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Development and application of bionic systems consisting of tumor-cell membranes

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Malignant tumors pose a serious threat to human health but during the past decade, great progress has been made in the treatment of tumors. The tumor-cell membrane is well constructed and can be used to solve problems in tumor therapy. Tumor-cell membranes exhibit not only high biocompatibility due to their homology but also enhanced therapeutic effects when combined with nanotechnology. Meanwhile, nanomaterials show high selectivity, sensitivity, and clinical transformation potential. Enhanced immunotherapy or tumor vaccines have potential clinical application because of tumor-membrane surface-specific antigens. Several studies have confirmed the feasibility and advantages of using tumor-cell membrane-incorporated nanosystems for tumor therapy. Considering all this, we focus in this review on the application of tumor-cell-membrane bionic platforms and, in the summary, provide ideas for new scientific developments.

Cancer therapy is not limited to chemotherapy and radiotherapy but includes targeted therapy, immunotherapy, gene therapy, and other therapies that confer greater survival benefits on patients. While the status of chemotherapy among tumor treatments cannot be overestimated, due to the lack of targeting, which causes a variety of serious adverse reactions, the medical applications of chemotherapy are limited. Many pharmaceutical and biological approaches have been proposed to solve the problem of these off-target effects. The first liposome drug, Doxil, is a two-component hydrogenated soy phosphatidylcholine/1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (HSPC/DMG-PEG) liposome coated with Doxorubicin for use in ovarian and breast-cancer chemotherapy, and it shows fewer toxic effects than free drugs (Barenholz, 2012). Some people are wondering how better targeting can be achieved while preserving biocompatibility. Red blood cells in the human body were the first candidates for improved chemotherapies. However, due to their targeting deficiencies, red blood cells are not the most suitable delivery tools (Li RX et al., 2018). The solution to this targeting problem involved binding of receptors affinity to ligand, such as folate and folate receptor, ARG-GLy-ASP (RGD) and integrin αVβ 3, ASN-GLy-ARG (NGR) and aminopeptidase N. Later, some studies attempted to use specific ligand epitopes to bind tumors, but the efficiency of these systems was poor, and therefore, these studies were not widely pursued.

However, since 1994, scientists have been compressing chemotherapeutic drugs into red blood cells, opening a new era of cell-membrane biomimetic systems to treat tumors (Wang et al., 2020). This self-derived cellular component shows good biocompatibility, a long circulation time, and appropriate biodegradability. However, because red blood cells are not targeted to a tissue and may cause abnormal activation of other signaling pathways in the preparation process, clinical transformation with a system based on erythrocytes is difficult to achieve (Wang et al., 2021). In addition, ideal nanodelivery systems require better targeting, longer blood circulation, and reduced attrition compared to lipid nanoparticles to realize precise treatment. Some scientists have wondered whether the homing effect of tumor cells can be used for therapeutic drug "hitchhiking."

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Faced with these problems and suggestions, scientists have looked to nature for new ideas. Hanahan (2022) updated a list of several tumor-cell features and summarized recent advances in biology. We can now more clearly understand the unique structure and signaling modalities of tumor cells, which is the basis of their abnormal biological characteristics. Most normal cells in the body need to adhere to the extracellular matrix, and once detached, they undergo apoptosis. However, tumor cells can play a role in invasion and metastasis by fine-tuning the molecular "anchors," by which cells adhere to the matrix through cell-membrane proteins (Zhu et al., 2016). In addition, in terms of immune escape, "do not eat me" protein-targeting immune cells are highly expressed on the surface of tumor-cell membranes. Therefore, leveraging many advantageous aspects of the tumor-cell membrane may be a new strategy in tumor treatment. Hu et al. (2011) first proposed membrane-coating technology, and since this discovery, this technology has been closely associated with the nanoparticle core. Later, because leukocytes show high migratory capacity and ability to cross biological barriers, coating the surface of leukocytes with nanoparticles was suggested. Chemotaxis of leukocytes to inflammatory sites in the microenvironment leads to tumor clearance (Parodi et al., 2013). Acting as specialized antigen-presenting cells (APCs) in the presence of leukocytes, dendritic cells can effectively recognize tumor cells, and this precise identification can be used to make cancer vaccines (Zitvogel et al., 1998). In addition, Hu et al. (2015) creatively proposed platelet-coated putamen-targeted nanocarriers, suggesting that metastatic cancer cells recruit platelets for survival during metastasis. However, we believe that these platelet-coated nanoparticles may have an additional advantage in the treatment of positive margins after surgery. Many people are thinking about how to improve bionic systems. Some scientists have suggested that tumor cells are complex and that most of the intracellular components contain genetic material that may pose a safety risk. Because APCs bind to tumor-cell surface receptors to specifically recognize and kill tumors (Li et al., 2021), cancer-cell membranes may be the best choice for nanomodification coatings.

Tumor-cell membranes are derived from patient-derived tissues and cells with infinite reproducibility in vitro. This makes the material readily available, and the bionic nanocoating developed from these membranes exhibits the properties of a tumor cell. During metastasis, cancer cells combine to adapt and reshape the tumor microenvironment. Aggregation and adhesion are reported to be based on the surface-adhesion molecules N-cadherin, galectin-3, and the epithelial-cell-adhesion molecule (EpCAM) on tumor-cell membranes (Zhao et al., 2010). Leveraging the related targeted adhesion property of these molecules, nanomaterials can be "navigated" to target tumor cells precisely and efficiently.

Cell-membrane-loading technology involves wrapping a tumor-cell membrane around the outer layer of nanomaterials, yielding nanoparticles with the composite properties of nanoparticles and tumor cells. These nanomaterials can be used as drug carriers with a high drug-loading rate, uniform controlled release, and high surface area for efficient drug delivery. Similar to the long-lived tumor cells, nanoparticles loaded with tumor-cell membranes are accepted by the body, which reduces their phagocytosis and elimination. Modification of a drug or nanomaterial with polyethylene glycol (PEG) can delay the clearance time, but repeated use of this material induces production of the specific antibody immunoglobulin M (IgM), mediating immune clearance (Li BW et al., 2018). In addition, reduced phagocytosis and internalization are keys to generating a useful bionic system. In drug delivery, sufficient blood-retention time is the basis of therapeutic efficacy. As a model of bionic membrane system therapy, the erythrocyte membrane relies on prolonged circulation time in the body for its efficacy and is widely used. The tumor-cell membrane is very important for preventing phagocytosis and inherently establishes an enhanced biological interface with nanoparticles. In one study, natural cancer-cell membranes were disguised as a pH-responsive nano coating (Liu ZW et al., 2021). This study confirmed that nanomaterials with a tumor-cell membrane can not only prevent phagocytosis but also promote the metabolism of glycan markers in vivo. Targeting-strategy experiments have elegantly demonstrated that multiple membrane receptors on tumor membranes exhibit higher affinity than single ligands and thereby facilitate tumor imaging. In addition, tumor progression and persistence are caused by immune tolerance. For instance, overexpressed cluster of differentiation 47 (CD47) and programmed death-ligand 1 (PD-L1) on

the surface of cancer cells play roles in immune escape. After intravenous injection in one study, nanoparticles modified with CD47 and other regulatory molecules were distributed in various lymphoid tissues and organs, and they were retained for longer than 36 h (Pei et al., 2018). This outcome suggested that using tumor-cell membranes as surface coatings could effectively prevent immune-response elimination of nanoparticles.

A biomimetic system that camouflages tumor-cell membranes enables fusion of nanoparticles with cell membranes through mechanical extrusion. We have the convention of evaluating the surface morphology and protein of a complex to verify whether the complex exhibited the properties of the original tumor-cell membrane. Considering the adhesion, chemotaxis, and exosmosis of tumor cells, biomimetic nanoparticles showed great development potential for surface modification with tumor-cell membranes. Most nanoparticles have a spherical structure, which allows for efficient transport and loading. Therefore, nanoparticles can be transported locally or through the blood and are widely present around tumor tissues. In addition to being a drug carrier, tumor-cell membranes can be combined with other strategies for photothermal therapy or cancer-vaccine development (Fig. 1).

The value of drugs in the treatment of cancer is obvious, but some chemotherapy drugs show poor water solubility or targeting ability or cause serious adverse reactions, affecting treatment effectiveness. The successful accumulation of drugs at a diseased site requires that many biological barriers should be continuously overcome, and finding a better way to deliver drugs has become an urgent problem. Nanoparticles were initially suggested for optimization of drug delivery, but they were later found to be more helpful in breaking through biological barriers. Novel cerium-oxide nanoparticles (CeNPs) have been proposed for treating breast cancer, which is prone to lung, liver, and bone metastases (Liu HJ et al., 2021). The nanoparticle was integrated with degradable mesoporous silica and mimicked superoxide dismutase and catalase, which enabled the delivery of the nanoparticle near tumors because it was disguised by a tumor-cell-membrane coating. This strategy effectively reversed cancer-associated fibroblast differentiation and reduced tumor volume. This experiment confirmed that the efficiency of tumor-cell-membrane delivery was better than that of ordinary nanodelivery systems. Chen et al. (2019) tried to combine a gene-therapy strategy with chemotherapy drugs and nanoparticles to prepare tumor-cell-coated nanoparticles for targeted coadministration. Moreover, immune system stimuli, including adjuvants, cytokines, and monoclonal antibodies, can be delivered through a bionic nanoplatform to improve unsatisfactory pharmacokinetics and promote easy degradation (Zhuang et al., 2019). The emergence of these approaches has increased drug bioavailability by conferring additional protection and targeting ability, promoting the enrichment and development of bionic strategies. In addition to enriching the diversity of loaded drugs, Gong et al. (2020) creatively developed a hybrid coating of macrophage and tumor-cell membranes that incorporated features of both types of cells. Due to the tendency of these

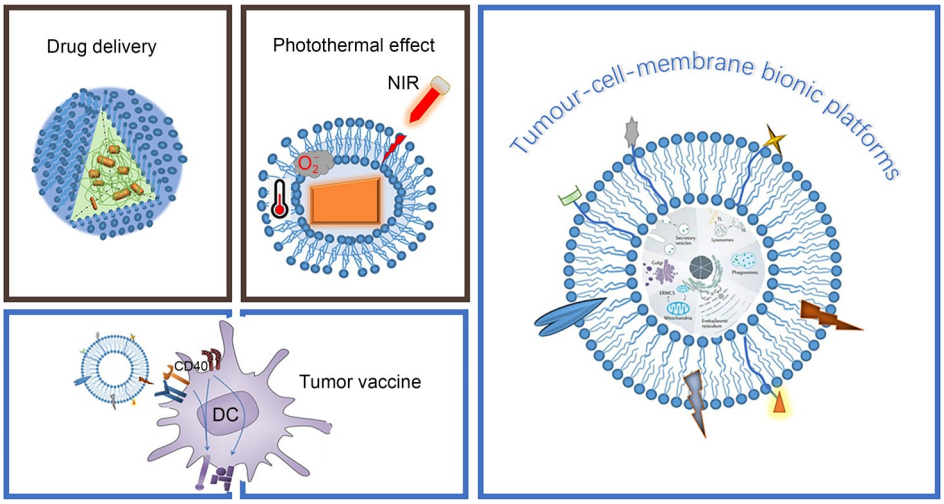

Fig. 1 Three main applications of tumor-cell membranes. NIR: near infrared; DC: dendritic cell.

cells to aggregate at inflammatory sites, they also had the ability to target specific metastasis and homogeneousness. This biomimetic system, in which a tumor-cell membrane was added after nanoparticle fusion, was robust and exhibited the function of a hybrid membrane. Therefore, this hybrid is a promising platform for nanobionic system development.

Photothermal therapy and similar chemodynamic therapies are based on the photothermal properties of nanoparticles for physical/chemical tumor treatment. The surface layer of this nanomaterial consists of tumor-cell membranes and the interior comprises various metals, metal compounds, and substances capable of producing photothermal effects. Using the homotypic targeting ability of the cell membranes, the photothermal effects of reactive oxygen species (ROS) alleviated hypoxia and glutathione depletion, thereby disrupting the tumor microenvironment (Liu et al., 2019). Upon exposure to near-infrared light, some of these nanoparticles were transported to the tumor microenvironment via the cell membrane to induce thermal effects. On the one hand, this system promoted the release of loaded drugs. On the other hand, the high temperature and ROS produced killed tumor cells. Chen et al. (2016) used core-shell nanoparticles composed of an indocyanine green (ICG) polymer core and a tumor-cell membrane shell for real-time monitoring of the dynamic distribution in vivo with near-infrared dual-mode imaging. The results confirmed that the nanoparticle effects were enhanced by the homologous binding and adhesion ability of the tumor-cell membranes, which contributed to high altitude resolution and deeply penetrating imaging. To achieve the optimal balance between prolonged blood circulation and homologous targeting, Jiang et al. (2019) fused erythrocyte membrane with melanoma tumor membrane in equal proportions. The photothermal effect increased with an increase in the number of nanoparticles, and targeted delivery of the tumor-cell membranes enhanced the efficacy of the system. This interesting approach enabled flexibility and control for photothermal therapy of solid tumors.

A variety of immunogenic antigens on the tumor-cell membrane can be leveraged not for use as drug-delivery carriers but for tumor-vaccine development. The strategy of using tumor-associated proteins on the cell membranes of cancer cells that can be processed and phagocytosed by APCs, natural killer (NK) cells, and M1 macrophages in the immune system is promising in theory. Unfortunately, it is difficult to directly activate the immune system even when stimuli are injected into an immune organ because of the surplus of nontumor-associated antigenic materials.

One important approach to inducing an immune response is breaking down the established immunosuppressive tumor microenvironment. Chen et al. (2021) attempted to use *Escherichia coli* plasma membranes with autologous tumor tissue as adjuvants to enhance immunogenicity and deliver nanoparticles on the basis of tumor-cell-membrane antigens. The system showed efficacy in colon-cancer and breast-cancer models and effectively induced tumor regression in melanoma mouse models. This tumor-vaccine-based treatment strategy demonstrated that the fusion of tumor membranes, which induce multiple forms of immunogenicity, to bacterial membranes, which exhibit an intrinsic adjuvant function, showed superior vaccine properties, enhancing vaccine efficacy. This engineered tumor-cell-membrane vaccine was a nanomaterial-based synthetic approach, and hybrid membranes may be used for enhancing immunotherapy (Jiang et al., 2020). Moreover, new functional vesicles can be formed by fusion and hybridization of tumor-derived cell membranes and bacterial outer-membrane vesicles (Zou et al., 2021). Simple bacterial fermentation can be used for mass production through bacterial genetic modification, and activated tumor-membrane components also enhance the killing function of splenic lymphocytes (Fig. 2). These advantages make these newly developed functional vesicles easy to use for vaccination, biological imaging, and targeted drug delivery.

In the United States Food and Drug Administration (FDA)-approved therapeutic tumor vaccine Provenge, after APCs are engineered, the precise operation of their surface membrane proteins activates a patient's autoimmunity. This drug is used to treat non-androgen-dependent prostate cancer (Burch et al., 2004; Kantoff et al., 2010). Unfortunately, Provenge has not changed the landscape of cancer treatment, perhaps because of its high price, but most likely because clinical trials have failed to show convincing improvement in overall survival. In addition, NeoVax, a vaccine comprising personalized antigenic peptides, is effective against melanoma (Keskin et al., 2019).

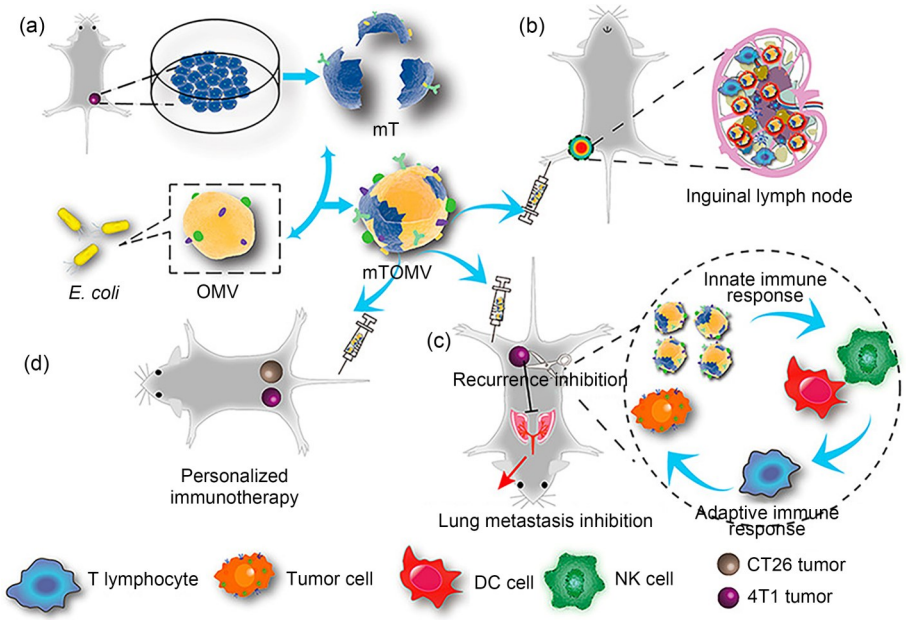

Fig. 2 Formation of new vesicles by extracting tumor-cell membranes and bacterial vesicles. Due to the immunogenicity of the tumor-cell membrane and the adjuvant effects of the bacterial vesicles, activation of immune organs was stimulated and an effective tumor vaccine was produced. These vesicles inhibited primary and metastatic tumor growth. Reprinted from Zou et al. (2021), Copyright 2021, with permission from the American Chemical Society. mT: tumor membrane; OMV: outer membrane vesicle; DC: dendritic cell; NK: natural killer.

NeoVax can effectively induce tumor-specific T-cell activation. Notably, this treatment is highly dependent on the immune microenvironment; dexamethasone cannot be used in the initial stage of treatment, and no systemic depletion of T cells is realized (Blass and Ott, 2021). These outcomes suggest that finding tumor-specific antigens or using them is not easily achieved and that significant challenges remain to be overcome before vaccines can activate immunity. Therefore, activating the tumor microenvironment using tumor-cell-membrane proteins combined with nanotechnology may lead to a breakthrough in future research and development.

Development of the tumor-cell-membrane bionic system has further enhanced the tumor-targeting strategy. Derived from autologous tumor cells, these membranes enable the elimination of abiotic factors and show high biocompatibility. In addition, the rapid proliferation and easy culture of tumors make tumor-cell membranes more readily available than other types of biofilms. Above-mentioned studies have shown that tumor-cell membranes, as drug delivery carriers, do not need to be specific to tumors because of the many tumor-antigen types on their surface, meaning that these membranes offer one-stop clearance for primary tumors and metastases. However, there is still room for improvement in many areas. First, the technology is not mature. Most nanoparticles are only partially coated by standard coating methods, and the degree of coating may influence the biological fate of the nanoparticles. A recent study has found that up to 90% of bionic nanoparticles are only partially coated; however, partially coated nanoparticles can still be internalized by target cells (Liu HJ et al., 2021). This finding suggests that more specific methods of coating membranes need to be developed. Second, the stability and safety of membrane-surface proteins need to be preserved during the synthesis of tumor-cell membranes. In addition, the ideal targeting state of the tumor-cell membrane is influenced by tumor-cell phenotype and cell-surface proteins, but it is difficult to determine whether the heterogeneity of a solid tumor affects its tumor-cell-membrane targeting.

The most important consideration is biosafety. Coating nanoparticles with a tumor-cell membrane by repeated extrusion or electroporation makes complete removal of biodetritus difficult, which may be a safety risk. Removing the nuclear component from the final formula has been suggested as a way to help allay concerns about genetic material and thereby reduce

safety concerns. The process of removing nuclear components, however, is complicated. After hypotonic treatment of tumor cells, eukaryotic cell membranes are collected by discontinuous sucrose-density gradient ultracentrifugation. The membrane coating structure is then fabricated by coextrusion or incubation (Fang et al., 2014). In addition, the first approved antitumor vaccine Provenge was composed of peripheral blood monocytes in the APC population that had been activated in vitro and then transfused back into the patient. In such a case, when a tumor-cell membrane is obtained from the patient's own primary tumor and undergoes engineered transformation, are potential safety risks minimized? With the development of science, an increasing number of new methods are being generated to solve biosafety problems. Attempts have been made to eliminate the conditions suspected to contribute to cancer metastasis by eliminating representative proteins (calreticulin and Sp1) and messenger RNAs (mRNAs) (*cyclin D1*, ataxia-telangiectasia mutated (*ATM*), ataxia telangiectasia and Rad3 related (*ATR*), and *p53*) (Lin et al., 2022). A constructed tumor-cell-membrane surface coating exposed to ultraviolet radiation has been suggested to induce tumor-cell apoptosis (Tan et al., 2015). In summary, no standardized safety assessment for the production of cancer-membrane debris has been established.

With insights gained from multidisciplinary integration, the previous questions have been answered. Tumor-cell membranes exhibit superior stability and delivery-carrier properties to nanomaterials. The unique characteristics of tumor cells have been leveraged to design nanomaterials. Through multidisciplinary research, more refined methods for treating cell membranes derived from tumor tissues have been developed. Whole-cell components can be used to determine the specificity of tumor-cell membranes through a precise approach called the high-throughput platform for the elucidation of membrane-receptor interactomes (RDIMIS) (Cao et al., 2021). The platform abrogates the membrane-protein purification step and can be used to characterize any naturally occurring target proteins expressed on the cell surface. Thus, the tumor-cell-membrane bionic system can be refined and subjected to innovation. In addition, the hybrid products of tumor-cell membranes and various other membranes have shown greater homologous targeting and penetration ability (e.g., the blood–brain barrier) (Wu et al., 2021). Compared to other systems, nanocarrier delivery directed by tumor-cell-membrane coating led to better long-term inhibition of tumor growth and metastasis. Most importantly, engineered improvements to tumor-cell membranes may differ from modifications that specifically activate a tumor vaccine. In this context, improvement refers to conjugation of multiple targets or inhibitors on cell membranes in addition to efficient encapsulation of the multiple substances within these cells (Meng et al., 2021). This modification can effectively activate the tumor microenvironment or enhance drug sensitivity and improve the efficacy of immunotherapy or chemotherapy. Based on these approaches to fine-tune treatment, the tumor-cell-membrane bionic system can be updated and improved through development and thus become even more promising.

Here, we have summarized a potential strategy for tumor diagnosis and treatment, and we hope that a greater number of improvement approaches will be proposed and that treatment of a greater variety of tumor species will be performed to ultimately obtain a universal treatment. We believe that the theory and processes undergirding the tumor-cell-membrane bionic system can be further optimized. First, processes need to be changed to ensure biosafety. We consider quantifying tumor derivatives or biological fragments, such as DNA and mRNA, to be an effective method for evaluating the control of tumor-cell-membrane infusion and membrane fragmentation. Second, tumor-cell membranes are loaded with a plethora of molecules, not merely loaded drugs or immune-related substances. For example, proteolysis-targeting chimeras (PROTACs) show limited bioavailability (Garber, 2022). However, by combining PROTACs with a tumor-cell-membrane delivery system, treatment penetration can be greatly improved. Finally, an intersection of multiple disciplines is helpful because it enables the incorporation of more materials to improve or replace tumor-cell-membrane delivery systems, offering better prospects. Overall, design of tumor-cell membranes has opened a new chapter in the story of cancer diagnosis and treatment. We expect more effective methods and strategies to be presented in the future.

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Author contributions

Jun YAO proposed the conjecture and design of the project. Tianjiao PENG studied relevant content and completed the manuscript. Both authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Tianjiao PENG and Jun YAO declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by either of the authors.

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