported transmembrane tumor-associated antigen in melanoma, which has been used to validate cell membranes originating from B16-F10 cells.[79, 80] Other markers analyzed in CCM drug delivery studies are glycoprotein CD63 melanoma-associated membrane protein,[81] and CD44 and CD47 antigen markers from MCF-7 cells surface,[81] which prevent macrophages phagocytosis in the reticulo-endothelial system.

CCMs used as ADDS

Various sources of ADDS based on tumor cell membrane are presented in Table S1, with breast cancer cell membranes constituting the most frequently utilized model system.[80] A synthesis of the data compiled in Table S1 reveals several key trends. First, there is a clear shift from single-source membranes to hybrid membrane systems (e.g., RBC-Cancer cell hybrids), which currently represent the most effective strategy for balancing long circulation with active targeting. Second, a cross-study comparison highlights a critical lack of standardized reporting for “circulation time” and “in vivo toxicity,” with over 30% of the cited studies omitting these metrics. This suggests that the field is currently prioritized toward proof-of-concept efficacy rather than pharmacological validation, marking a crucial area for future standardization.

The most commonly chosen cancer CCM originate from breast cancer cell lines MDA-MB-231, MDA-MB-381, MDA-MB-435, MCF-7 and 4T1. The team of Zhang’s

group[80] used B16-F10 mouse melanoma cells and MDA-MB-425 cells as model cancer cell lines to obtain CCMs, which were then coated onto PLGA nanoparticle cores. The CCM-coated NPs displayed a classical core-shell structure after being negatively stained with uranyl acetate.[80] Evidently, these biomimetic ADDSs demonstrate superior therapeutic efficacy.[82] It was found that the B16-F10 CCM extended the stability of CCM coated NPs up to 5 folds when compared to the absence of coating. Then the ability of homotypic targeted delivery was assessed by using MDA-MB-435 cell membranes, red blood cell membranes, B16-F10 membranes and none-coated membrane. Flow cytometric analysis of these abovementioned groups displayed that MDA-MB-435 membrane coating enabled approximately 40-fold and 20-fold increases in tumor uptake compared with RBC coated NPs and bare PLGA cores, respectively. These results indicated that coating CCM onto the surface of NPs can preferentially increase the affinity to the source cancer cells. Of note, the circulation time of ADDS based on tumor cell membranes was not sufficiently analyzed in these studies, despite being an important and indispensable delivery factor in ADDS research.

Stem cell membranes (CSCMs) used as ADDS

Stem cell-based delivery of drug-loaded nanoparticles with inherent tumoritropic property is an interesting alternative.[83] However, several challenges including the stability, potential biological contamination, and biosafety concerns have so far limited their practical clinical applications in cancer treatment. To our knowledge, 3 studies have been reported. He et al[84] have developed gelatin nanogels coated with bone marrow derived mesenchymal stem cell membrane (SCMGs), which were loaded with DOX as the model drug. Because of the non-specific tumortropic properties, the tumor target ability was evaluated by HeLa cells. Non loaded SCMGs displayed negligible toxicity at the concentrations ranging from 25 to 400 μg/mL over a 24 h period. HeLa cells treated with SCMGs-DOX showed a nearly 100% of DOX internalization, superior to other DOX loaded formulations. Additionally, the *in vivo* targeting ability and safety have been studied.[85] The team of Jiang[86] developed umbilical-cord mesenchymal stem cell membrane-coated polydopamine NPs for chemo-photothermal

therapy (CPT) of malignant bone tumors. SN38 is a hydrophobic drug[87] that can be efficiently loaded into polydopamine NPs mediated by π-π stacking interactions. The human osteosarcoma MG63 cells were used as cell model. In a recent report, the combination of mesenchymal stem cell membrane-coated polydopamine NPs with 808 nm laser irradiation led to a 60.0% reduction in tumor volume. The SN38 release at pH 5.0 was approximately three times higher than that at pH 7.4. These results indicated that mesenchymal stem cell membrane might possess an effective pH-responsive drug release behavior, which is favored in the acidic tumor microenvironment. A similar acid-responsive drug release profile has been described by the study of He's group [84] in which drug release from gelatin-DOX and SCMGs-DOX was significantly lower at pH 7.4 than at pH 5.0.

Overall, the stem membrane-functionalized biocompatible NPs represent a new class of nanocarriers. Until now, only mesenchymal stem cell membranes have emerged as a promising therapy for tumors. Stem cells[88] can be derived from bone marrow, blood, adipose tissue, umbilical cord, placenta, and amniotic fluid.[89] The properties of stem cells include self-renewal and tumor tropism, which points to them as a potential new class of effective targeting drug delivery systems.

Hybrid CCMs

While single cell membrane coating strategy has enhanced the use of ADDS, other biological functions can also be added for peculiar applications. The selection of the cells from which membranes are produced mainly depends on the unique features of the source cells and the requirements of disease therapy.[90] Erythrocytes membranes significantly improve the immune evading capability,[91, 92] stem cell-derived NPs display excellent cancer targeting properties, macrophage cell membranes reduce opsonization and prolong circulation lifetime in vivo, [93] leukocyte membrane coated ADDS[94] have the potential to promote the ability to traverse endothelium, and CCMs from diverse cancer type allow targeting selectivity.

A few recent reviews[95, 96] have reported the hybrid cell membrane strategies for cancer treatment (summarized in Table S1). Yang et al[97] have produced erythrocyte-

cancer (RBC-M) hybrid membrane by fusing RBC membrane with MCF-7 cell membrane. Different weight ratios of RBC to MCF-7 membranes (1:0, 2:1, 1:1, 1:2, and 0:1) were used for in vivo photothermal therapy, using techniques such as FRET pair of fluorescence dyes, capturing images using CLSM, SDS-PAGE and western blot analysis. In the reported study, Band 3, characteristic RBC membrane markers, including glycophorin A, CD55 and CD47 was detected. CD340, EpCAM, N-cadherin, and galection-3 were identified as MCF-7 membrane markers. Moreover, the use of different ratios of RBC membrane to MCF-7 membrane in constructing ADDS resulted in distinct behaviors. Increasing MCF-7 membrane ratio significantly enhanced the homotypic targeting capability, while increasing RBC membrane components could effectively reduce the cellular uptake by macrophages in vitro and improve blood circulation time. The anticancer efficacy was remarkable. With the 1:1 group (ratio of RBC to MCF-7) a 100% response without any residual tumor or recrudescence was observed. A tumor weight reduction of 92.3%, 98.0%, 81.9%, 61.0%, and 30.0% for 1:0 group, 2:1 group, 1:2 group, 0:1 group, and 0:0 group, respectively was observed. These results were in agreement with the local temperature elevation at the tumor site. Thus, the crucial factors in this hybrid cell membrane strategy were the components and the proportions of the source cell membrane, which would direct the ADDS to where "they" are aimed to reach.

The presence of Gram-negative bacteria cell membranes, which is known to contain many bacterial antigens, has gained considerable attention for antitumor treatment.[98, 99] Zhang et al[100] reported that combining the bacterial outer membrane vesicle (OMV) with B16-F10 CCM synergistically activates antitumor immunity upon tumor accumulation, offering promising perspectives for combinational immunotherapy. The monocytes of lymph nodes were clustered and measured. The frequencies of $CD11c^+$ DCs in the tumor-draining lymph nodes of mice treated with OMV/B16-F10 CCM-NPs were 4.2-fold higher than those of mice injected with PBS. Meanwhile, the treatment with B16-F10 CCM-NPs alone did not display significant difference in comparison with PBS treated mice. The results indicated active efficacy of OMV associated with B16-F10 CCM-NPs in elevating DC recruitment into lymph

nodes. A similar result was observed in the expression of CD80 and CD86, which are considered as mature DC surface markers. These results validated that OMV with B16-F10 CCM-NPs could stimulate the immature DC in vitro. C57BL/6 mice bearing melanoma were chosen as in vivo analysis with the PPT treatment. With NIR irradiation, the tumor growth inhibition rate of OMV with B16-F10 CCM-NPs nearly reached 99.9%, while the B16-F10 CCM-NPs alone, or OMV-NPs alone led to a tumor growth inhibition of 68.4% and 31.7%, respectively. These promising results prompt to further explore the combined methods of immunotherapy with PTT.

Compared to single cell origin of tumor cell membranes, this combined membrane approach offers a greater efficacy. The combination of other cell membranes with CCM to avoid ADDS recognition and clearance by the innate immune system has been shown to be an effective strategy.[90, 101-103] Furthermore, the observed synergy suggests investigating more cell membranes types, such as DC membranes, NK cell membranes or neutrophil membranes.

THERAPEUTIC MERITS OF CCMS

CCMs as a promising tool for cancer diagnosis

Circulating tumor cells (CTCs) play an important role in liquid biopsy as they represent a potentially rich source of information for cancer diagnosis, monitoring, prognosis, and treatment guidance. Cell-cell interactions involving CTCs can significantly improve their capture efficiency. The epithelial cell adhesion molecule (EpCAM), as a specific affinity molecule on the surface of breast cancer CTCs, was designed as a target core to realize the specific capture of CTCs.[104] In the work conducted by Ding et al,[47] a biointerface was fabricated for efficient capture and release of CTCs from human blood samples through the help of MCF-7 breast cancer cell membranes. This biointerface was composed of a natural CCM, on which an EpCAM-binding DNA aptamer was grafted through a PEG polymer or albumin linker. Peripheral blood samples were collected from five breast cancer patients in this study to isolate the CTCs. As anticipated, there were no CTCs in the blood sample of five negative control healthy volunteers. Three cell lines, namely MCF-7 cells (EpCAM-positive cancer cell line), HeLa cells (EpCAM-negative cancer cell line), and 293T cells (normal cell line), were used to investigate the interaction specificity between target cells and cellular biointerfaces. The non-specific adhesion of the cellular biointerfaces to different types of cells was less than 0.25%, reflecting its targeted homing capability. The capture efficiency with the PEG linked was 32.6% and was distinctly increased with a bovine serum albumin linker. Remarkably, the captured CTCs could be intactly released from the biomembrane by applying complementary strands of the capture aptamers. This study provided an intelligent strategy for the isolation and release of CTCs with high purity for quantification and biochemical characterization and can be generalized to other cell types.

CCMs for improving the therapeutic effect of chemotherapy drug

The shape of nanoparticles significantly influences their biological performance. A study by Zhang et al compared PLFA nanospheres (CS) and nanorods (CR), both coated with membranes from BxPC-3 pancreatic cancer cells.[105] In a mouse model bearing a BxPC-3/HPSC hybrid tumor, the CCM-coated nanorods (CR) demonstrated superior properties. Specifically, CR exhibited enhanced immune evasion, an 8.2-fold higher penetration rate through the extracellular matrix, and greater tumor accumulation than their spherical counterparts (CS). Consequently, DOX-loaded CR showed improved antitumor efficacy, highlighting the importance of nanoparticle geometry in CCM-based ADDS design. This study advances our knowledge of the trafficking pathway of CCM-coated nanorods and provides guidelines for the rational design of subcellular-targeting and efficient DNA toxin drug delivery systems.

CCMs antimetastatic capacity

Tumor metastasis represent a significant and prevalent challenge in cancer therapy, usually accompanied by higher mortality rate.[106-108] Tang's colleague[109] have described a multifunctional tumor-targeted ADDS (TiO_2@MnO_2-GOx@CCM) combining radio-starvation therapy to decrease the tumor metastatic. The mechanism of action combines glucose oxidase (GOx) mediated starvation therapy, GOx conversion of glucose into toxic gluconic acid and hydrogen peroxide (H_2O_2), MnO_2 production of O_2 from H_2O_2, and ROS production by TiO_2 under X-Ray activation.[107, 108] The ADDS was coated with the B16-F10 cell membrane for treating a metastatic B16-F10 tumor. Cell membrane coated NPs were detected in tumors, contrary to those without the membrane coating, demonstrating the excellent cancer targeting property of the TiO_2@MnO_2-GOx@CCM camouflaged by cell membranes. Administration of these ADDS together with x-ray led to complete disappearance of lung metastatic tumors This current multifunctional ADDS may provide a promising candidate way for tumor metastasis therapy in clinic.

CCMs for reversing multi-drug resistance

Because of multidrug resistance (MDR) in various types of cancer, the administration of a single drug molecule usually fails to effectively control the progression of the disease. Consequently, the combined administration of different types of drugs has gradually emerged as an alternative to enhance the efficacy of cancer therapy. The combination therapy greatly relies on using ADDS to precisely control the dosage, proportion, and even the sequence of loaded cargos. A zeolitic imidazolate framework hybrid nanoparticle coated by bladder cancer cell SW780 membrane was successfully constructed in Li's group[110] to co-deliver cisplatin (DDP) and oleanolic acid (OLA). The results showed the effectiveness of these platforms (CCM@DDP@OLA-NPs) for the treatment of bladder cancer. Specifically, DDP@OLA-NPs enhanced apoptosis in multidrug-resistant SW780 cells as compared to free drugs alone or single drug delivered by ADDS. CCM surface decoration was shown to promote the accumulation of DDP@OLA-NPs in SW780 cells. In an in vivo mouse tumor model, fluorescently labeled CCM-indocyanine green (ICG)-NPs group showed a 2.9-fold increased accumulation in tumor as compared with that in the non-coated ICG-NPs, and the fluorescence intensity in liver was only 23.5% of that of CCM-ICG-NPs in tumors. The above observations clearly demonstrated that the tumor targeting nature of CCM not only enhances uptake at the cellular level but also facilitates the accumulate of NPs in *in vivo* tumor tissue with reduced capture by Kupfer cells from the liver reticulo-endothelial system. Finally, the group of Wan[111] has isolated membranes from MDR lung carcinoma cell line (LLC/Dox) in mice to construct tumor homing ADDS and showed the therapeutic advantage of this ADDS.

CCMs eliciting multi-antigenic antitumor immunity

Cancer cell membrane coatings can serve as an ideal source of antigen, providing a complete repertoire of the tumor surface neoantigens, while minimizing inclusion of extraneous proteins that can dilute immune responses. Zhang et al[109] explored the presentation of B16-F10 mouse melanoma cell membrane in a context that could enable potent, multiantigenic immune responses for anticancer vaccine design. CpG oligodeoxynucleotide 1826 (CpG), a nucleic acid-based immunological adjuvant

known to trigger the maturation of antigen presenting cells, was encapsulated into PLGA nanoparticle cores using a double emulsion process, and these CpG-loaded cores were coated with the membrane of B16-F10 cells. The fact that CpG-NPs alone had no effect demonstrated that the inclusion of cancer membrane material helped to provide appropriate cues for the specific detection and elimination of malignant cells by the immune system. The upregulated expression of costimulatory markers CD40, CD80, and CD86, as well as MHC-II from bone marrow-derived dendritic cells (BMDC) and dendritic cell (DC) is largely driven by the detection of pathogen-associated molecular patterns, including CpG. The antigen-only NPs coated with cancer cell membranes exhibited significantly decreased activity in the absence of CpG. The results suggested that codelivery of both tumor cell membrane and the CpG adjuvant together in the same vehicle is necessary for eliciting maximal antitumor immunity.

In another study, tumor growth was significantly inhibited by co-administration of a checkpoint blockade cocktail consisting of anti-CTLA4 and anti-PD1antibodies, with a median survival extended from 18 days in the blank control to more than 48 days in the group treated with the combination procedure. Thus, the ADDS design incorporating both checkpoint blockaded and cancer cell membranes might bring the new outcome in cancer therapy.

Zhang et al[112] explored a B16-F10 cancer cell membrane-coated NPs, which retained multiple antigens on the particle surface. When the adjuvant monophosphoryl lipid A (MPLA) was inserted into the membrane coating, incubation of the particles with dendritic cells induced their maturation. These particle-pulsed dendritic cells were shown to physically interact with and stimulate antigen-specific T-lymphocytes, indicating potential for generating strong and specific antitumor immune responses. The in vivo long-term immune modulatory effect should be further investigated.

CCMs supplying the function of subcellular organelles

The development of subcellular organelles-based platforms is emerging as an appealing approach to address cellular dysfunctions associated with pathological conditions. CCM-derived materials through biomimetic engineering have gained great attention for

mimic subcellular organelles function. A report from the colleagues of Hélder A. Santos[65] has described a biomimetic cellular nanoreactor using the membrane originated from MDA-MB-231 breast cancer cells to coat undecylenic acid modified thermally hydrocarbonized PSi (UnPSi) nanoparticles. The UnPSi-NPs entrapped horseradish peroxidase (HRP) enzyme as a model biomimetic nanoreactor, and exhibited a high activity to decrease paraquat-induced reactive oxygen species (ROS) generation. The results suggested that the biomimetic nanoreactors exerted intracellularly a peroxisome-like activity against paraquat-mediated oxidative stress and protected the cells from death.

CCMs enhancing the therapeutic effect of sonodynamic therapy

In the past few years, ultrasound activated ROS-mediated sonodynamic therapy (SDT) has emerged as a viable alternative to traditional treatments of cancer, which has benefited from its deep tissue penetration and noninvasive features. The Zhang's group[62] hypothesized that CCM could minimize leakage of drugs in circulation and simultaneously ensure an ultrasound-responsive drug release in the tumor site with the help of CCM and SDT altogether. They developed a MCF-7 derived CCM biomimetic NP based on hollow mesoporous titanium dioxide loaded with hydroxychloroquine sulphate-loaded hollow structure with a particle size of approximately 100 nm; after loading with HCQ, the hydrodynamic diameter of HMTNPs/HCQ increased to 110.4±2.3 nm. Further coated with MCF-7 cancer cell membrane, the final CCM-HMTNPs/HCQ displayed a larger hydrodynamic size of 131.7±1.6 nm, accompanied by a CCM shell thickness of around 9.1 nm. In the initial *in vitro* drug release analysis, the cumulative release at 36 h of hydroxychloroquine sulphate decreased from 98% to 30% by CCM coating, and this release from CCM-coated NPs could be increased up to 90% with ultrasound. TEM analysis showed that the CCM outer shell was destroyed into fragments after ultrasound delivery, resulting in an ultrasound-responsive drug release profile. In vivo, CCM-NPs led to a strong inhibition of tumor growth, which was ultrasound-dependent. In an interesting experiment nude mice bearing dual tumors of HepG2 and MCF-7 cell lines origin were treated, and a strong preferential

biodistribution was observed in the homologous MCF-7 tumor as compared to the heterologous HepG2 tumor, presumably resulting from membrane-mediated homotypic adhesive interactions. This study suggests that CCM-based NPs offer new possibilities for sophisticated on-demand cargo delivery when combined with ultrasound.

Improving photodynamic and photothermal therapy

Similar to SDT, photodynamic therapy (PDT) has attracted increasing attention for its appealing advantages in precise ablation of local tumors in the presence of photosensitizer, oxygen and light. Zhang et al[113] developed 4T1 cell membrane coated NPs loaded with bioreductive drug tirapazamine into the porphyrinic metal organic framework PCN-224 (CCM@TPZ). The acidic tumor microenvironment (pH 5.5) was shown to be more suitable for tirapazamine release from CCM@TPZ compared to pH 7.4. A heterotypic CT26 tumor was implanted on the left hind leg and a homotypic 4T1 tumor was implanted on the right hind leg region of female Bal b/c mice to further validate the targeting specificity of CCM@TPZ. The dual tumor-bearing mice were administrated intravenously with CCM@TPZ. The strongly predominant accumulation in 4T1 tumors compared to the CT26 tumor demonstrated the highly specific homotypic targeting ability of 4T1 cell membrane. In this in vivo mouse model CCM@TPZ displayed a 6 to 10 folds antitumor activity enhancement compared with free drug or non-coated NPs. The mechanism was demonstrated whereby light irradiation could generate large amounts of ROS to kill tumor cells, while this further aggravated tumor hypoxia through photochemical oxygen depletion. Consequently, this accelerated the activation of the delivered tirapazamine for bioreductive chemotherapy. Similar results demonstrated that the combination of CCM with PDT therapy represents a promising strategy for future cancer treatment.[113]

Photothermal therapy (PTT) is also a rapidly developing technique that employs photothermal agents to heat tissues upon near infrared NIR light excitation, leading to cytotoxic effect on tumor cells. PTT has been widely acknowledged for its high anticancer efficacy, especially when combined with chemotherapy.[114] To combine

CCM and PTT, silica nanoparticles (SLN) with an amine-generated positive surface charge were synthesized and indocyanine green (ICG) was trapped into the SLN matrix, as described by Zhang et al.[69] Through theory of self-assembling positive and negative charges surfaces, the negatively charged membrane of 143B human osteosarcoma carcinoma cells was coated onto the positive surface of ICG loaded silica nanoparticles (zeta potential 35.4±1.8 mV) to construct a tumor-homing DDS (CCM@ICG-NPs, of final zeta potential -31.6±2.5 mV). The photothermal conversion efficiency of CCM@ICG-NPs under laser irradiation (1 W/cm^2) for 5 min could be detected by a temperature jump from room temperature (25°C) to 29.1°C. Moreover, the released ICG from CCM@ICG-NPs led to a temperature rise up to 57.9°C, similar to that observed with free ICG. These results indicated that the ICG molecules within CCM@ICG-NPs were well protected, leading to a comparable photothermal conversion capability to that of free ICG. Following the validation of photothermal conversion capability, the focus shifted to exploring the *in vitro* uptake rate. Not surprisingly, the ICG signals were highest in the group of CCM@ICG-NPs, being 4.5 folds and 1.3 folds that of free ICG and ICG-NPs, respectively. To investigate the role of CCM in the cellular uptake of 143B cells, the scientists pretreated with excess 143B cell membrane prior to the addition of NPs. As expected, it was observed that the cellular ICG intensity in CCM@ICG-NPs group not only significantly decreased but also returned to the level of ICG-NPs. These results suggested that the internalization of CCM@ICG-NPs into 143B cells was positively related to CCM modification. The CCM based ADDS showed great potential to target tumors for effective PTT.

ADDS DERIVED FROM TUMOR EXTRACELLULAR VESICLES (TEVS)

While the top-down approach of utilizing whole cancer cell CCMs to camouflage synthetic nanoparticles has achieved remarkable success in ADDS, it requires complex extraction and coating procedures. Alternatively, cancer cells naturally secrete TEVs that intrinsically inherit a highly similar lipid and protein composition from their parent CCMs. Because TEVs naturally possess nanoscale dimensions and inherent biocompatibility, transitioning from artificially engineered CCMs to these naturally

secreted TEVs represent a logical progression in the design of tumor-homing delivery systems. TEVs are small lipid membrane vesicles secreted by almost all kinds of tumor cells.[115] The exosomes (50-200 nm),[116] ectosomes (100-1,000 nm) and apoptotic bodies (50-5,000 nm)[117] represent different TEVs populations. Currently, the majority of TEVs studies focus on exosomes. The gold-standard technique for TEVs isolation is ultracentrifugation. However, this step is time-consuming and has low yields, which has restricted so far TEVs clinical application. In spite of this disadvantageous complex extraction process, the huge application potential of tumor TEVs has stimulated intensive research. The present review focuses on the comparison between CCM and tumor TEVs, especially tumor exosomes, which has rarely been carried out in previous reviews.[118, 119]

The term EV is currently used as a general term to describe virtually any type of membrane particle released by different type of cells.[120] The distinction between diverse EV subpopulation is primarily based on size and origin.[121]

Exosomes

Exosomes are extracellular vesicles secreted by cells into bodily fluids, with a size ranging from 50 to 200 nm.[122] They contain a variety of biomacromolecules such as RNA, DNA, proteins and lipids.[123] According to the latest guideline, namely the Minimal Information for Studies of Extracellular Vesicles 2018 guidelines,[124] isolated exosomes must be characterized by at least three positive protein markers, including at least one transmembrane/lipid bound protein (such as CD63, CD9) or cytosolic protein such as HSP70, as well as at least one negative protein marker which should be absent, such as lipoproteins).

Ectosomes

Microvesicles seem to originate directly from the plasma membrane, and are often classified as ectosomes.[125] While the formation of exosomes depends on local microdomains assembled in endocytic membranes, ectosomes derive from plasma membrane.[126] The process that leads to ectosomes generation starts from the formation

of outward buds at specific sites of the membrane, followed by fission and subsequent release of the vesicles into the extracellular space.[126, 127] Because ectosome formation relies on membrane budding, fluctuations in lipid and protein composition, and especially in the level of Ca^{2+}, are crucial.[128, 129] The externalization of phosphatidylserine (PS) phospholipid heads has been considered as one of the characteristic features of ectosomes, regardless of their origin from platelets, erythrocytes, HUVECs, neutrophils, monocytes and lymphocytes.[130-132] Moreover, lipid raft domains seem to be abundant in ectosomes. These lipid rafts are enriched in free cholesterol (FC) and glycosphingolipids, and are essential for maintaining cellular functions, including signal transduction, receptor activation and resistance of cancer therapy.[133] Several studies have reported that ectosomes formation is impaired by cholesterol depletion.[134]

Apoptotic bodies

Apoptotic bodies are released exclusively during apoptotic cell death, and this represent the most significant difference from other types of extracellular vesicles, such as exosomes and ectosomes, which are constantly generated by viable cells.[135] Another feature of apoptotic bodies is a wide range of sizes from 50-5,000 nm, as compared to exosomes (50-200 nm) or ectosomes microvesicles (100-1000 nm). [104]

Apoptotic bodies are produced during apoptotic cell disassembly, with for most of them an entire content made of condensed nuclear chromatin, whereas others EVs carry only cytoplasmic components.[104] This difference in composition is important to distinguish apoptotic bodies from exosomes and ectosomes, especially in their respective purification method,[104] since tightly packed DNA is denser compared to the enclosed cytoplasm, and it carries a large amount of negative charge.

Oncosomes

A more recently identified cancer-derived EV population from the brain tumors termed "large oncosomes", has been reported by Rak's group in 2008, [136] who found them to emanate from large protrusions of the cellular plasma membrane in metastatic prostate

cancer cells.[137] In this study, oncosomes were clearly structurally and morphologically unique.[138] Because of their atypical size (1-10 μm diameter), they were subsequently termed as "large oncosomes". [139-141]

Despite the apparent differences mentioned above among exosomes, ectosomes and apoptotic bodies, it is experimentally challenging to discriminate between them. Furthermore, there is no standardly descriptive physical property or clear molecular markers that can unambiguously distinguish them.[142-144] Therefore, we refer to these mixed vesicle populations as extracellular vesicles EVs, and in the frame of the tumor focus of the present review, we have concentrated on tumor extracellular vesicles TEVs.

TEV biogenesis and composition

The biogenesis of TEV is an interesting process, which is highly related with that of endosomes. TEV release involves four essential steps. (1) Plasma components and/or particles are internalized by various endocytic trafficking processes into transport vesicles.[145, 146] (2) The vesicles are budded in early endosomes.[147, 148] (3) The early endosomes collect proteins and other essential components, which then develop into late endosomes; late endosomes may recycle part of its components back to the plasma membrane or discard the vesicle for degradation by lysosomes.[149] (4) When late endosomes develop to become multivesicular bodies, they fuse with cell membrane by exocytosis and are released into the extracellular space.[150] After going through all these intracellular[151] processes, the exosomes are created.[127] TEVs and TEV sub-types biogenesis is depicted in Figure 3A,B.

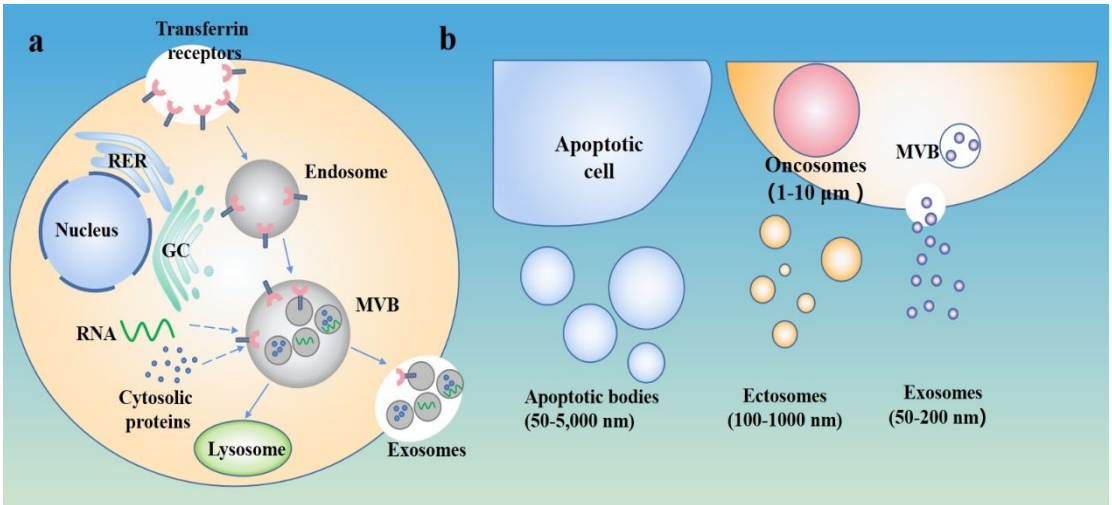


Figure 3. Biogenesis of TEVs and TEV sub-types. (A) Exosomes form via endosomal - lysosomal pathway (receptors, RER, GC involved). (B) TEV sub-types including apoptotic bodies, ectosomes, exosomes.

Given the crucial role of TEVs in intercellular communication through the transfer of their molecular cargo, it is essential to elucidate their composition. The most important TEV biomolecules include heat shock proteins,[152] cell adhesion proteins,[153] cell signaling proteins,[154, 155] tetraspanin membrane proteins,[156] and membraned related components, among them phosphatidylserine, phosphatidic acid, sphingomyelin, cholesterol and other lipids.[157, 158] In addition to these proteins and lipid components, various types of RNAs molecules are abundant in TEV, including small nuclear RNAs, non-coding RNAs, long non-coding RNAs, micro-RNAs, piwi-interacting RNAs, rRNAs, and tRNAs.[159, 160] Some components of TEV are similar to those of CCM.

TEV isolation and characterization

The most common methods for isolating and purifying TEVs are similar to those of CCMs, and involve a series of centrifugation steps. In addition to the traditional centrifugation-based isolation approach, several other methods have been developed to efficiently isolate tumor-derived exosomes from cells: (1) ultracentrifugation-based isolation techniques; (2) size-based isolation techniques; (3) immunoaffinity capture-based techniques; (4) TEV precipitation; (5) microfluidics-based isolation

techniques.[161] The choice of isolation strategies varies, based on the purpose of each research. However, the isolation process based on ultracentrifugation isolation techniques is much more complicated than for CCM isolation. An illustration of the collecting TEVs steps is depicted in Figure 4.

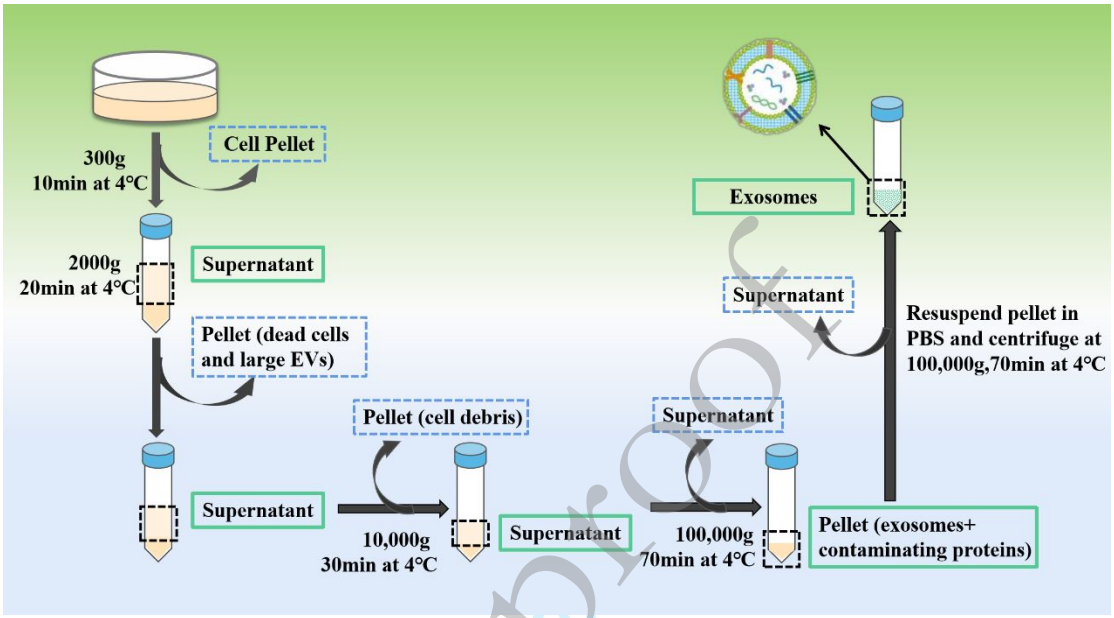


Figure 4. The brief process of TEV isolation. Cell pellet is sequentially centrifuged to remove dead cells, large EVs and debris. Supernatant is ultracentrifuged to pellet TEVs (with contaminants), then resuspended and re-centrifuged for purification.

TEVs characterization methods have been developed for both basic research and clinical purposes. They are based on a large array of techniques such as, in a non-limiting list, TEM,[162] SEM,[136] AFM,[163] nanoparticle tracking analysis (NTA),[164] DLS,[165] enzyme-linked immunosorbent assay (ELISA),[166] flow cytometry,[167] fluorescence-activated cell sorting (FACS),[141] microfluidics and electrochemical biosensors.[168] Most TEVs characterization assays are similar to those of CCMs. In the following section, we discuss the various source of TEVs in the frame of their application for ADDS. Some concerns have however to be considered when using EVs as drug delivery vectors. For instance, a group of studies has reported that mesenchymal stem cells derived EVs could promote tumor progression,[169, 170] while some reliable evidence points out that stem cell derived EVs can inhibit the occurrence and development of tumors.

TEVs used as ADDS

A rare type of exosome modification consists in the formation of vector exosomes. Maguire et al[171] have named vexosomes this type of exosomes. For instance, exosomes associated with a fraction of Adeno-associated virus (AAV) vectors, are referred to as vexosomes. AAV vectors are one of the frontrunners for gene therapy in humans due to the vector's good safety profile in clinical trials.[172] However, limitations exist for AAV vectored gene transfer following intravenous administration, including off-target gene delivery and low transduction of target tissue.[173] Exosomes have been shown to effectively shuttle between different cell types and deliver proteins and nucleic acids to recipient cells.[174] The association of AAV capsids with host cell-derived exosome may alter cell binding and transduction properties. Based on these hypotheses, researchers constructed vector exosomes and conducted a systemic evaluation.[146] A single-stranded AAV2 encoding GFP was produced by standard triple-transfection of AAV plasmids in 293T cells. After transfection, the EVs were isolated and observed upon TEM assay. The picture revealed that the EVs were near the surface of 293T cells and budding from the membrane of these cells. The ability of vexosomes to deliver AAV genomes to cells in vitro was evaluated on the cell line of 293T cells and human U87 glioma cells. As

expected, both AAV1-Fluc vexosomes and AAV2-Fluc vexosomes mediated enhanced transduction (3-5-fold) compared to their cell lysate purified parental serotypes, in both 293T cells and U87 cells.

In a separate study, Khan et al[175] developed AAV serotype vexosomes containing an inducible caspase 9 (iCasp9) suicide gene and the AAV293 cell line as the carrier. This modified AAV-iCAsp9 vexosomes along with a pro-drug (AP20187) caused a significant reduction in cell viability in Huh7 (human hepatocellular carcinoma) cells. This study highlighted the effectiveness of vexosome-based cancer gene therapy, while the specific efficacy of the vexosomes generated will be dependent on the source and type of packaging cells, on the physical parameters of vector packaging, on AAV serotype employed, and on size difference in the packaged expression cassettes. Further detailed mechanistic studies should be conducted urgently.

Delivery studies basing upon vexosomes are very few, which should be related with the safety and immunogenicity of vexosomes especially influenced by uncertainties associated with viruses and exosomes.[176] Furthermore, standardizing methods for scaling up vexosomes production presents a significant challenge. Despite having received less attention, vexosomes exhibit a high-efficiency plasmid delivery capacity, positioning them as a promising non-viral strategy for in vivo gene therapy.

Special advantages of TEVs

As reported by Yliperttula et al,[177] two TEVs populations (microvesicle- and exosome-enriched) derived from prostate cancer cells as carriers of paclitaxel (PTX) could deliver the drug to cells through an endocytic pathway, leading to an increased cytotoxicity. However, cancer cell-derived unloaded EVs increased cancer cells viability. The 110K exosome-enriched population seemed to enhance cell viability more than 20K microvesicles. So, a larger dose of the drug was required to counteract this enhanced viability effect. However, according to other reports,[178] EVs from non-cancer cells are capable of suppressing tumor proliferation, thereby presenting an appealing alternative to cancer cell-derived EVs.[179] Further, several studies verified that EVs derived from tumor cells could adopt the same repertoire of surface receptors and

extracellular matrix-binding proteins as their parental cell of origin,[180] which is different from those of non-malignant cells. These functions could be used as an advantage to increase the specificity of targeting and uptake to tumor tissues via TEVs.

Numerous reviews pointed out that TEV could be supplied as the carriers for targeting tumor tissue, delivering or co-delivering small molecules, nucleic acids, RNA and proteins. Xiao et al[181] exploited the simultaneous delivery an anticancer drug 5-FU and miR-21 inhibitor oligonucleotide (miR-21i) into mice bearing 5-FU-resistant colorectal cancer cell lines HCT-116^{5FR} and HCT-116^{5FR}. Exosomes were engineered to possess an anti-Her2 affibody on their surface by fusing it with LAMP2. LAMP2 is a surface protein abundantly expressed on exosomes. Meanwhile, GFP was fused at COOH-terminal for labeling the exosomes membranes. By modification the surface of exosomes with anti-Her2 affibody, engineered exosomes achieved cellular tropism in vitro and exhibited significantly enhanced accumulation in tumors in vivo.

Comparison of CCMs and TEVs lipid composition

Tumor exosomes are a type of extracellular vesicles released from tumor cells through the fusion of multivesicular bodies with the cell membrane. As a result, this might be one of the factors contributing to the observed similarities with CCM. Currently, the composition of tumor exosomes, as well as that of CCMs, has not been fully elucidated. Lipids play an important role in both CCM and tumor exosomes, having a structural role in exosomal or cancer cell membranes, and also being essential players in exosome/CCM formation and release to the extracellular environment. [182]

The lipid composition varies between malignancy types.[183] Moreover, the lipid composition may fluctuate in time depending on physiological conditions.[184] Here, we present the comprehensive overview about lipid composition between CCM and tumor exosome, as shown in Table 1.

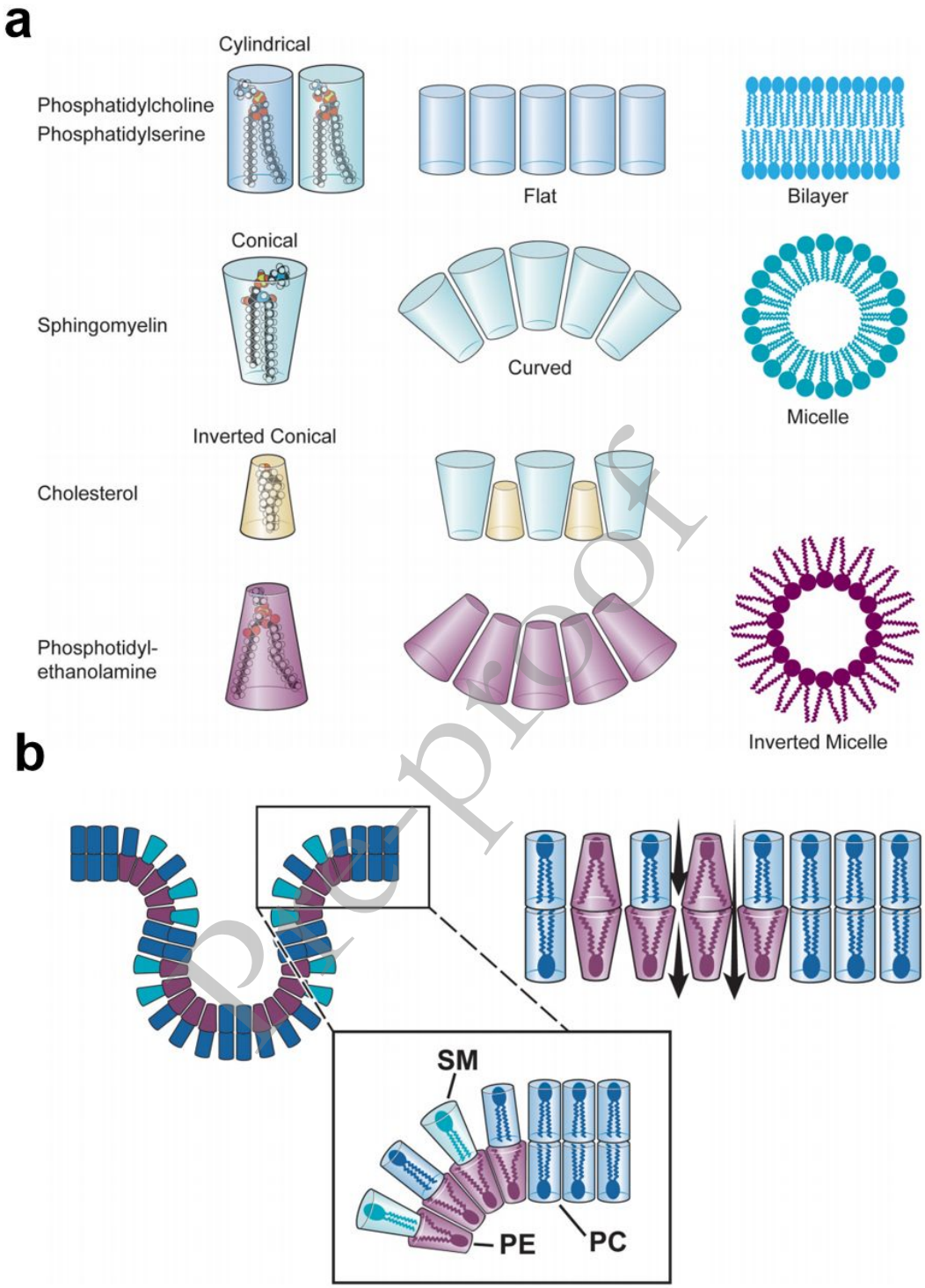
Table 1. Lipid composition of tumor exosomes and CCM released by various cancer cell lines.

Type (%)	Tumor exosomes			CCM	
Lipids/cell line	PC-3 cells[185]	PC-3 cells+HG[186]	HepG2/C3a[187]	HT-29[188]	MDA-MB231[188]
Cholesterol	43.5	59	43		
Sphingomyelin	16.3	9.1	9.7	2.5	8.3
Diacylglycerol	1.5	1.1	/	45.8	51.7
Phosphatidylserine	11.7	6.9	15.6	4	4
Phosphatidylethanolamine	5.8	1.1	7.4	2	4
Phosphatidylethanolamine eter	3.3	4.7	/	7.25	10.5
Phosphatidylcholine	15.3	10.8	20	9.5	13
Phosphatidylcholine eter	0.81	0.7	/	16.75	1.5
Phosphatidylglycerol	0.17	0.1	/	0.5	0.5
Phosphatidic acid	0.16	0.1	/	0.5	0.5
Phosphatidylinositol	0.13	0.3	4.1	4	4
Ceramide	0.32	0.7	0.63	/	/
Hexosylceramides	0.76	2.3	/	/	/
Dihexosylceramides	/	/	/	/	/
LacCer	0.12	0.7	/	/	/
Lipid analysis assay	MS	MS	HPLC/MS	MS	MS

%: Percent of total lipid quantified.

According to Table 1, only a few lipid compositions were analysis among various cancer cell lines, and they displayed an important diversity. Unexpectedly, the lipid compositions of CCM and tumor exosomes derived from the same cell line has not been described up to now, to our knowledge. Some lipids are critically important for cancer treatment. For instance, cholesterol content is related to cancer cells metastatic potency. A key mechanism involves its role in constructing and stabilizing lipid rafts-specialized membrane microdomains enriched in cholesterol and sphingolipids-which serve as signaling hubs that cluster receptors and downstream effectors to amplify pro-metastatic signaling essential for cell migration and invasion. Ceramide could induce cytochrome C release from mitochondria and consequently activate the cancer cell apoptotic pathway,[189], which was correlated with cancer cell proliferation and proper regulation of the cell cycle.[190] Phosphatidylserine has emerged as a prominent biomarker for targeting cancer cells, which is present on the inner leaflet of the cell membrane.[191] The oxidative stress causes exposure of phosphatidylserine on the surface of the cancer cells, while normal cells remain unaffected.

The major membrane lipids can be divided into three groups: cylinder-shaped lipids, cone-shaped lipids, and inverted-cone-shaped lipids.[192-194] As shown in Figure 5A on the examples of the phosphatidylserine, sphingomyelin, cholesterol and phosphatidyl-ethanolamine. Different lipid compositions affect the fluidity and thickness of cell membranes, consequently influencing their properties as carrier materials. Therefore, the lipid composition and ratio control the properties of CCM and tumor exosome used for “homogenous targeting” (Figure 5B). However, the specific lipid compositions have been poorly investigated, most of our knowledge of membrane compartments concerning predominantly protein content. Recent reports estimate a ratio of 50-100 lipid molecules per membrane protein,[195] therefore suggesting that lipid composition assessment is critically important to understand the biology of these vesicles and to investigate possible medical anticancer applications. Therefore, elucidating the lipid compositions of these membranes and integrating them with biomacromolecules and cells enables on-demand agent release at targeted sites, thereby mitigating overdose-associated toxicity and alleviating off-target effects.[196]



795

796 Figure 5. (A) Schematic illustration showing the relationship between lipid molecular shape and
797 membrane structure (illustrating how different lipid geometries dictate the formation of specific
798 membrane curvatures and extracellular vesicle structures). (B) Taking phosphatidyl-ethanolamine
799 as an example to explain how lipid arrangement influences the membrane permeability. Reproduced
800 with permission.[197] Copyright 2013, Elsevier

Comparison of CCMs and TEVs protein composition

The protein composition of CCM and tumor exosome has been studied using SDS-PAGE analysis, which is most widely used analytical approach based on 1-D gel electrophoresis separation.[198] Besides, western blotting, flow cytometry, mass spectrometry[199] and multi-dimensional protein identification technology, such as DISER,[200] profiling NRASQ61R-induced proteins using 2-dimensional difference gel electrophoresis coupled with serological proteome analysis, are often applied after the SDS-PAGE analysis. A promising strategy has been reported recently from the team of Di's group,[201] which is called nanozyme-assisted immunosorbent assay (NAISA). This technology is based on the grafting of peroxidase-like nanozymes onto the phospholipid membranes of exosomes and could avoid the need for post-labelling detection antibodies. The exosomal proteins are determined by a sensitive nanozyme-catalyzed colorimetric assay in less than 3 h, without the need for multi-step incubation and washing operations. Exosomes are engineered with DSPE-PEG-SH through hydrophobic interaction, and then are assembled with gold nanoparticles to produce Exo@Au nanozyme. The immobilized Exo@Au shows peroxidase-like activity allowing colorimetric assays by reaction with 3,3',5,5'-tetramethylbenzidine and H_2O_2 and protein level recording on a microplate reader. CCM proteins could likely also be detected through this technology allowing to compare the two populations.

Several studies have demonstrated that CCM and tumor exosomes from different tumor cell origin share common groups of proteins, which are classified into five groups:[202] (1) proteins with antigen binding and presentation capacity such as heat-shock proteins,[203] major histocompatibility complex (MHC) class I, and II proteins; (2) proteins related to intracellular membrane fusion and transport such as annexins,[204] E-cadherin,[205] and sorting nexin protein;[206] (3) proteins involved in targeting and cell adhesion, such as tetraspanins and integrins;[207, 208] (4) cytoskeletal proteins such as actin and tubulin; (v) metabolic enzymes such as ATP-binding cassette (ABC) transporters.[209] To date, the ExoCarta (http://exocarta.ludwi-g.edu.au/) references more

than 2590 distinct proteins.[210] However, the databank for cell membrane proteins has not been established yet.

Considering the wide variety of proteins expressed on the membrane of tumor exosomes and the insufficient information concerning tumor CCM proteins, we have collected in Table 2 the listed marker proteins of CCM and tumor exosomes, which might allow to distinguish differences between CCMs and tumor exosomes. The functional significance of the difference in protein biomarkers is still non elucidated.

According to the Table 2, the majority of the "markers" are transmembrane proteins, which could serve as both tumor cell membrane and tumor exosome "markers". While CD63 and CD82 are recognized as tumor exosome markers, CD166 is considered a marker of cancer stem cell membrane. Studies focused on these markers would be highly valuable. A good biomarker should not only distinguish between different states but also differentiate between cell condition. Through the assay of proteomic studies, a wealth of information regarding CCM and tumor exosomes might represent a highly effective tool. Recently, Ochiya's group[211] established a novel platform called ExoScreen, which enables direct and easy analysis of EVs. This platform can directly quantify the amount of EVs in blood samples based on an amplified luminescent proximity assay using two kinds of antibodies against proteins located on the surface of EVs, which can be detected by photosensitizer beads.[187] In this study, the researchers employed anti CD9 and anti CD147 antibodies and revealed that a higher number of CD9/CD147 double-positive EVs were contained in serum from colorectal cancer patients. The advantage of this assay is that it requires a very small sample volume, directly captures EVs and avoids a complicated isolation process.

Table 2. Identified candidate marker proteins of cell derived-CCM and tumor exosome.

Protein	Biomarker	Potential biological significance	Ref
CD9	Exosome CCM	CD9, a 24 kDa tetraspanin membrane protein, is known to regulate cell adhesion and migration, cancer progression and metastasis, immune and allergic responses, and viral infection.	184, 212
CD24	Exosome CCM	CD24 on tumor cells was identified as a phagocytic inhibitor ("don't eat me" signal) having a suppressive role in tumor immunity.	213, 214
CD44	CCM	CD44, a complex transmembrane glycoprotein, exists in multiple molecular forms. It could be regarded as stem cell-like marker and cancer membrane marker.	188
CD47	Exosome CCM	CD47 is a cell surface and exosome glycoprotein (Integrin-associated protein/IAP), originally identified as a regulator of integrin-dependent responses to extracellular matrix proteins.	62, 215
CD63	Exosome	CD63 is the first characterized tetraspanin protein encoded on human chromosome 12q13. It is a type III lysosomal membrane protein and plays important roles in membrane transport, fusion, and protein kinase signaling. CD63 is a biomarker of MDA-MB-231 and HT29 exosome.	216, 217
CD81	Exosome CCM	CD81 is a cell surface protein which belongs to the tetraspanin family. Exosome subpopulations derived from the same culture-batch of cells could be distinguished based on their glycomic signature. The CD81-positive exosomes preferentially expressed haseolus vulgaris agglutinin-L-binding proteins on pancreatic cancer cell lines surfaces. CD81 may be a new prognostic marker and a potential therapeutic target in acute myeloid leukemia.	218
CD82	Exosome	Similar with CD81, CD82 is a member of tetraspanin family. It is a multifunctional molecule involved in cell activation, costimulation, and cell spreading of T cells. Nowadays, CD82 is used as a diagnostic biomarker for precision medicine for breast cancer and pancreatic cancer.	219, 220
CD166	CCM	CD166, a 100 to 105 kDa transmembrane immunoglobulin is, used as a cell surface marker to enrich cancer stem cell from head and neck squamous cell carcinoma and nasopharyngeal carcinoma.	191, 221

TUMOR ASSOCIATED ANTIGEN USED IN ADDS

Cancer is recognized as a complex and dynamic disease that is very hard to cure by monotherapy. Consequently, combination therapy is a primary trend, particularly leveraging various nanomaterials. It reported that a triple immunotherapy strategy that combines bacterial-mediated dendritic cell maturation, PTT for generating tumor-associated antigens, together with PD-1 blockade.[222] This led to advanced melanoma growth inhibition and relapse prevention. In this study, PTT effectively eradicated the majority of tumor cells, with their subsequent lysis serving as tumor-associated antigens. These antigens could help stimulating an antigen-specific strong immune response. Triple therapy resulted in a 3.0-fold increase in $CD8^+$ T cells and a 1.3-fold increase $CD4^+$ T cells in animal spleens. This approach provides a new concept for oncotherapy, centered around leveraging tumor associated antigens and immunotherapy to increase tumor penetration efficiency.

SUBCELLULAR ORGANELLE-MEDIATED ADDS

Mitochondria targeting and use for ADDS

Research in the field of cancer therapy targeting mitochondria has primarily focused on developing drug delivery systems specifically designed for mitochondria. Despite intensive research, viable mitochondrial drug delivery systems are still missing. To achieve efficient mitochondrial drug delivery, methods of drug encapsulation into carriers that take the physical characteristics of the drugs into account must first be developed. Secondly, the carriers must be efficiently targeted and internalized by specific cell types. Finally, sophisticated regulation of intracellular trafficking is necessary to release the drug carrier from the endosome to the cytosol and subsequent delivery to the mitochondria.[223] Delivery to mitochondria might require using a mitochondrion-targeting peptide. Meanwhile, a tumor-targeted ligand on the ADDS is also indispensable to achieve cancer treatment. Lo et al[224] developed dual-nanoparticle formulations for the co-treatment with a microRNA (miR-125) and a phytochemical (Ellagic acid). Both solid lipid nanoparticles (miR-125/SLN-KL) and lipid-polymer

nanoparticles (E/LPN-KL) were modified with the same dual peptides—an L peptide for EGFR targeting and an M peptide for mitochondria targeting (referred to as the K peptide herein). This co-treatment strategy regulated multiple pathways related to tumor metabolism, mitochondrial dynamics, apoptosis, drug resistance, and metastasis in SAS cells.

Zhang's group[225] developed a single-agent self-delivery chimeric peptide for mitochondria and plasma membrane dual-targeted photodynamic tumor therapy. This peptide consists of PpIX-KrFxrFxrFxr with PEG_8, where r represented D-arginine and Fx represented L-cyclohexylalanine. This chimeric peptide could destroy the 4T1 tumor cell membrane, leading to a degree of cell necrosis. Consequently, the membrane permeability change is aimed at enhancing the ADDS cellular delivery. Thereafter, this peptide could selectively aggregate on mitochondria and synergistically promote cell apoptosis when exposed to light irradiation. This stepwise delivery design was validated by confocal microscopy. It simplifies the complex multi-carrier scheme used in previous examples and represents a promising direction for future delivery research.

Recently, it has been reported that mitochondrial membranes in prostate and colon cancer cells, as compared to normal mitochondria, have an enhanced rigidity, more pronounced anionic lipid headgroups, and higher cytochrome c oxidase activity in cancer cell samples than normal cell samples.[226] This finding suggests investigating the potential of cancer cell specific mitochondrial membranes as a carrier for drug delivery.

Golgi apparatus targeting and use for ADDS

Golgi apparatus is an organelle composed of many flat vesicles,[227] whose main function is related to the processing, sorting, and transport of different types of proteins synthesized by the ER, and then sending them to the proper cellular localization. Cargo transport through Golgi apparatus occurs through vesicles and is bidirectional, anterograde and retrograde, both vesicular transports being mediated by coatomer protein complex I (COPI). According to a recent study,[228] the transcriptional regulator YAP can potentially regulate COPI-associated inflammatory diseases, including cancer.

YAP plays an important role in development, regeneration, and tumorigenesis.[228] Consequently, Golgi apparatus has been proposed as a target for cancer therapy.[229] Gong et al[230] reported the production of a Golgi-targeting prodrug nanoparticle system, through the synthesis of retinoic acid-conjugated chondroitin sulfate (CS-RA). This selective targeting strategy is based on the high affinity of chondroitin sulfate nanomicelles for the Golgi apparatus in hepatic stellate cells. The anticancer compound paclitaxel (PTX) was encapsulated into this Golgi-targeting formulation, in which the released retinoic acid inhibited the expression of metastasis-associated proteins. The mouse group treated with PTX-CS-RA exhibited the lowest rates of breast cancer and lung metastasis incidence.

Yi et al[231] assembled a pH-responsive dye and bovine serum albumin (BSA) into BSA-pH-PTT nanoparticles. The extracellular pH around cancerous cells has been reported to be weakly acidic (pH<6.5), while the cytoplasmic pH in both normal and cancer cells is weakly alkaline (pH>7.2).[232] Furthermore, the endoplasmic reticulum (ER) and mitochondria are weakly alkaline, while lysosomes and the Golgi apparatus are weakly acidic.[233] Yi et al chose cyanine dye as the pH-sensitive marker, which is highly sensitive to pH in the range of 6.2 to 7.5. Due to the hypertrophic morphology of the Golgi apparatus in cancer cells, BSA-conjugated-pH nanoparticles accumulated in the Golgi apparatus of cancer cells. As the laser irradiation time increased, HepG-2 cells (human liver cancer cell) and HL-7702 (human normal liver cells) exhibited distinct behaviors. Specifically, obvious cell death occurred in HepG-2 cells (marked by red fluorescence). In this study, the authors verified that BSA-pH-PTT could distinguish cancer cells from normal cells might be attributed to the pH gradient and the fragmented morphology of the Golgi apparatus.

Endoplasmic reticulum targeting and used as ADDS

The endoplasmic reticulum (ER) is a central organelle where secreted and transmembrane proteins are synthesized, folded and modified.[234] Most of the time, this process is strictly regulated, except when multiple external factors and cell-intrinsic

events disrupt the function of protein-folding, provoke a state of ER stress induced by reactive oxygen species (ROS), and lead to immunogenic cell death. You et al[235] have generated a double ER-targeting strategy via two nanosystems: ER-targeting pardaxin (FAL) peptides modified nanospheres (FAL-ICG-HAuNS) and an oxygen-delivering hemoglobin liposome (FAL-Hb-lipo), both designed to reverse hypoxia and modulate dendritic cell maturation. Basu et al[236] have described a self-assembled hexameric structure comprising an ER-targeting moiety, an ER-stress inducer (triazine) and a DNA damaging drug (5-FU). These components self-assembled to form ER-targeting nanoparticle (ER-NP). These ER-NPs were internalized by HeLa cervical cancer cells via macropinocytosis and specifically localized into ER to induce ER stress and DNA damage leading to cell death through apoptosis. In this process, the ER membrane wraps around nucleus and forms double membrane nuclear envelope, leading to ER-nuclear cross-talk as reported by some experts, and 5FU increased delivery to the nucleus.[237] This suggests that the ER membrane might be a next breakthrough in drug delivery to nuclear therapy.

Nucleus targeting and used as ADDS

Alterations in nuclear shape in cancer cells are often related with altered organization of the chromatin, which in turn can influence patterns of gene expression and potentially contribute to cellular transformation.[238] It has been confirmed that the nucleus, its nuclear membrane and chromatin are directly wired to the cytoskeleton through the nucleo-cytoskeleton complex, the nuclear pore complex, and the underlying lamina.[239] Nuclear targeting is of crucial importance for gene therapy and cancer therapeutics. Several nuclear targeting strategies have been proposed.

Tang et al[240] developed a nuclear-targeted photothermal strategy based on copper sulfide nanoparticles (CuS NPs) equipped with two peptides: RGD peptides, which bind to angiogenic endothelial cells in tumors and minimize damage to normal tissues, and the TAT peptide considered as a nuclear localization signal for uptake through the

nuclear pore complex. These nucleus-target ADDS with the help of an irradiation laser led to tumor complete regression.

Another strategy targets the nucleus membrane. Recent studies have demonstrated that mechanical stiffness of cancer cells correlates with their metastatic potential in patient tumor cells.[241, 242] Lower stiffness is related to more invasive cells. Nuclear lamin A protein correlates with tissue stiffness and generates a barrier to cells migrating in three-dimensional environments.[243] El-Sayed et al[244] used three ligands, PEG for increasing the biocompatibility of gold AuNPs, RGD peptides for binding to the surface integrin of HEY A8 cancer cells and NLS (CGGGPKKKRKVGG) peptides for targeting to the nucleus. The aim of this study was to enhance nucleus stiffness to decrease the metastatic potential of cancer cells. In this study, cell stiffness and thickness were assayed using AFM, and a recently-developed differential interference contrast (DIC) microscopy-based 3D imaging method to visualize and locate plasmonic AuNPs inside the cells.[245] The study revealed that the gold nanoparticles increased in the cell stiffness. Finally, a third strategy to target the nucleus is to use nuclear localization sequence (NLS) residues to accumulate nuclear and perinuclear targeting efficiency.

In summary, nuclear targeting has been less investigated as compared to other cellular organelles. However, it is now recognized that the nucleus is not a passive intracellular structure but can regulate the distribution of intracellular and modulate cell resistance to strength.[246] Hence, this should foster further nucleus-target studies in ADDS strategies.

CONCLUSIONS AND REMARKS

Biomimetic ADDS has evolved from PEGylated nanocarriers to sophisticated cell membrane-derived and organelle-targeting platforms, addressing tumor specificity, immune evasion, and intracellular precision. CCM-coated nanoparticles demonstrate exceptional homotypic targeting through preserved membrane proteins (such as cadherins, integrins, CD47), yet suboptimal circulation times and lack of standardized

isolation protocols impede clinical translation. TEVs, particularly exosomes, offer naturally occurring carriers with superior biocompatibility, but low isolation yields, population heterogeneity, and potential protumorigenic risks require rigorous evaluation. A critical knowledge gap lies in lipid composition: lipids dictate membrane fluidity and targeting efficiency, yet direct CCM-versus-TEV lipidomic comparisons remain absent. Besides, subcellular organelle targeting (mitochondria, ER, Golgi, nucleus) represents an underexplored frontier, with cancer-specific membrane signatures offering selective delivery opportunities, though technical hurdles in organelle isolation persist. To achieve superior therapeutic selectivity, the most promising trajectory involves hybrid systems integrating CCMs, TEVs, and organelle-targeting peptides for sequential targeting from circulation to intracellular compartments. Nevertheless, for successful clinical translation, three critical priorities must be addressed: (1) mechanistic deconvolution of membrane-mediated recognition through integrated lipidomics and proteomics; (2) scalable manufacturing with defined quality attributes; and (3) comprehensive immunogenicity and toxicological profiling. By harnessing the biological intelligence of cancer cell membranes, extracellular vesicles, and subcellular organelles, next-generation ADDS can transcend conventional nanomedicine limitations, ultimately realizing the long-standing vision of precision cancer therapy.

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FUNDING AND ACKNOWLEDGMENTS

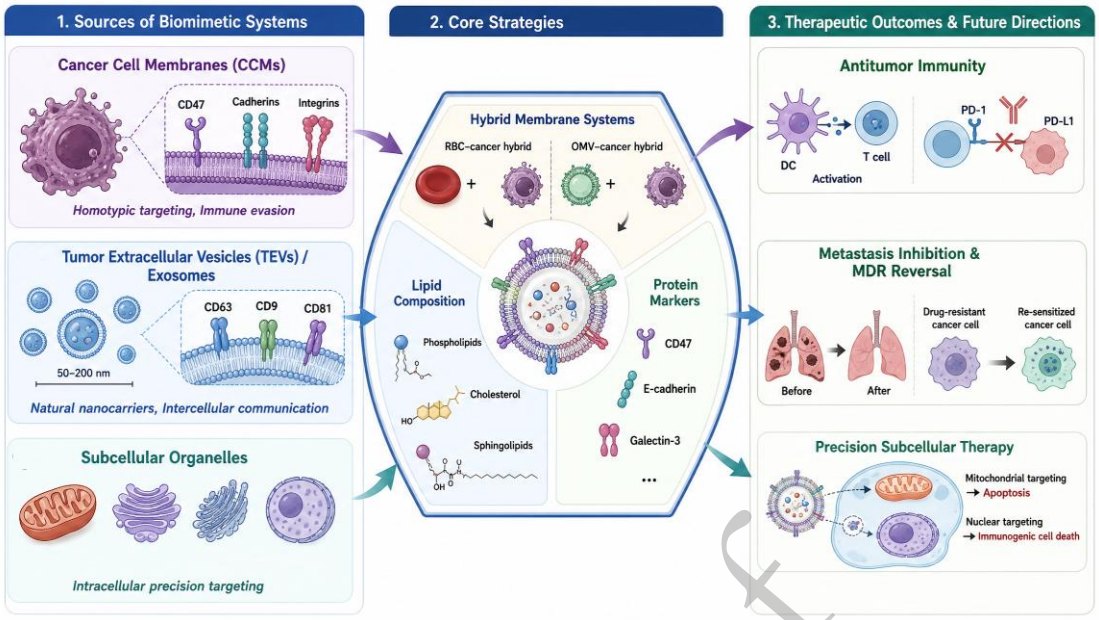
This work was supported by the Chongqing Natural Science Foundation (No. CSTB2022NSCQ-MSX0350); Open Fund of Personalized Drug Therapy Key Laboratory of Sichuan Province (No. 2021YB03); Sichuan Cancer Hospital Outstanding Youth Fund (YB2023026) and Chinese Pharmaceutical Association Hospital Phamacy Fund (CPA-Z05-ZC-2022-002). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

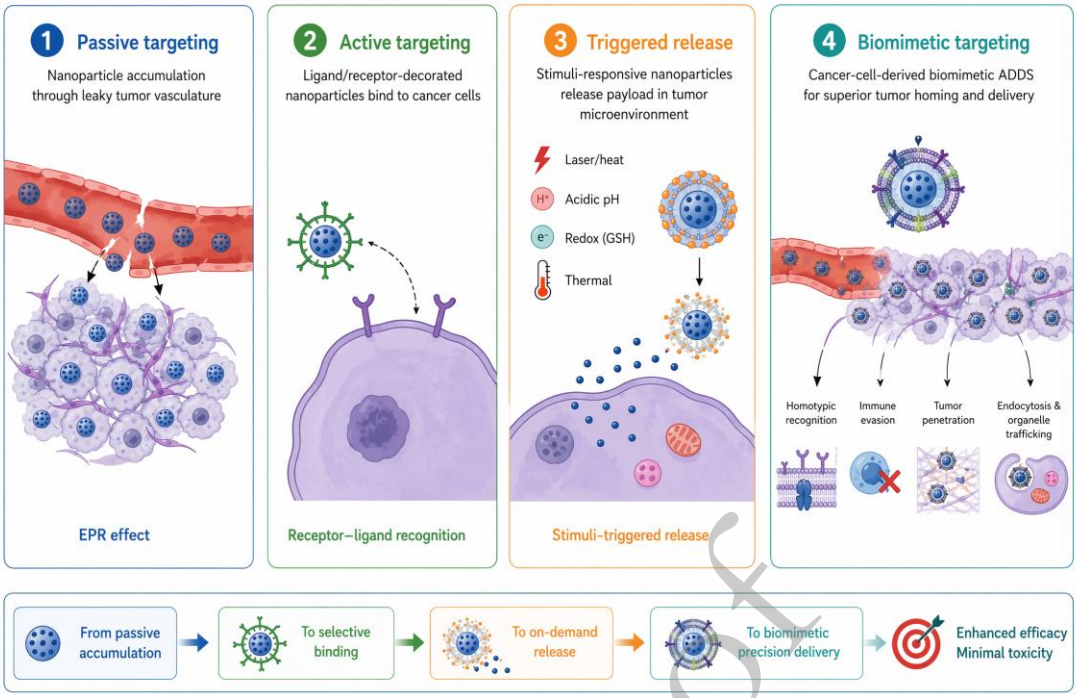
AUTHOR CONTRIBUTIONS

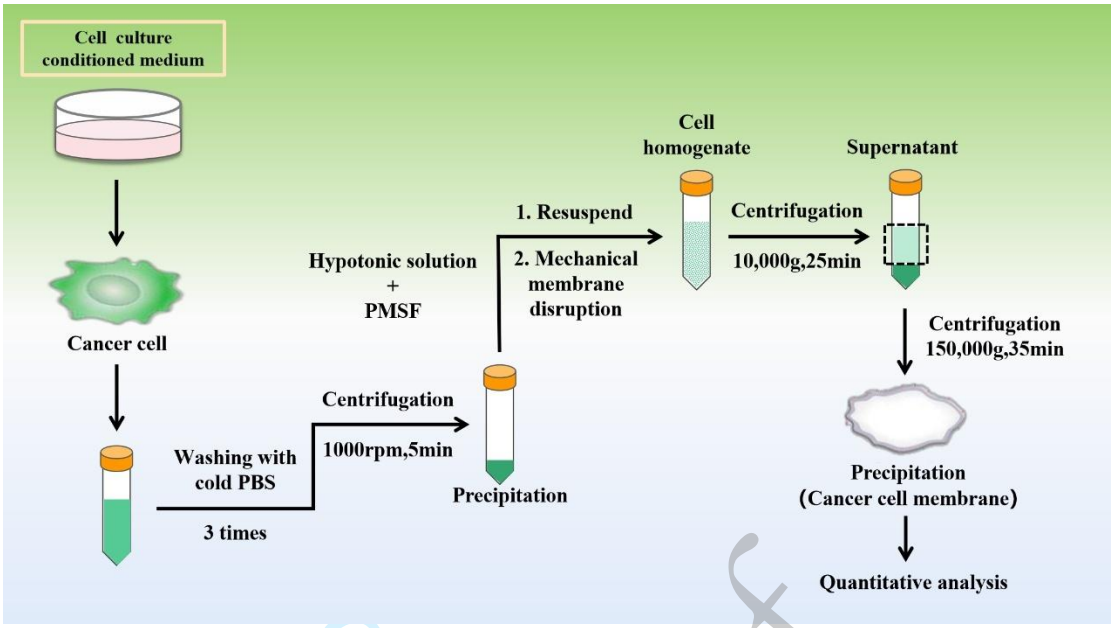
Y.C. conceived and wrote the paper, drew the picture and analysis the table data; H. X. revised the paper; H.Z. downloaded the copyright and made the revision; N.X. checked the references and collected the data from references; D.S. supervised the project and contributed to reviewing and editing the manuscript. C.W. and S.S. contributed to the conceptualization, supervision, project administration, funding acquisition, writing-review & editing; W.T. reviewed the manuscript. All authors contributed to the manuscript and approved the final version.

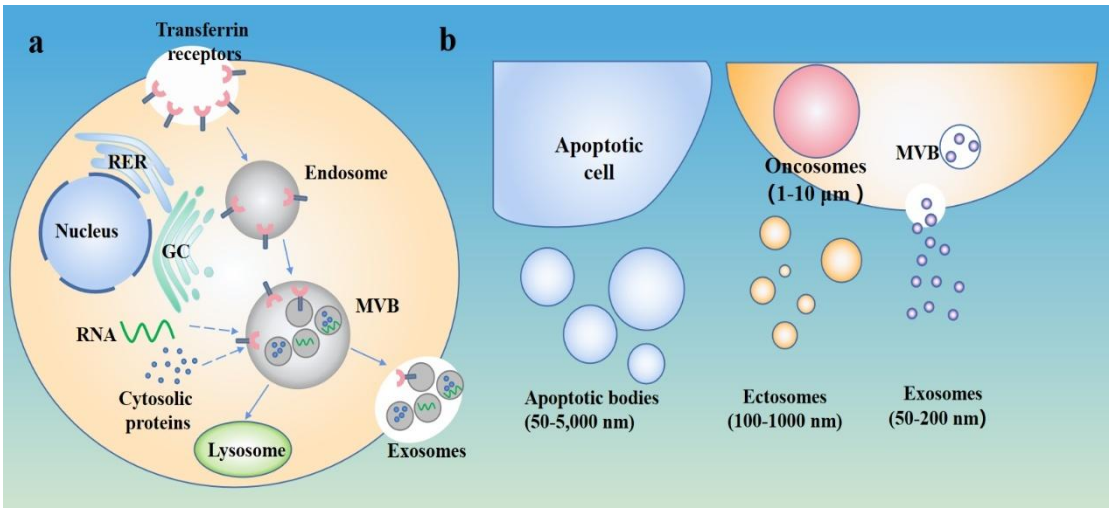
DECLARATION OF INTERESTS

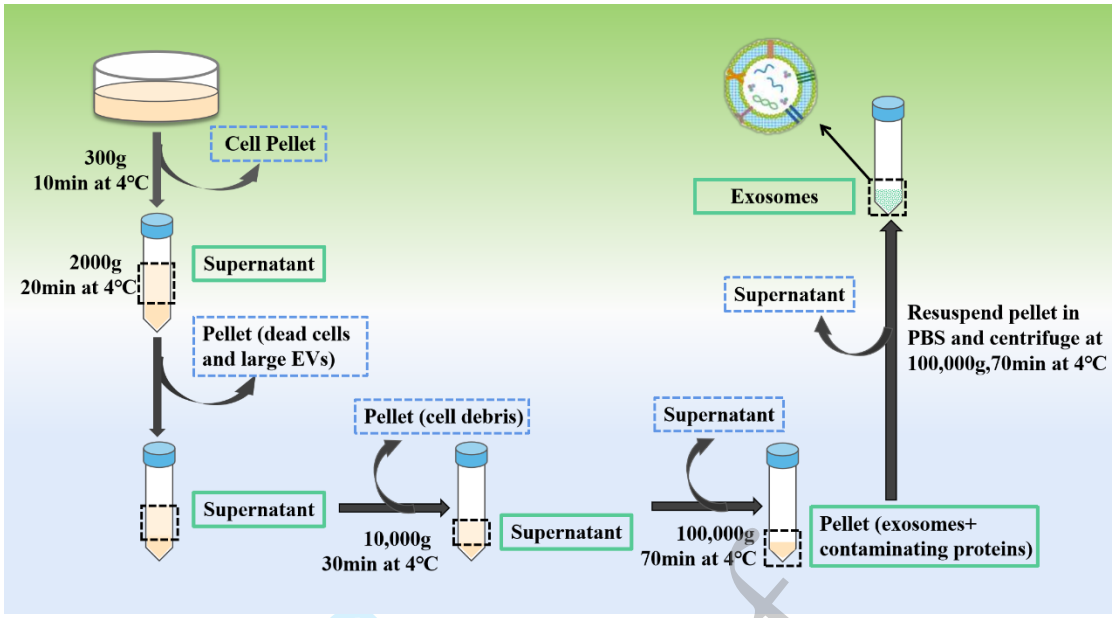
The authors declare no conflicts of interest.

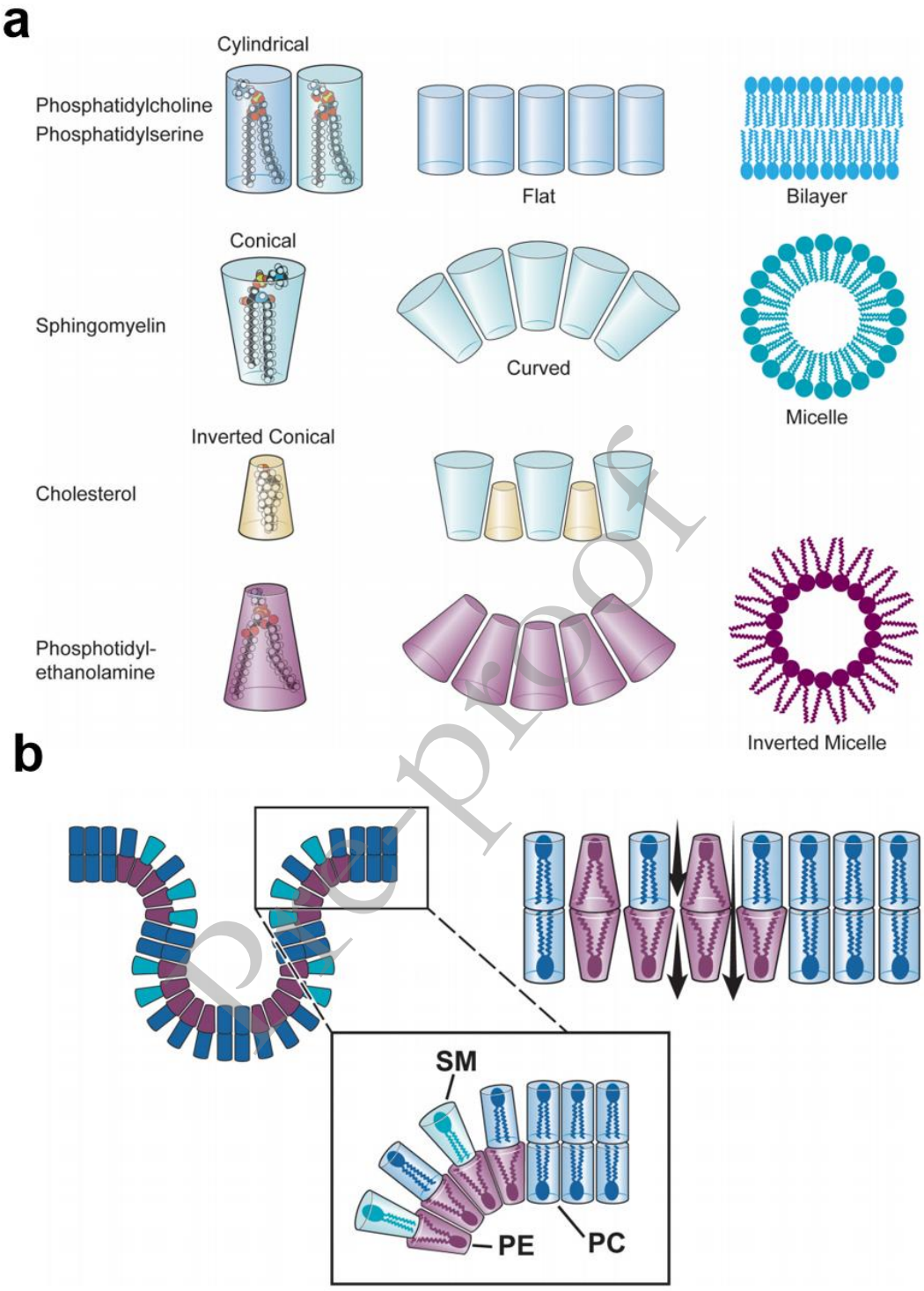








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SUPPLEMENTAL INFORMATION

Cancer cell membranes, tumor extracellular vesicles, and subcellular organelle targeting as promising biomimetic drug delivery systems

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Table **S1**. The representative CCM-derived ADDS with antitumor properties.

No.	Membrane source	Formulation	Loading drug	Carrier materials of ADDS	Circulation time	Targeting efficiency of CCM-ADDS	Cell membrane protein analysis	In vivo toxicity	Reference
1	MDA-MB-435	Nanoparticles	NA	PLGA	NA	CCM coating enabled approximately 40-fold and 20-fold increases in uptake compared with RBCNPs and bare PLGA cores, respectively.	Cadherins;Na+/K+-ATPase; Glycoprotein 100	NA	[1]
	MDA-MB-231 and Hela	Nanoparticles	DOX and siRNA targeting PD-L1	PLGA	NA	An approximating 100-fold in terms of the mean fluorescence intensity was observed in Hela cells while no obvious uptake of Hela coated nanoparticles was found in MDA-MB-231 cells.	Pan-cadherin and GAPDH	Hela membrane coated nanoparticles induced a much higher cytotoxicity in Hela cells while no significant effect was observed in MDA-MB-231 cells. The unique cytotoxicity of Hela membrane coated nanoparticles in Hela cells implicated the self-selective cellular uptake and biosecurity of CCM.	[2]

4	MDA-MB-831	Nanoparticles	DOX	mPEG-PLGA	At 24 hours, the total intensity of the organs from the animals treated with CCM coated NP was slightly higher than that of uncoated NP and then started reducing thereafter till 120 h.	Whereas, the intensity of CCM coated NP fluorescence in the lungs was near to 2-fold higher compared to none coated NP fluorescence ($P<0.05$). In contrast to lungs, the fluorescence intensity of the CCM coated NP in the spleen was similar to the fluorescence intensity of NP at 24 h ($P<0.05$), while CCM coated NP intensity was increased by 2.5-3-fold ($P<0.001$) from 24 h to 48 h.	SDS-PAGE	To demonstrate the biocompatibility of these nanoformulations histopathological evaluation of the extracted organs (brain, heart, lungs, liver, kidney, and spleen) were performed. No major perturbations to normal organ tissue structure were observed.	[3]
5	MCF-7	Nanoparticles	ICG	PLGA	The blood circulation time curve revealed that the ICG blood concentration when loaded in CCM coated NP was 7-14 times higher than when given as free ICG at the first 60 min after injection. The AUC_{24} of ICNPs was 411 $\mu g \cdot min \cdot mL^{-1}$, which was significantly higher (11.7 times) than that of free ICG(35$\mu g \cdot min \cdot mL^{-1}$).	CCM coated NP possessed homologous tumor targeting and reduced interception of the liver and kidney and finally obtained a 3.1-fold and 4.75-fold increased tumor accumulation compared with that of none coated NP and free ICG.	N-cadherins; Na+/K+-ATPase;Gelactin-3	Concentration of ALT/AST/CRE/BUN showed no obvious change compared with PBS control group. H&E staining indicated that treatment with CCM coated NP was biocompatible and safe in nude mice.	[4]
6	4T1	Nanoparticles	Tirapazamine (TPZ)	Porphyrinic metal organic frameworks	NA	Much stronger red fluorescence was observed in the homotypic 4T1 cells than that in the other kinds of cell lines.	Pan-cadherin and Na + /K + -ATPase. The absence of intracellular markers.	Levels of TP, ALB, GLO), ALT, AST, GLU were found roughly the same and remained at the normal range, suggesting a low systemic toxicity of these formations during the treatments. By the H&E staining analysis. Of note, there were little	[5]

								metastases found in heart, spleen and kidney tissues of all mice.	
12	4T1	Micelle	Conjugated chimeric peptide	NA	The CCM coated micelle presented more remarkable cell membrane retention capacity than none-coated micelle.	The tumor growth in the CCM coated micelle was restricted effectively (about 0.78-fold of relative tumor volume at 15th day, while in none coated group the tumor growth was moderately restricted (about 2.34-fold of relative tumor volume at 15th day).	SDS-PAGE	The H&E analysis of the main organs(brain, heart, lungs, liver, kidney, and spleen) of the four groups verified no obvious systemic toxicity was found.	[6]
13	4T1	Nanocrystals	Hydroxycamptothecin	Nanocrystals	The half-life was extended to 7.9 h (≈50-fold increase compared to none coated nanocrystal.	The maximum signals inside 4T1 cells that were approximately 20-fold greater than the none coated nanocrystal.	EpCAM and E-cadherin	NA	[7]
15	4T1-Luc and B16-F10	Nanoparticles	TiO_2	GOx decorated TiO_2@MnO_2 core-shell nanoreactor	NA	The cell survival rate of the X-ray treated CCM coated NP group is about 10%, while the survival rate of the cells in the pure X-ray treatment group or none coated NP group is more than 90%.	SDS-PAGE	H&E staining of other organ tissues (heart, kidneys, liver, and spleen) revealed that the nanoreactors have no obvious toxicities.	[8]

16	OCI-LY10	Nanoparticles	MSN	Silicon	NA	This preparation could block the lymphoma cell cycle and promot mitochondrial-mediated apoptosis to enhance antitumor effect.	E-cadherin Pan-cadherin	No abnormal changes were present in WBC, HGB, PLT, ALT, AST, BUN, CRE, CK and Myo. Similarly in H&E staining.	[9]
20	143B	Nanoparticles	ICG	Silicon	NA	The cell uptake rate of CCM derived NP was significantly higher than none-CCM derived. *In vivo*, the distribution profile of CCM- derived NP was significantly changed alleviate with less accumulation in liver and kidney while enhanced homing to tumor tissue.	AT1R and CXCR4	NA	[7]
21	HepG2	Nanoparticles	DOX	PLGA	NA	The fluorescence intensity of HepG2 cells treated with CCM derived NP was approximately 4- to 5-fold stronger than none coated NP.	Galectin-1; galectin-3; CD47; H3; COXIV	CCM derived NP was observed barely tissue damage were observed in all the extracted organs.	[10]
22	SW780 cell	Nanoparticles	Cisplatin and Oleanolic acid	Zeolitic_x005f imidazolate framework nanoparticles	NA	CCM derived NP group showed 2.91-fold of fluorescence signal in tumor compared with that in the none coated group.	AT1R and CXCR4	It was suggested that CCM derived NP was a highly biocompatible DDS.	[11]
23	HeLa/DOX cells	Nanoparticles	siRNA with DOX	Silica	NA	After 48 h of treatment using CCM derived NP, the intracellular DOX level in HeLa/DOX cells increased 1.46-fold (4 h) and 1.35-fold (8 h), respectively, than untreated group. The extended treatment with CCM derived NP (72 h) further enhanced the drug accumulation in Hela/DOX cells to 1.77-fold (4 h) and 1.91-fold (8 h), respectively.	AT1R and CXCR4	NA	[12]

24	BxPC-3	Nanorods	DOX	Silica	NA	The retention amount of CCM derived nanorods at 24 h was up to 20%, which was almost 4 times and 10 times higher than the retention amount of liposome membrane-coated NP and none coated NP, respectively.	SDS-PAGE	NA	[13]
25	KB	Nanorods	NA	Au	The blood clearance half-lives of CCM derived NP and none coated NP were 4.36 h and 2.71 h.	The tumor in CCM derived NP group had a much higher dose of gold than none coated NP.	SDS-PAGE	The blood concentrations of AST and ALT, which are indicators for liver function, and BUN and CRE, which are indicators for kidney function, in the CCM derived NP treated group were comparable to that of the control group (p=0.05).	[14]
26	UM-SCC-7 and HeLa	Nanoparticles	DOX	Fe_3O_4	NA	The fluorescence intensity originating from UM-SCC-7 and Hela cell membrane coated NP was far superior in the corresponding source cells over those in heterotypic cells, which approximated to 12~18 folds in terms of the mean fluorescence intensity inside cells.	Cadherins; Na+/K+-ATPase, glycoprotein 100; Histone H3; COXIV; GAPDH	NA	[15]
27	MDA-MB-435 , DU 145, CAL 27 and HCT 116	Nanoparticles	NA	β -NaYF 4 :Er3+ ,Yb 3+ as the core of UCNPs, and PEGylated phospholipids	NA	The mice injected with CCM derived exhibited extremely effect in the tumor site, even brighter than the mice treated with FA-coated NP in the same site.	Carcinoembryonic antigen (CEA) and galectin-3	We observed no significant differences between the treatment groups and the control group in the blood parameters and blood biochemistry indicators (ALT, AST, ALP, BUN, and CRE). Furthermore, no noticeable signal of major organ damage was observed from H&E-stained slices.	[16]

28	SGC7901	Nanoparticles	chlorins e6	Silica	NA	The CCM based NPs was 2.0 and 4.0 folds to NPs and free drug on the SGC7901 cell uptake. *In vivo* tumor target rate also verified 3 folds compared to none CCM based NP.	AT1R, CXCR4	No significant differences between the mice body and no major organ damage were observed from H&E-stained slices.	[17]
29	LLC/Dox (drug resistant cell line)	Miclelle	Sorafenib and Dox	NA	NA	The CCM based NPs was about 2.0 folds to NPs on the LLC/Dox cell uptake.	AT1R and CXCR4	NA	[18]

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