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Review Article

Advances in Tumor Targeting Biomimetic Drug Delivery Systems: A Promising Approach for Antitumor Therapy

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Abstract

Cancer is one of the most fatal diseases that attract numerous efforts and attention from researchers. Among plentiful therapeutic agents, chemotherapy is frequently used in treating virulent tumors, and its insistent administration is useful in the ablation of cancers; however, it also produces side effects. Biomimetic drug delivery systems (BDDSs) provide an alternative route for antitumor therapy. Their endogenous substances may be extracellular vesicles, living cells, cell membranes, etc., which optimize single-agent chemotherapy. They "upgrade" traditional drug delivery platforms by combining the original drug with itself, disguised as a Trojan Horse, to trick the immune system or tumor tissues to achieve higher targeting and lower immunogenicity. Herein, we review three BDDS strategies being used recently in antitumor drug development and their advances, aiming at providing general guidelines and opportunities in this field in the future.

Keywords
- biomimetic drug delivery system
- antitumor
- nanoparticles
- endogenous substances

Introduction

Since its discovery, cancer has been considered to be one of the most lethal diseases with a high mortality rate and a heavy social burden. Unfortunately, its occurrence is rising dramatically across the globe, preventing people from reaching a higher life expectancy.[1] It brings patients not only physical and mental pain but also a burden on their lives. Chemotherapy, especially combination chemotherapy, is the most prevalent strategy in cancer treatment,[2] which uses small molecules to eliminate tumors. However, these small-molecule drugs would cause some adverse reactions under normal circumstances, leading to a decrease in patient compliance.

With the widespread application of nanomaterials in the medical industry, nanoplatforms have been the most commonly used materials in drug delivery.[3] The platforms are usually meticulously fabricated. By manipulating these platforms, nano-drug delivery systems (NDDSs) can achieve enhanced permeability and retention (EPR), improved circulation capability, reduced toxicity as well as increased penetration of biological barriers when compared to traditional chemotherapy.[4–6] Thus, these drug delivery systems (DDSs) have the advantages of prolonging the half-life of drugs, boosting drug accumulation, and conducting controllable release at the target site, leading to minimized side effects on the nontargeted tissues.[7] These advantages give DDS an

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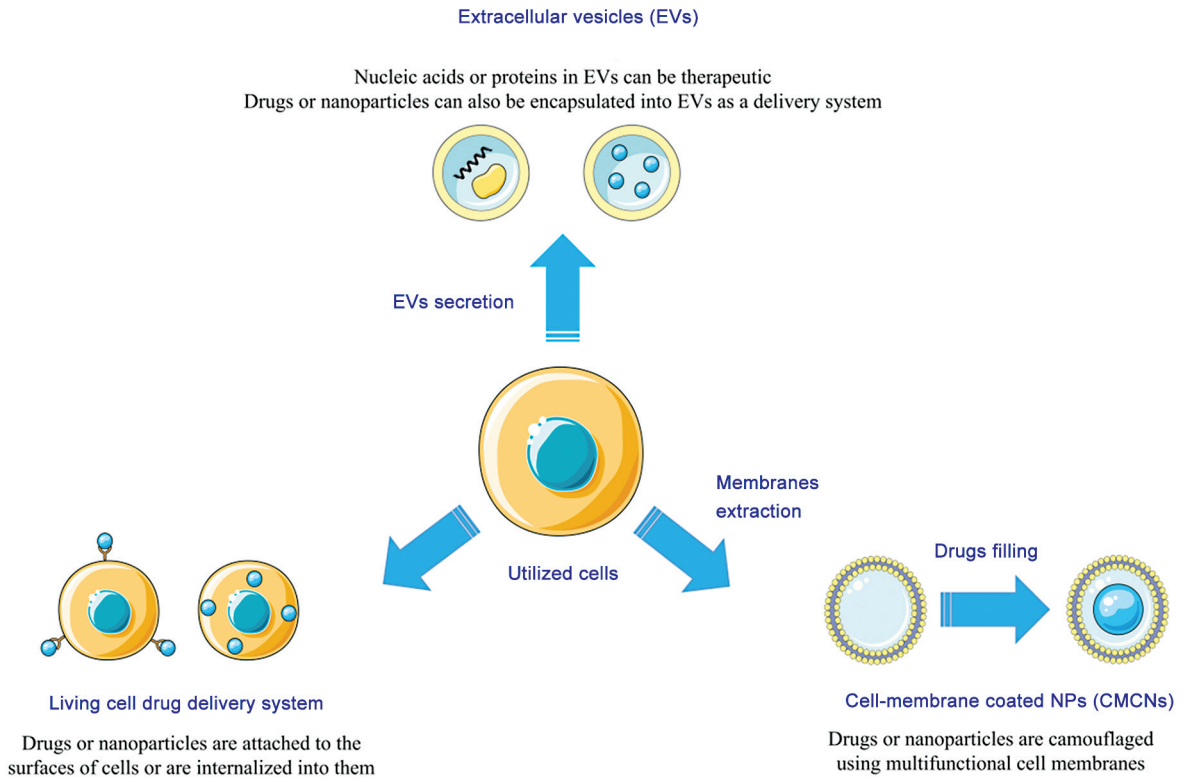
outstanding ability to treat various diseases, especially cancer, making it a benign influence in medical applications.

Nowadays, significant advancements have been made in the field, with multiple nanomaterials being adapted to DDS. They can be categorized as "hard nanomaterials" (including metals, metal oxides, carbon, graphene quantum dots, etc.) and "soft nanomaterials" (including liposomes and polymer nanoparticles [NPs], etc.).[8] Although the traditional DDS mentioned above facilitates better cancer treatment, setbacks and challenges still exist, including poor tumor penetration, high immunogenicity, rapid clearance of the reticuloendothelial system, unsatisfactory toxic side effects, etc.[9] Nevertheless, the "off-target" effect is the most critical one that needs to be addressed. The "off-target" effect, in which a drug relocates an unintended drug target or "non-canonical" target, is due to the similarity of the pharmacological target protein or pathway between the proper target sites and other parts of the body. After intravenous administration, the structure of the NDDS is greatly affected by the complex environment in the body, resulting in inefficient drug delivery and off-target biological distribution.[10] This "off-target" property damages normal tissue and organs, produces numerous side effects, reduces the quality of life of patients, and affects the effectiveness of chemotherapy to a certain extent.[11,12] The unsolved limitations have triggered researchers to escalate and alter the original nanoplatforms.

Biomimetic DDSs (BDDSs) came into people's view. BDDS made full use of the "Trojan Horse" tactics by coating traditional DDS or chemotherapeutic drugs with cell membranes to better "deceive" the body's immune system and lesions (e.g. tumors, inflammations, etc.) to obtain higher targeting accuracy, longer circulating time, and better EPR effects and bioavailability. Drugs are encapsulated into extracellular vesicles (EVs) secreted by the host cells, or attached to intrinsic proteins or the living cells (►**Scheme 1**). In general, compared to traditional DDS, BDDS significantly increases the proportion of "self-components" and improves drug delivery performances in terms of reducing the "off-target" effect, promoting precision therapy, reducing immunogenicity, and boosting drug accumulation at tumor sites by using the camouflage with autologous cells or components (e.g., the homing characteristics of tumor cells), and this high-potency medication is available in smaller doses, or longer duration of therapy, and triggers fewer side effects.

EVs are natural drug carriers with well-regarded intrinsic abilities, including high stability with negatively charged surfaces and the ability to avoid clearance, and are now regarded as an acclaimed platform to deliver drugs to tumor sites.[13,14] Then, the cell membrane-coated platforms show their advantages in interacting with biological substrates and provide DDS with desirable targeting ability.[15] In addition, living cell-based carriers are rich in surface ligands that can effectively interact with specific cells or tissues according to their different physiological functions, giving them the potential to target different tumors.[16] Given above, it is crucial to prevent damage to living cells during drug loading, and correspondingly, the immunogenicity of these living cell carriers is the greatest among the aforementioned BDDS.



Scheme 1 A brief introduction of the biomimetic drug delivery system.

Herein, based on antitumor therapy, we select and summarize different kinds of BDDS exhibiting high tumor-targeted delivery and therapeutic efficiency to demonstrate the latest advancements in this field.

EVs for Targeted Drug Delivery

EVs are particles composed of artificially manufactured lipid bilayers, and secreted by a variety of cells currently identifiable in the human body,[17] and can be classified as exosomes (50–150 nm), microvesicles (150–500 nm, or even >10 μm), and exomeres (~35 nm) according to the sizes.[18] EVs, as communicators between different cells in the body, are considered prospective drug carriers with therapeutic implications. The past decades have witnessed a great deal of enthusiasm and passion among researchers for the advantages of EVs in blocking various diseases, particularly malignant tumors.

EVs have a stronger enhanced delivery ability compared with traditional DDS-like liposomes. Liposomes can only rely on some coatings to avoid rapid clearance and a few targeting ligands to increase cellular uptake, while EVs can not only express various endogenous self-markers to escape the recognition by the immune system but also use these makers to interact with recipient cells and promote their internalization.[19] Piffoux et al modified EVs by fusion with liposomes.[20] They found that after the incorporation of EV, the uptake of modified liposomes was significantly increased (approximately 50%) compared to liposomes without EV incorporation, suggesting the good performance of EVs in enhancing cellular uptake of the carriers and also implying that EVs have better cellular uptake than liposomes.

EVs are internalized by various pathways, including passive membrane fusion and endocytosis. After being internalized, some EVs can escape from the endosomal/lysosomal pathway,[21] and at the same time have an immuno-evasive function and good biocompatibility.[22] The surface of EVs can be modified by a variety of engineering techniques to enhance cell-specificity or prevent nonspecific uptake,[23] to further strengthen their delivery ability. The Endosomal Sorting Complex Required for Transport (ESCRT) Pathway is the best-known pathway for EV production and cargo sorting, which facilitates the loading of certain proteins and RNAs with potential therapeutic options.[24] EVs with these characteristics have made certain progress in clinical trials.[25] For example, a phase I trial (NCT03608631) conducted by MD Anderson Cancer Center investigated the efficacy of mesenchymal stromal cell-derived exosomes with KrasG12D siRNA (iExosomes) in participants with pancreatic cancer whose KrasG12D mutation had spread to other parts of the body. In addition, a phase II trial (NCT01159288) to vaccinate tumor antigen-loaded dendritic cell (DC)-derived exosomes in patients with unresectable non-small cell lung cancer has now been completed.

Due to imperfection of isolation processes, the materials used in a large number of studies contain compounds from different kinds of EVs. Therefore, the article used the term EVs to symbolize any of the types we mentioned above.[26]

Mesenchymal Stem Cell-Derived EVs for Targeted Drug Delivery

First discovered in 1976,[27] the mesenchymal stem cell (MSC) is regarded as a kind of multipotent cell with differentiation potential and self-renewal abilities,[28] and can be isolated from a variety of different organs or tissues such as bone marrow, heart, lung, and adipose tissue,[29] with the characteristics of "double-edged sword." On the one hand, MSCs have immunosuppressive and anti-inflammatory properties,[30] which inhibit the activation of T cells, and change the phenotype of macrophages and DCs,[31] and are the basis for the treatments of inflammatory disorders. On the other hand, it establishes a tumor microenvironment (TME), redounds tumor growth and metastasis,[32] and participates in TME formation.[33] Nonetheless, it still holds the ability to improve antitumor therapy due to its outstanding tumor tropism ability, low immunogenicity, and applicability for large-scale production.[34] However, the safety of using it for cell-based antitumor therapy remains debated in academia.

MSC-derived EVs (MEVs) are similar to MSCs in many aspects. However, it is worth noting that it has the advantages of small size, prominent half-life, inferior immunogenicity, and good penetration compared to the application of MSC as a delivery platform.[35] In mice experiments, the cell-like lipid membrane also provides them with downregulated cytotoxicity. More importantly, MEVs seem to act as a "mailman" to consign the information including DNA, RNA, proteins, etc. to targeted cells,[36] and therefore bear the innate capacity to target malignancy sites *in vivo*,[37] making them natural vehicles for tumor-targeted drug delivery. The ability of MEVs to transport functional endogenous biomacromolecules has been confirmed by many researchers. Of all the components, nucleic acid is the most abundant. Jahangiri et al suggested that miRNA (miR)-100 and miR-143 were transferred from MEVs to human colorectal cancer cells, and inhibited cell proliferation and metastasis by manipulating the miR-100/mTOR/miR-143 axis.[38] Accordingly, Yao et al showed for the first time that circRNA circ-0030167, isolated from bone marrow MEVs, acts as a molecular sponge for miR-338-5p while increasing the expression of a tumor suppressor gene *WIF1*, thereby significantly arresting the progression of pancreatic cancer (►**Fig. 1**).[39] In addition, their potential to upload exogenous compounds is being simultaneously investigated. Pascucci et al found that paclitaxel (PTX)-treated MSCs were characterized by high drug concentrations and low cell mortality, and were able to secrete EVs that also contain PTX to inhibit tumor cell proliferation and growth.[40] Meanwhile, Pinto et al examined the effectiveness of MEV-encapsulated meta-tetra(hydroxyphenyl)chlorin (mTHPC) in combination with photodynamic therapy (PDT) against peritoneal carcinomatosis. They reported that due to the outstanding tumor-targeted function of MEVs, few organs were harmed under the violent stimulation of PDT, and a stronger anti-metastasis effect was detected.[41] However, it is worth noting that MEVs, secreted by cells treated with doxorubicin (DOX), would enhance breast cancer resistance when delivered to the tumor,[42]

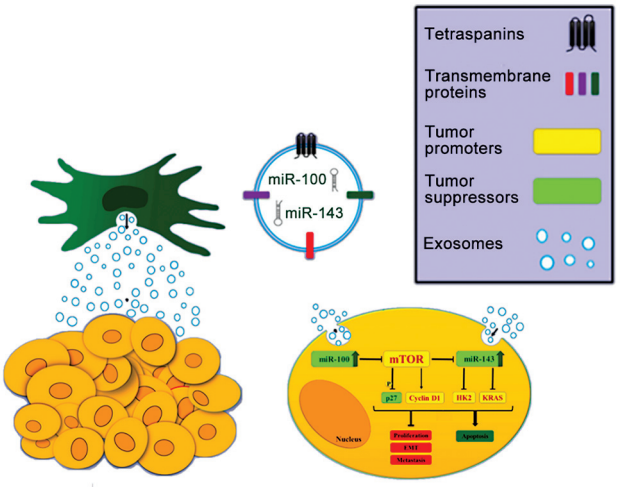


Fig. 1 A schematic representation of the molecular mechanisms by which MSC-Exos affects cell proliferation and metastasis in CRC cells. CRC, colorectal cell. (Reproduced with permission from Jahangiri et al[38], copyright 2022 Elsevier B.V. All rights reserved.)

suggesting that the antitumor effect may be related to the type of cancer and the drugs loaded into the EVs.

DC-Derived EVs for Targeted Drug Delivery

DCs are specialized antigen-presenting cells (APCs) that patrol humans' bodies and are responsible for adaptive immune responses,[43] including immune surveillance,[44] antigen presentation,[45], stimulation of naïve T cells,[46] etc. They are characterized by a stellate morphology and sustained expression of major histocompatibility complex class II (MHCII), and can uptake antigens and migrate to the draining lymph nodes to prime naïve T cells to generate a strong immune response.[47] Due to the great potential of DCs in eradicating tumors, a great deal of effort has been invested in the development of DC-based antitumor vaccines. However, vaccine manufacturers might face issues like high cost, relatively time-consuming,[48] and the risk of *in vivo* DCs being influenced by immunosuppressive factors produced by the tumor.[49] In this case, DC-derived EVs (DEVs) have many of the key immunostimulatory properties of DCs, with the benefits of a long shelf-life when frozen and relatively simple good manufacturing practices (GMP) handling, and therefore lower cost but the same or greater anticancer efficacy.[50] DEVs would be a better option for malignancy therapies.

DCs are capable of secreting EVs with multiple functions,[51] mainly targeting immune cells. Compared with DCs, DEVs have inherited characteristics from their parent cells, especially in terms of surface molecules such as costimulatory molecules, MHCI, MHCII, etc.[48] Membrane proteins bound to externalized phosphatidylserine, such as milk fat globule EGF factor 8, act as intermediary between DEVs and αvβ3 or αvβ5 integrins on the membranes of recipient cells, facilitating the penetration of DEVs into the target cells, and thus are essential for the enhancement of the targeted ability of DEVs.[52] Thus, proper modifications to the surface of DEVs could further enhance their tumor elimination effect. For example, by applying the DSPE–PEG–NHS linker, Fan and colleagues inserted an anti-CD3 antibody into the membrane of DEVs to activate T cell response while also embedding an anti-epidermal growth factor receptor (anti-EGFR) antibody to direct mature T cells to the tumor sites (►**Fig. 2**).[53] Notably, Zhu et al showed that the direct conjugation of MUC1 glycopeptide (a molecule overexpressed in various cancers) on the surface of DEVs could upregulate the titers of immunoglobulin G antibody and inhibit tumor growth.[54] Infection of DCs with lentivirus-containing special genes prior to isolation of EVs is another tool for effective DEV surface engineering.[55] Despite investigation claiming that DEVs produced according to GMP can trigger proliferation and activation of natural killer (NK) cells to destroy tumors, this is mainly because the NK group 2 member D (NKG2D) ligands and IL-15Rα that are originally bound on the membrane,[56] artificially engineered surfaces of DEV, still proved to be a more effective way of targeted delivery.

Unlike MEV strategies, which load drugs more often, DEVs are usually used to carry antigens to enhance the efficacy of immunotherapy. One of the most important jobs of DEVs is to demonstrate their immunostimulatory potential to stimulate cytotoxic T lymphocyte responses, thereby controlling the tumor as a "lifeless" antigen presentation machine. Therefore, DEVs and their antigen fragments need to maintain a certain degree of immunogenicity to achieve better therapeutic efficacy. Antigens not only from tumors but also from other immune adjuvant-loaded DEVs are also commonly used as vaccines to prevent and treat established tumors by activating naïve T cells in a (cross) presentation manner.[50,57] Li et al reported that DEVs loaded with a multi-neoantigen peptide exhibited excellent antitumor responses in melanoma models, stimulating a broad-spectrum immune response and preventing immune escape.[48] Interestingly, Damo et al loaded DEVs with antigens from the melanoma model B16F10, and when these EVs were incubated with toll-like receptor agonist poly (I:C), they showed a proinflammatory Th1 response in tumor-bearing animals. This suggests that the antitumor effect may be related to their maturation environment.[58]

Tumor Cell-Derived EVs for Targeted Drug Delivery

Tumor cells usually secrete more EVs than other cells in the body due to the formation of a TME that creates hostile conditions like high acidity, hypoxia, genotoxic stress, etc. Survival pressure caused by therapeutic factors like applying chemotherapy drugs may also lead to increased secretion of tumor EVs (TEVs).[59,60] EVs from those malignant cells are usually associated with tumor initiation, progression, metastasis drug resistance, etc., leading to poor patient prognosis.[61,62] Specifically, TEVs have the role of inducing tumor immune tolerance, promoting tumor angiogenesis and vascular permeability, and developing chemoresistance during the natural generation by the tumor cells.[63–65] However, concerns arise when those exosomes are delivered to the body as free, circulating particles, where causing tumor metastasis is one of the biggest obstacles to the use of those TEVs as drug delivery platforms because lipid-rich TEVs can subvert normal cells and bring them into an abnormal state in integrin and miRNA-dependent manner.[66–68]

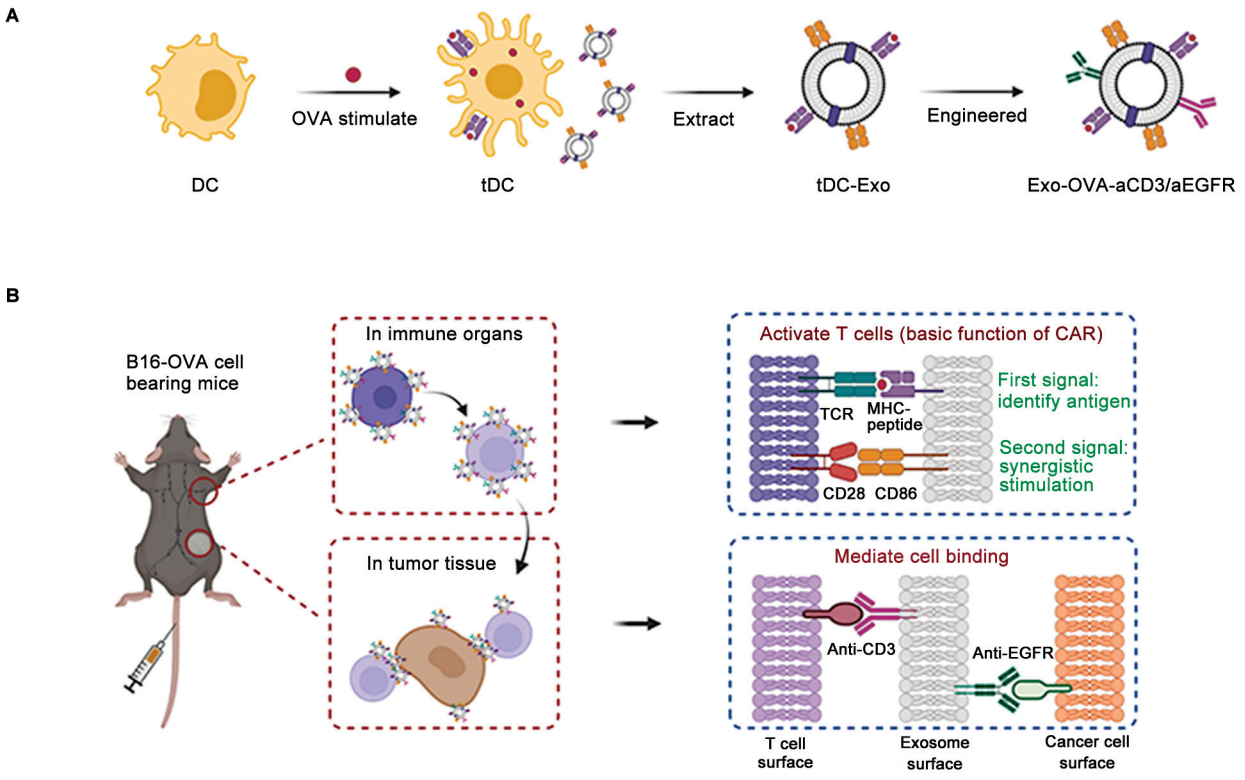


Fig. 2 Schematic diagram. (**A**) Schematic of the construction of anti-CD3 and anti-EGFR antibody-engineered tDC-Exo (Exo-OVA-aCD3/aEGFR). (**B**) MHC–antigen complex and a co-stimulating molecule CD86 on Exo-OVA-aCD3/aEGFR can be regarded as the CAR of CAR T cells which could activate endogenous T cells *in vivo*. (Reproduced with permission from Fan et al[53], copyright 2022 Elsevier B.V. All rights reserved.)

Despite this, TEVs have great potential for targeted drug delivery. The homing characteristics remain decisive. Qiao et al designed a "Trojan horses" platform to encapsulate DOX into TEVs on the basis that TEVs are more likely to interact with the tumor cells than other cells due to the shared protein and lipid composition. More importantly, the level of TEVs absorbed by tumor cells was closely related to their types, with the highest absorption efficiency occurring in TEVs secreted by the aimed tumor, indicating the magnitude of using specific TEVs in the preparation of drug carriers.[69] In addition, TEV, as an endogenous antigen itself, can be used to sensitize immune cells, such as DCs, to boost antitumor efficacy. Derived from the tumor cells, specific antigens shared by the TEVs are displayed on their surfaces and can be presented to $CD8^+$ T cells by DCs through an MHCI-dependent way.[70] From this perspective, on the one hand, when TEVs are used to deliver therapeutic agents, it is important to minimize the immunogenicity of TEV to ensure that more of the drug can reach the tumor site. We can do this by inducing tumors by transplanting targeted cancer cell lines into nude mice and isolating TEVs from tumor cells harvested from the transplanted tumor. On the other hand, a certain degree of immunogenicity should be kept to stimulate immune cells to activate the intrinsic antitumor response. Finally, some chemotherapy drugs (e.g., DOX) have high selectivity toward TEVs and high stability in these carriers,[71] further confirming the excellent encapsulation ability of TEVs.

In summary, EVs are natural carriers secreted by multi-types of cells, with great potential for targeted drug delivery and broad application prospects. Their innate malignancy-targeting ability, tumor penetration redounding, and easy surface modification enable them to achieve comprehensive antitumor functions. Although EVs are superior to traditional DDS in at least the aspects mentioned above, their low yield and unsatisfactory retention time in the body still limit their clinical use. Therefore, further research studies are needed before entering clinical studies.

Cell-Membrane-Coated NPs for Targeted Drug Delivery

In addition to using cell-mediated drug delivery to treat cancers, cell membranes with naturally complex structures and functional properties have gradually attracted the attention of some researchers in the field of targeted administration. Different cell membranes prepared from erythrocytes, platelets, cancer cells, immune cells, etc., provide NPs with a series of cell-specific proteins that can be leveraged for dynamic and multiplex binding interactions, resulting in function-driven and broad-spectrum bio-activity.[72,73] The prepared cell-membrane-coated coated NPs (CMCNs) are usually made up of two parts, including (1) synthetic NP cores, the inorganic or organic NPs that function as antitumor drugs, and (2) layer of natural cell membranes, camouflage clothing that mimics the antigenic diversity of the

source cells. The combination of these two elements displays characteristics of the parent cells on artificial NPs.[74]

CMCNs are constructed following an effective top-down strategy, which has the potential to simplify the development of drug delivery platforms with the required performances that can be customized for a wide range of applications. The preparation of CMCNs mainly involves two stages: membrane derivation and membrane coating. The first step usually contains methods like homogenization, hypotonic lysis, and centrifugation, the latter possesses procedures like co-extrusion, sonication, microfluidic electroporation, cell membrane-templated polymerization, etc.[75] While natural membranes can be used directly as coatings for NPs, they can also be modified through lipid insertion, membrane fusion, or genetic engineering to form hybrid clothing to obtain better performance.[15,75] During the manufacturing process, however, attention should be paid to NPs partially coated with membranes when those membranes were subjected to mechanical forces such as extrusion or sonication.[76]

In general, CMCNs provide more opportunities for custom-tailored therapies. In this review, we focus on membrane coats of erythrocytes, cancer cells, leukocytes, and the hybrid membranes, because they are wildly investigated.

Erythrocyte Membrane-Coated NPs for Targeted Drug Delivery

Erythrocyte membranes (EMs) are commonly used as a naturally mimicking material in drug delivery because of their unique benefits of extending from the original cells.[77] First, the human body contains a large amount of erythrocytes, and the raw materials are readily available, making the preparation process economic and elementarily achieved. Second, membrane proteins on EMs are crucial in helping them evade the immune system. CD47 is a protein highly expressed in EMs that interacts with signal regulatory protein-α (SIRPα) on macrophages to inhibit phagocytes.[78–80] However, there are still limitations, i.e., EMs from donors should be matched to the patients' blood type and Rh compatibility to reduce the chance of inducing alloimmunization, which hinders large-scale production and prevents researchers from translating this advanced strategy into clinical applications.[81,82] There are fixed standards and specifications for EM extraction. Briefly, whole blood is centrifuged to remove serum and fluffy precipitation, then erythrocytes are subjected to hypotonic treatment to shed intracellular components. Subsequently, after washing, sonicating, or extruding through porous membranes, EMs can be coated on the NPs.[77,80]

EM-based passive delivery is widely used by many researchers, such as combining EMs and photothermal therapy according to EM carriers without targeting pieces. Because under irradiation of near-infrared laser, EMs would be disrupted, thus increasing the release of the drug.[83] Unfortunately, the effectiveness of this strategy which mainly relies on the EPR effect for passive targeted delivery faces controversy due to the lack of tumor-specific adhesion molecules and low drug-loading capacity. EM-based nanocarriers require special structural modifications to enhance their tendency toward tumors and the ability to deliver drugs to the site.[84] RGD peptide is a tumor-penetrating and cell-internalizing peptide that interacts with αvβ3/αvβ5 integrin receptor overexpressed in tumor tissues. Among all the targeting molecules, RGD peptide is commonly used and shows good performance during drug delivery. Xie and colleagues coated tranexamic acid + DOX NPs with EMs modified by cRGD peptide to induce tumor thrombotic infarction by precisely targeting and damaging tumor vascular endothelium.[85] Instead of delivering chemotherapeutics directly to the tumor tissues, Wang's group first used EMs to cloak worm-like siRNA; however, in this case, the surface of the siRNA vector is positively charged, leading to the adsorption of serum proteins and a much shorter circulation time. By adjusting the ratio of siRNA to cationic bovine serum albumin (cBSA), the surface charge can be controlled to be negative at neutral pH but positive at low pH, resulting in the release of EMs released and lysosomal escape through the proton sponge effect. Therefore, RGD is also applied in the construction of carriers.[86] In addition, targeting molecule combinations, such as combining anti-EGFR and RGD peptide, also improves delivery.[87]

Interestingly, deformability is an important characteristic of natural erythrocytes, and EMs derived from different life stages will have different delivery functions. Deformability, pH, etc. are critical conditions that should be emphasized when using EMs as a basis for targeted delivery.[88]

Cancer Cell Membrane-Coated NPs for Targeted Drug Delivery

Cancer cell membranes (CCMs) are likewise considered effective drug delivery carriers. The anti-immune clearance and homotypic binding capacity of the malignant cells are of great importance during tumor formation and progression (including tumor growth and metastasis). CCMs have been reported to play a key role in fostering these competencies of tumors. Specific molecules such as integrin αvβ3, *N*-cadherin, epithelial cell adhesion molecule (EpCAM), and galectin-3 have been demonstrated to help cancer cells camouflage and recognize homologous cancer cells under the surveillance of the immune system to lower their immunogenicity. Therefore, CCMs should endow NPs with superior homotypic targeting and immune escape abilities.[89–91] In this case, CCMs should be the basis of the DDS. In addition, tumor cells, tumor cell membranes, and whole tumor lysates are considered to be perfect polyvalent antigens, and therefore rather than shipping drugs into the tumors, their membranes could be used as cancer vaccines, which is a feasible cancer therapy. For example, cloaking aluminum phosphate absorbing adjuvant CpG can provide comprehensive tumor antigens to APC and other relevant immune cells, and enhance specific antitumor immunity.[92]

Covering NPs with CCMs has proven to be a valid and commonly used method of drug delivery. The coated NPs gain a membrane phospholipid bilayer structure as well as cancer surface proteins to be decoys or Trojan horses for precise treatment of cancer. Jin et al demonstrated that simply fabricating CCMs on poly (lactic-co-glycolic acid)

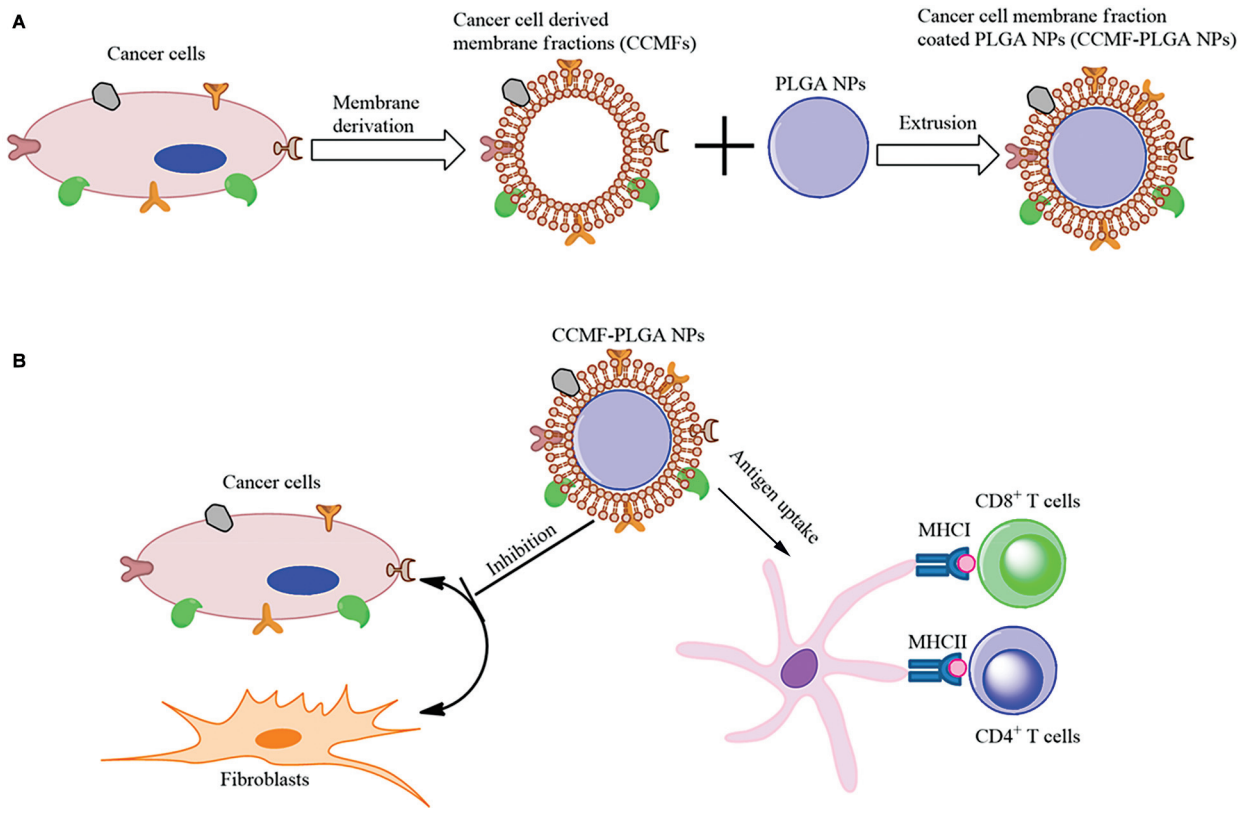


Fig. 3 (A) Schematic illustration of the preparation of cancer cell plasma membrane fraction-coated PLGA NPs (CCMF-PLGA NPs). (B) The purpose was to determine the ability of these cancer cell-mimicking NPs to disrupt cancer cell–stromal cell interactions, reduce metastasis, and prime the immune system for cancer immunotherapy. NPs, nanoparticles. (Reproduced with permission from Jin et al[93], copyright 2019 American Chemical Society.)

(PLGA) NPs can interfere with cancer cell – stromal cell interactions to reduce fibroblast-mediated invasion and metastasis while activating the following-up immune response (►**Fig. 3**).[93]

Compared to other NDDSs, CCM-coated NPs are more capable of crossing biological barriers such as the blood–brain barrier, blood–brain–tumor barrier, etc., without redundant decorations on CCMs themselves. Wang and colleagues designed a novel brain tumor imaging and surgical navigation system by coating Er-based lanthanide-doped NPs (LnNPs), NPs which have excellent near-infrared-IIb luminescence performance, with CCMs. Thanks to the excellent tumor-homing ability, the system can visualize brain tumor boundaries and guide surgical resection.[94] Some researchers, when trying to increase the accumulation of NPs at the tumor site, choose ligands like Asn-Gly-Arg (NGR) on the CCMs for better targeting.[95] In the process of surface modification, to improve the target capability of CCM, it is necessary to pay attention to the modification efficiency. Zheng et al reported that when decorating bladder cancer membranes that will subsequently be camouflaged on PLGA NPs, proceeding on live tumor cells before isolating the membranes will help to sustain the correct positioning of modifiers at the extracellular side of the membrane.[96]

As we mentioned before, these carriers may increase the risk of tumor metastasis and progression, and thus face some controversies. TEVs contain nucleic acids and proteins that are already present in parent tumor cells and may be a set of pro-tumor progression, pro-metastasis, and pro-drug resistance messengers. Encouragingly, CCMs with simple membrane structures can be a solution to this dilemma. In conclusion, CCM-coated NPs are foreseeable promising materials for future precise medicine manufacture.

Leukocyte Membrane-Coated NPs for Targeted Drug Delivery

Leukocytes can be divided into granulocytes and agranulocytes which can differentiate into neutrophils, eosinophils, and basophils, or monocytes and lymphocytes, respectively. Same as other cell membrane-coated NPs, leukocyte membranes (LMs) enable NPs to escape from the rapid clearance and increase their circulation time. Due to their high affinity for inflamed areas (e.g., tumor sites peculiarly), they are now regarded as a new carrier for targeted delivery of antitumor drugs.[97] NPs mimicking leukocytes, as well as other types of cell membrane-coated NPs, can mimic the interaction between leukocytes and cancer cells, thereby enhancing tumor therapeutic capacities (►**Fig. 4**).[98]

Interestingly, LM-coated NPs can be used for drug delivery, as well as for isolation and downstream studies of circulating tumor cells (CTCs). These NPs can bind to CTCs because they are homologous to leukocytes and simultaneously repel the living leukocytes to make up a high-density CTC environment. Zhou et al first prepared graphene nanosheets that combined

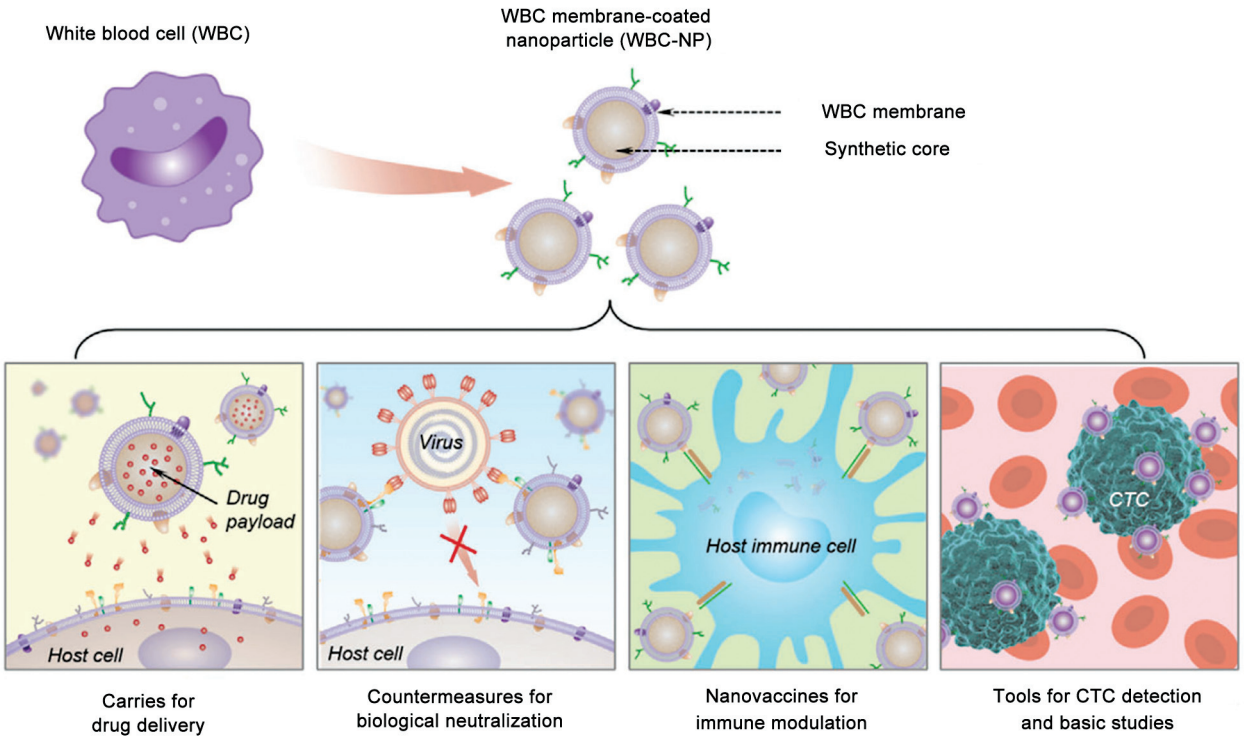


Fig. 4 Schematic summary of using LM-coated nanoparticles for medical applications. LM NPs are made by cloaking plasma membranes derived from natural lymphocytes onto synthetic cores. LM, leukocyte membrane; NP, nanoparticle. (Reproduced with permission from Wang et al[98], copyright 2022 Wiley-VCH GmbH.)

Fe_3O_4 NPs and disguised them with LMs. By inserting lipid linkers onto the membranes, the antibodies could be conjugated to the LMs, resulting in high capture efficiency and enhanced anti-leukocyte absorption.[98,99]

Macrophages are specialized APC with long blood half-life and specific binding ability with tumor tissue. In addition, their superior ability to recognize antigens, better cellular interactions, gradual drug release, and reduced toxicity *in vivo* contributed to their availability in antitumor drug development. This targeted nature makes macrophages and macrophage membranes (MMs) excellent materials for carrying therapeutic drugs for cancer treatment. By co-extruding NPs from the extracted MMs, successfully MM-coated NPs have a thin layer on the surface, are slightly larger in size, have a negatively charged surface zeta potential, and contain membrane proteins.[100,101] Li et al created an MM-coated nano-gemcitabine system that restores the tumoricidal function of lymphocytes by upregulating PD-L1 expression. The study used MMs with tumor-tropism characteristics to enhance drug accumulation at tumor sites.[102] Tumor-associated macrophages (TAMs), living in the TME, have high levels of colony-stimulating factor 1 receptor on their surfaces, and CSF1 secreted by cancer cells significantly promotes the polarization of TAMs toward M2-macrophages, which are responsible for immunosuppressive characteristic in TME. Inspiringly, Chen et al fabricated TAM membrane-coated NPs that would selectively bind CSF1 as a mock TAM to eliminate primary tumor growth.[101]

In addition to macrophages, the membranes of T cells and NK cells have also been significantly studied. T cell, as an instinctive killer in humans, displays numerous receptors on its membrane aiming at recognizing abnormal cells like cancer cells. Inspired by chimeric antigen receptor (CAR) therapy, a number of immunotherapies based on T cell membranes (TMs) have been exploited. Different antibodies (e.g., anti-EGFR) can be decorated on the TMs while chemicals can be loaded inside the membranes, resulting in CAR-T like nano-robot that can be used to breach biological barriers and improve therapeutic outcomes.[103] Furthermore, Kang et al proposed a technique to combine different molecules including FasL, PD-1, LFA-1, and TGF-β1R to activate strong immunoresponses. T-cell-membrane-coated nanoparticles and anti-cancer drug loaded T-cell-membrane nanoparticles can perform tasks like "real" T cells via FasL and release drugs inside, what's more exciting is that those NPs are free from immunoexhaustion because they are not living cells and they can block the immune checkpoint interactions.[104]

Hybrid Cell Membrane-Coated NPs for Targeted Drug Delivery

Hybrid cell membranes (HCMs) are a new type of cloaking membrane for NPs that inherit unique characteristics from two-parent cell lines.[105] In contrast to single-cell membrane (SCM)-coated NPs, which can only be characterized from one type of cell, HCMs have the gifted ability to overcome the

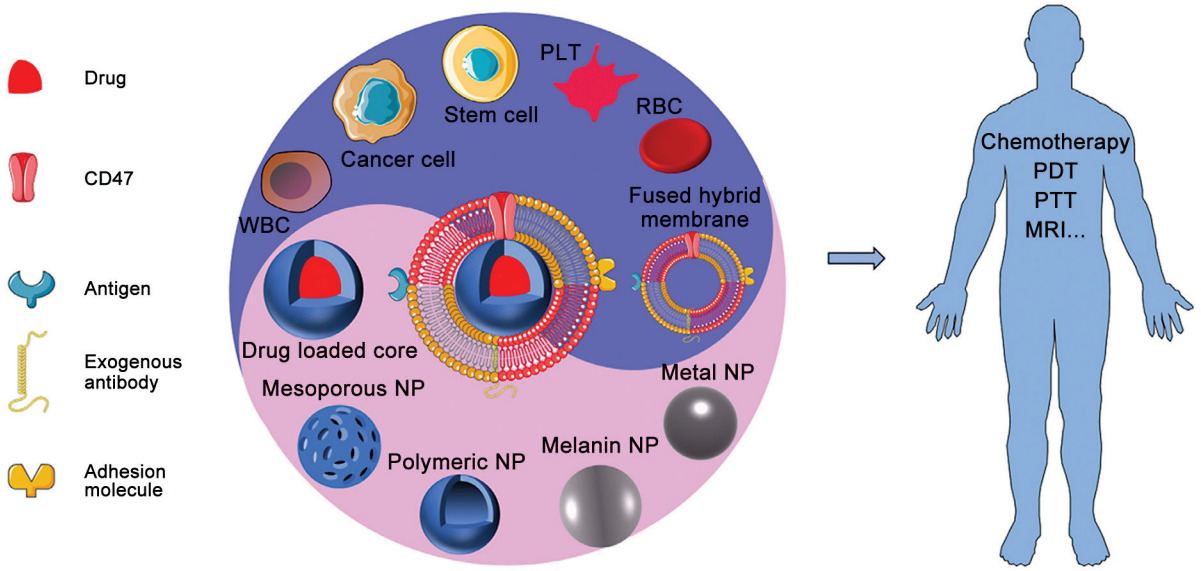


Fig. 5 Hybrid cell membrane-camouflaged nanoparticles (HMC@NPs) designed for cancer diagnosis and treatment. Cell membranes from different types of natural cells were extracted and leveraged to wrap around different nanoparticles for the theranostic of cancer. (Reproduced with permission from Chen et al[6], copyright 2020 Elsevier B.V. All rights reserved.)

limitations of SCMs to enhance the functionality of nanomaterials.[106] The pivotal proteins and properties inherited from both of the parent cells enable multifunctional biomimetic nanomaterials to perform increasingly complex tasks in dynamic biological environments more effectively and safely.[107] When we prepare HCMs, we need one more step than SCMs, which is the fusion of two different membranes. This procedure can be accomplished by two respective methods. One is, of course, to extract the membranes before fusion and the other is to fuse cells before extraction. Among the two membranes used for constructing the drug delivery platform, one should at least offer the targeting ability and the other should offer favorable characteristics for drug administration and release (►**Fig. 5**).[108]

Based on this thread, many drug delivery platforms have emerged. Shen et al prepared a self-assemble Nano/ZnO and miR21 antagomir NPs and coated them with the membranes of LnNPs and cancer cells, which enabled NPs to have immune escape and homologous targeting abilities.[109] Novel frameworks, such as tetrahedral framework nucleic acid consisting of four single-stranded DNAs with ingeniously designed sequences, can also be modified with HCMs made from DSPE-PEOz liposomes and EMs, which can speed up drug the release process in acidic environments, as well as enhance circulating time and NP accumulation at tumor sites. In this study, in order to overcome the dilemma of the lack of targeting tendency of erythrocytes, an anti-HER2 aptamer was utilized to direct the NPs to the right place.[110] Besides, delivery systems combining the membranes of erythrocytes and cancer cells, liposomes and cancer cells, etc. have also been explored.[111,112] Rather than delivering drugs directly to tumor cells, Zang et al shifted the focus to using cancer-associated fibroblasts to cut off the nutritional supply of tumors by delivering solid lipid NPs containing PTX and glycolysis inhibitor PFK15 coated with hybrid membranes. Evidence suggests that the hybrid biomimetic camouflage formed by breast CCMs and activated fibroblast membranes improves antitumor efficiency.[113] However, despite many attempts to explore NP coatings combining different membranes, much remains unknown. Therefore, further efforts in this field are still needed.

Living Cells for Targeted Drug Delivery

The study of cell-mediated drug delivery methods has been an attractive area in recent years, as these DDSs show great potential for targeted drug delivery. The traditional DDS may be fast and prematurely cleared by the mononuclear phagocytic system and loss of efficacy of PEG-modified NPs under continual administrations because of the stimulation such as the immune system.[114,115] Compared with traditional DDS, cell-mediated drug delivery has the advantages of hypoimmunogenicity, good stability, biocompatibility, and extended circulating time (►**Fig. 6**).[116,117]

In this case, in terms of different types of circulatory cells, including erythrocytes, leukocytes, platelets, and DCs, living unfettered cells can be used as efficient delivery machines to transport NPs, e.g., those synthetic carriers are bound to circulatory cells by loading the drugs into their internal volume or binding the drugs to their surface via covalent or noncovalent coupling.[118]

Erythrocytes Used for Cell-Mediated Targeted Drug Delivery

Erythrocytes are the most abundant cells in human blood, accounting for 40% of the total.[119] Mature cells are oxygen-carrying cells, disc-shaped, biconcave, and without a nucleus.[120] In the process of antitumor therapy, erythrocytes act as carriers of drugs and transfer the loading drug from the carrier cells (i.e., erythrocytes) to the malignant cells, which

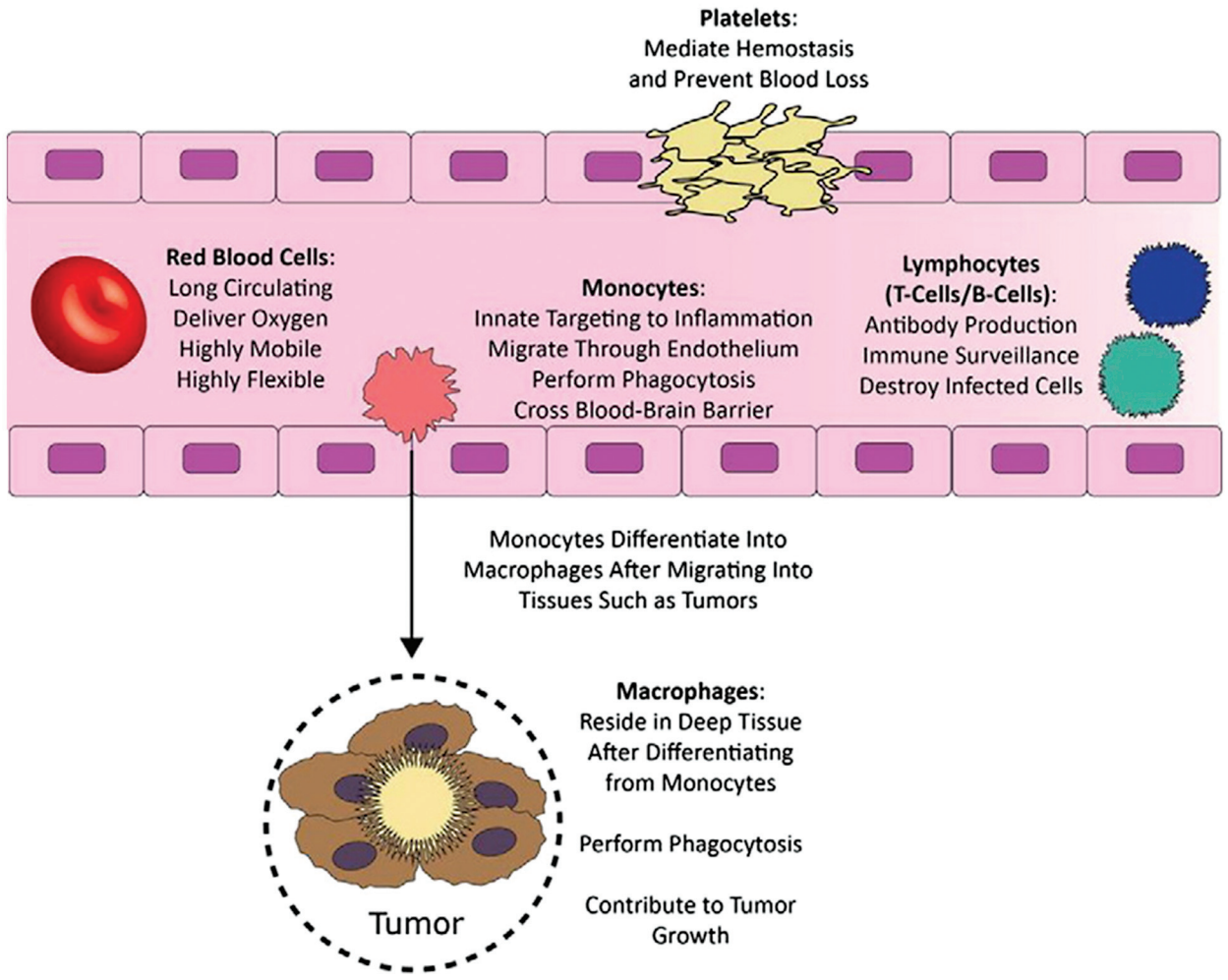


Fig. 6 Advantages of nanoparticles and circulatory cells in drug delivery. Circulatory cells, including red blood cells, monocytes, platelets, and lymphocytes, have natural drug-delivery abilities. (Reproduced with permission from Anselmo et al[118], copyright 2014 Elsevier B.V. All rights reserved.)

is characterized by long circulation time and better biodistribution.[121] Specifically, the "Don't eat me" sign displayed by CD47 and other receptors on their surfaces helps them avoid the degradation of the phagocytosis and assist the NDDS to escape from the clearance of the immune system at the same time.[122]

To establish a living erythrocyte-based DDS, several approaches have been commonly explored, known as erythrocyte hitchhiking (passive adsorption) and attachment. Traditional NDDSs already contain chemotherapeutics or protein pharmaceuticals or small-molecule drugs, and delivery in combination with erythrocytes is one of the methods we are currently exploring to enhance the efficacy of the carriers.

The erythrocyte hitchhiking is proposed to solve the problem that NPs injected into the body are rapidly eliminated by the liver and spleen, thus causing "off-target" effect when drugs are particularly targeted for the lungs and brain.[123] In erythrocyte hitchhiking, changes in shear stress are critical for triggering the release of NPs in microcapillaries. We found that the detachment rate of NP hitchhiking on the cell surfaces increases with elevated stress, implying that this strategy can be used for recognition between abnormal sites and normal sites for more efficient drug delivery.[124]

Erythrocyte attachment, on the other hand, is the most commonly used antitumor strategy. With different techniques, NDDS can be affixed to erythrocytes. Among them, lipid insertion, biotin–avidin bridges, EDC/NHS coupling, and antibody/ligand-receptor conjugation are the four commonly used methods to construct erythrocyte-based DDS (►**Fig. 7**).[125]

Liu et al reported an erythrocyte-based DDS that unites an oxygen-transporting function (correcting tumor hypoxia environment) with PDT-sensitive NPs through the interaction of avidin and biotin. They stated that owing to the erythrocytes, the DDS could achieve long tumor retention, therefore enhancing therapeutic efficacy.[126]

Efforts have also been put into combining the two approaches, and it is believed that we can fully utilize the advantages of each. Ferguson et al reported an intravascular nanocarrier that combines erythrocyte ligand conjugation and hitchhiking. By applying different kinds of antibodies or adhesion molecules, NPs can achieve erythrocyte hitchhiking at the beginning, and then due to the proximity between the

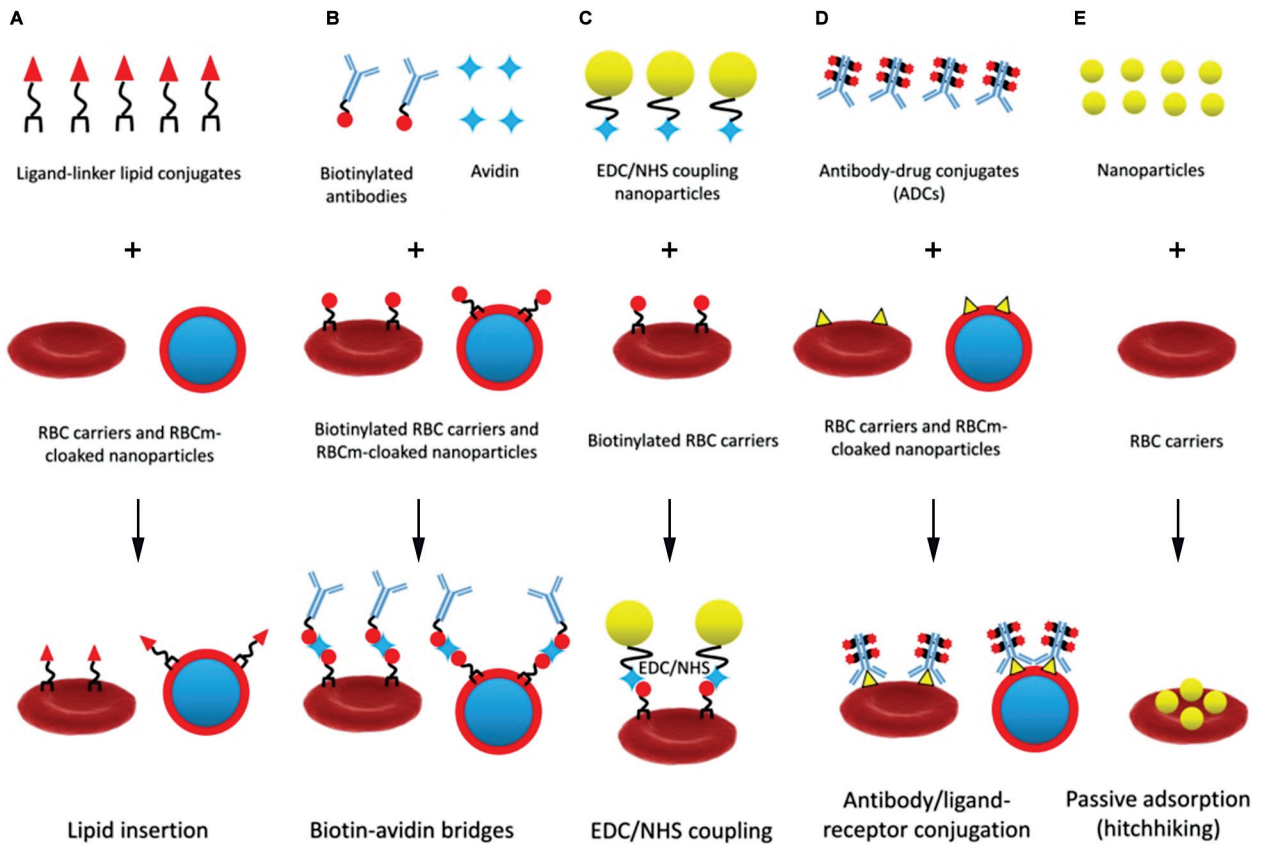


Fig. 7 A schematic diagram of (**A**) lipid insertion, (**B**) biotin–avidin bridges, (**C**) EDC/NHS coupling, (**D**) antibody/ligand-receptor conjugation, and (**E**) passive adsorption (hitchhiking) methods for refunctionalization of erythrocyte-based nanomedicine. (Reproduced with permission from Sun et al[125], copyright 2019 Ivyspring International Publisher.)

erythrocytes and the NPs, the ligand–receptor bound to the targeted cells (e.g., tumor cells), thus releasing the NPs.[127]

Platelets Used for Cell-Mediated Targeted Drug Delivery

Platelets are disc-shaped, anucleate fragments derived from megakaryocytes that play a critical role in maintaining hemostasis and thrombosis in the body, including those in tumor vasculature. Increasing evidence suggests that platelets are also involved in other processes such as immune responses, angiogenesis, and lymphatic vessel development, which may be relevant to tumor occurrence, growth, and metastasis. Platelets generally have a lifespan of 7 to 10 days.[128,129]

There is an interaction between cancers and platelets. Recent studies have pointed out that tumor cells promote platelet production and aggregation, leading to a number of cardiovascular diseases. Platelets, on the other hand, are responsible for cancer progression and metastatic dissemination by modulating the TME by releasing multiple growth factors and binding to the surfaces of tumor cells to protect CTCs from shear stress and shield them from recognition by immune cells.[130–132]

Platelets are natural carriers for antitumor drug delivery, and platelet-mediated platforms offer the advantages of readily available, well-tolerated, and relatively low direct production costs in comparison to traditional DDS.[133] These carriers can be hypoimmunogenic as they can be harvested from the patients themselves.[134] When an *in situ* tumor is seeking metastasis, selectins and integrins' interactions between the two substances are significant during platelet contact with tumor cells. This character makes platelet hitchhiking NPs possible.[135] On this basis, N_3-mediated click chemistry can be utilized to fasten Granzyme B-loaded NPs on the surface of platelets, and by hitchhiking platelets, the system can respond to acidic TME and release NPs to attack tumor cells.[136] The platform is highly suitable for postsurgical cancer treatment. Platelets here are called "bridges" which fill the gap between NDDS and tumor cells.[137] At the same time, the use of platelets as a basic component of immunotherapy is also a hot area of research. Anti-PD-1 antibodies (aPD-1) are conjugated on the surfaces of platelets. When platelets are activated after arriving at tumor sites, aPD-1 is released in the form of platelet-derived microparticles that can subsequently bind to T cells to enhance the efficacy of immunotherapy.[138,139]

Leukocytes Used for Cell-Mediated Targeted Drug Delivery

Leukocytes are important participants in the body's innate and adaptive immunity, which are involved in the protection of the body from infectious diseases and the removal of cell debris and foreign antigens.[140,141] Leukocytes can be divided into five categories according to their physiological functions and characteristics: neutrophils (amount in blood: 50–70%), lymphocytes (25–35%), monocytes (2–8%), eosinophils (1–3%), and basophils (0.4–1%). Leukocytes provide an excellent

opportunity for drug delivery due to their long-circulating time, tumor penetration tendencies, and the capability to cross biological barriers. While traditional NDDS is hindered by a variety of biological barriers, such as blood vessels, agents such as leukocytes hijacked by NPs can take full advantage of the targeting motility and transmigration ability of leukocytes to deliver NPs to inflammatory such as tumors.[142,143] Similar to erythrocyte carriers, leukocyte-based platforms can be constructed by NPs, free drug hitchhiking, or internalization.[144] In this review, we focus on neutrophil- and lymphocyte-based DDSs.

Neutrophils are the largest group of leukocytes. Administration via activated neutrophils is a promising approach to antitumor drug delivery, as neutrophils have natural chemotaxis to inflammatory signals from progressing tumors. Using their sophisticated cellular machinery, neutrophils can penetrate the tumor-associated endothelium and infiltrate the TME.[145] There are two methods to construct DDS, including incubating neutrophils with drugs before administration or hijacking neutrophils in the bloodstream. For the former method, neutrophils act perfectly as Trojan Horses, releasing the therapeutic cargoes at the tumor site by releasing neutrophil extracellular traps (NETs).[146] Inflammation is one of the main causes of NET release. Thus, Ren et al designed a neutrophil-mediated liposome co-loaded with PTX and hydroxychloroquine to form NETs that "open" the cells and release the liposomes when activated by cytokines secreted by the tumor-related cells.[147] By inducing tumor cell death and inhibiting their autophagy at the same time, a better antitumor effect can be achieved. This technology can also be applied to deliver drugs to different organs such as bone marrow.[148] For the latter, antibody conjugation can be used to capture and internalize NPs via activated neutrophils after intravenous injection.[149] However, this method might encounter problems with the rapid clearance of injected NPs by the immune system and therefore requires further investigation.

T cells interfaced with antitumor agents have also been explored in recent years, and the distinctive features of cytotoxic T-lymphocytes (CTLs) have been exploited to design a T cell-based platform for cancer therapy. When CTLs interact with tumor cells, they release perforin and granzymes into the immunological synapse formed between the CTLs and target cells. The nanocapsules attached to the surfaces of the CTLs entered the synapse and met the perforin secreted by CTLs, leading to the disruption of the nanocapsule and release of encapsulated drugs in tandem with the lysis of the tumor cells.[150] In addition, innovative carriers, as shown in ►**Fig. 8**, a TA-encapsulated polymeric micelle decorating with aPD-1 on the surface, which can bind circulating PD-1+ T cells to overcome immune checkpoint blockade resistance, are still under careful research.[151]

In summary, the use of living cells for the targeted delivery of antitumor agents or diagnostic reagents is an emerging approach that has made significant progress to

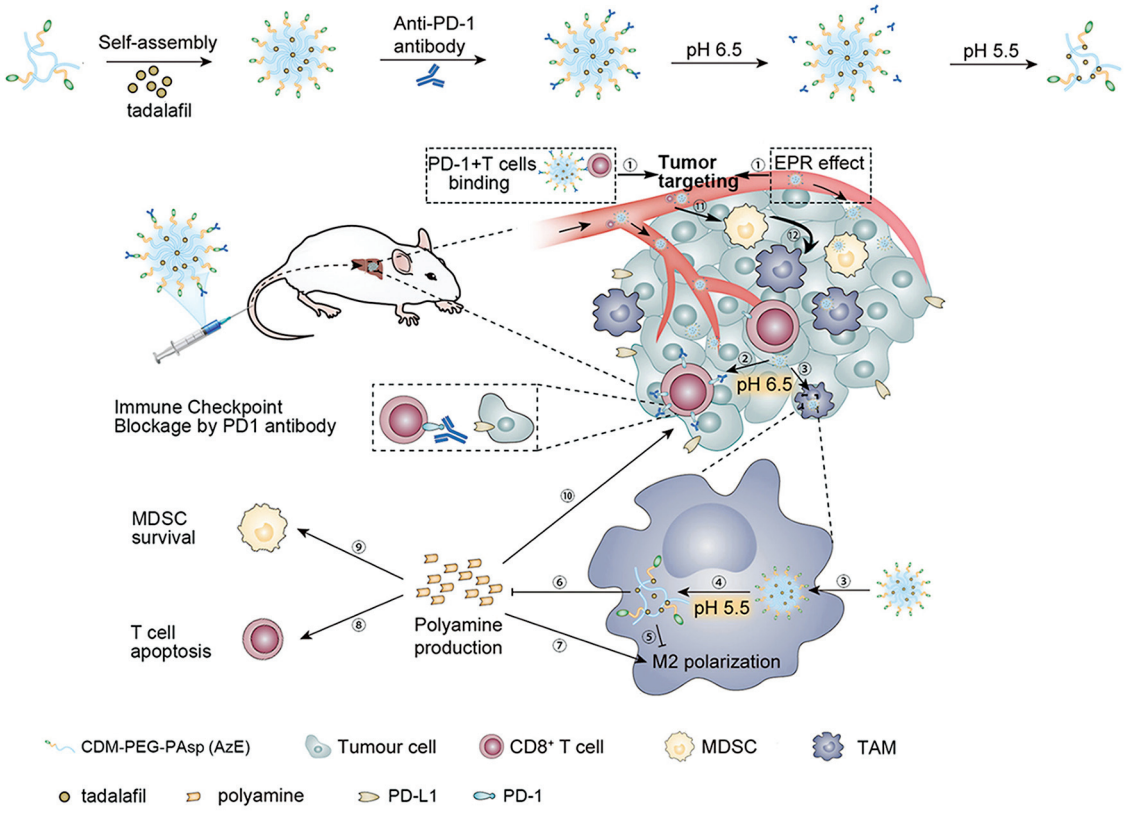


Fig. 8 Schematic illustration for the antitumor mechanism of nanodrug in overcoming immune checkpoint blockade resistance in HCC. HCC, hepatocellular carcinoma. (Reproduced with permission from Wang et al[151], copyright 2023 BMJ Publishing Group Ltd & Society for Immunotherapy of Cancer.)

date, but the challenges in this field cannot be ignored. First, the most common strategy is to separate carrier cells and load drugs into these cells before administration, which may affect the original characteristics of cells, and the drugs may undergo complex intracellular processes in living cells. In addition, drug-loading efficiency is relatively low due to the limited drug-cell binding capacity. Also, the leaking of drugs into the body from the exogenous cells is an urgent issue. Once these issues are addressed, this therapy could have a revolutionary impact on the process of eliminating tumors.

Summary

BDDSs mimic the structures and functions of various natural substances. BDDS, like well-trained and well-equipped plainclothes policemen, can achieve better targeting, improve the efficiency and accuracy of drug delivery, and make up for the shortcomings of existing NDDS. BDDS is able to better address the current problems faced by traditional chemotherapeutics and DDS, and thereby an ideal candidate for cancer treatment. In this article, the performances and advances of three BDDS, i.e. EVs, living cell-based drug carriers, and membrane-coated NPs, have been reviewed in antitumor therapies, and are summarized in ►**Table 1**. The emergence of BDDS breaks through the limitations of traditional nanomedicine, with higher targeting ability, longer circulating time, excellent capacity to cross biological barriers, and higher drug accumulation at the tumor sites, and brings more opportunities for targeted tumor therapies. In the future, biomimetic systems can produce unified and standardized formulations for most patients on the one hand, and can also design more adaptable drugs for specific patients, achieving personalized precision medicine on the other.

Table 1 Brief introduction of the current BDDS

BDDS type	Source cells	Advantages	Disadvantages	Tumor cell model	Pharmacological factors	Ref.
EVs	MSC	Smaller size, prolonged circulating time, industrial application, malignancy-targeting ability	Building tumor microenvironment, immunosuppressive behavior	CFPAC-1	Paclitaxel	40
				PANC-1, MIA-PaCa-2, CFPAC-1	circRNA circ_0030167	39
				B16/F10	PI3Kγ inhibitor	154
				CT26	Photodynamic therapy agent mTHPC	41
	DCs	Boost the efficacy of immuno-therapy	High cost, time-consuming	B16-OVA	Anti-CD3 antibody membrane insertion	53
				B16-MUC1	Tumor antigen MUC1 glycopeptide membrane conjugation	54
				B16F10	CTX	155
				B16F10	Tumor antigen-loaded inside	58
	Tumor cell	Homing, immune cell sensitization, and high absorption	Induce tumor immune tolerance, promoting neoplastic angiogenesis	MDA-MB-231/luc	TLR3 agonist and ELANE	156
				4T1	FeS_2 nanozyme	157
				HT1080, HeLa	Doxorubicin	69
CMCNs	Erythrocyte	Sufficient raw materials, immune escape	Induce alloimmuniza-tion, complex extraction process	B16F10	Worm-like siRNA	86
				HepG2	Mesoporous silicon nanoparticle	158
				Saos-2	DOX-loaded ZC NPs	159
	Tumor cell	Homotypic targeting and immune escape abilities	Difficult extraction	SMMC-7721	Lenvatinib@PAE NPs	160
				HeLa, MCF7, etc.	AuNPs	161
	Leukocyte	Increased circulation time, high affinity toward tumors	Lack of economic manufacturing process-es and high-standards of quality assurance	Kasumi-1, U937, MV4–11, etc.	Glycyrrhetinic acid/PLGA NPs	162
				KYSE-150	DOX-loaded lipid nanovector	163
	Hybrid cell membrane	Multi-features from parent cells	Cell membrane damage caused by hybridization	SKBR3, BT474	Maytansine-loaded tetrahedral framework nucleic acid	110
Living cell drug delivery system	Erythrocyte	Long circulation time and immune escape	Lack of targeting molecules	–	Upconversion NPs, hitchhiking	125
	Platelet	Low costs, hypoimmunogenic	May contribute to cancer progression and metastatic dissemination	C1498	Anti-PD-L1 antibody surface conjugation	137
				B16F10, CT26, 4T1		138

(*Continued*)

Table 1 (*Continued*)

BDDS type	Source cells	Advantages	Disadvantages	Tumor cell model	Pharmacological factors	Ref.
	Leukocyte	Targeting movement and transmigration ability toward tumor cells	Interfered by the immunosuppressive factors secreted by tumor cells	4T1	Paclitaxel and hydroxychloroquine-loaded liposomes	146

Abbreviation: BDDS, biomimetic drug delivery system; CMCNs, cell-membrane-coated NPs; CTX, cyclophosphamide; DCs, dendritic cells; DOX, doxorubicin; EVs, extracellular vesicles; MSC, mesenchymal stem cell.

One of the most challenging problems faced by traditional small-molecule chemotherapy drugs and conventional DDS is the adverse effects caused by the "off-target" effect, relatively high dose, and high immunogenicity. BDDS offers a possible solution to these problems. BDDS carriers not only have a variety of natural targeting molecules on their surfaces that can precisely direct the drugs to the tumor sites but also have "self" characteristics that allow them to avoid rapid clearance by the immune system. In this case, the adverse effects can be minimized by applying smaller doses while achieving the same therapeutic effect as before or even better.

BDDSs are all obtained from bio-materials and carry a large number of biological macromolecules, so one of the key issues of BDDS is their immunogenicity. Overcoming the inherent immunogenicity of BDDS will be an urgent problem to be solved in large-scale industrial production in the future. We believe that by modifying cell biofilm, controlling the composition of biomimetic membranes, ensuring consistency of source, avoiding heterologous issues, etc., more BDDSs will enter clinical trials and even be on the market.

The advanced DDS still has many other challenges and difficulties in ensuring carrier separation and purification effect, unclear mechanism of functioning *in vivo* and clinical transformation. Questions such as "Will there be interactions between natural components of the human body and artificially modified components that are not conducive to drug delivery?," "Can artificially processed natural materials still efficiently maintain the functions of their parent tissues or cells?," or "Can current technology support the mass production and clinical application of BDDS?" still need to be answered. In addition, the safety of various materials currently used to construct BDDS has not been thoroughly and meticulously evaluated and has rarely been approved by the U.S. Food and Drug Administration, which to some extent limits the subsequent clinical conversion of such drugs.

To solve these problems, several new strategies have been proposed. Recently, EVs isolated from natural grapefruit and ginseng, instead of from mammals, were reported in antitumor therapy in combination chemotherapeutics. Those plant-derived EVs are low immunologically, green, renewable, and mass-producible, and are expected to ameliorate the shortcomings of EVs and bring new hopes for patients.[152,153] Many researchers have been trying to combine traditional DDS with biomaterials to achieve better therapeutic effects by using hybridizing liposomes, cell membranes, and other materials. It seems that strategies applied to traditional DDS, such as modification of the NP surfaces using PLGA and targeted molecules, appear to be equally feasible with BDDS and could improve antitumor efficacy.

Despite the issues encountered with BDDS, as mentioned earlier, the advantages of these systems are also evident. EVs seem to be the most promising carrier for tumor diagnoses and treatment. To date, several EV-based drugs are in clinical trials. The large number of EVs currently points to new directions in the treatments of Crohn's disease, chronic obstructive pulmonary disease, empyrosis, etc. The smaller size and "lifeless" characteristics give them a better ability to evade immune clearance and stability compared to living cell-based nano-carriers. While the proteins and nucleic acids contained within them may be sources of immunogenicity and a driver of tumor metastasis (especially EVs derived from tumor cells), some of the endogenous substances in EVs have intrinsic antitumor activity, which to some extent gives them an advantage over cell membrane-coated NPs.

It is believed that with further research in the fields of materials science and molecular biology, BDDS will be more widely used and play an important role in weaponizing common substances in the body to fight tumors.

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Conflict of Interest
None declared.

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