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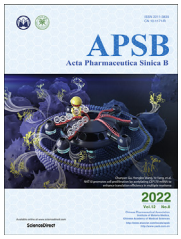

REVIEW

Cell membrane coated-nanoparticles for cancer immunotherapy

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Immune checkpoint blockade inhibitors

Abstract Cancer immunotherapy can effectively inhibit cancer progression by activating the autoimmune system, with low toxicity and high effectiveness. Some of cancer immunotherapy had positive effects on clinical cancer treatment. However, cancer immunotherapy is still restricted by cancer heterogeneity, immune cell disability, tumor immunosuppressive microenvironment and systemic immune toxicity. Cell membrane-coated nanoparticles (CMCNs) inherit abundant source cell-relevant functions, including "self" markers, cross-talking with the immune system, biological targeting, and homing to specific regions. These enable them to possess preferred characteristics, including better biological compatibility, weak immunogenicity, immune escaping, a prolonged circulation, and tumor targeting. Therefore, they are applied to precisely deliver drugs and promote the effect of cancer immunotherapy. In the review, we summarize the latest researches of biomimetic CMCNs for cancer immunotherapy, outline the existing specific cancer immune therapies, explore the unique functions and molecular mechanisms of various cell membrane-coated nanoparticles, and analyze the challenges which CMCNs face in clinical translation.

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1. Introduction

According to *A Cancer Journal for Clinicians*, the incidence and mortality rates of cancers are increasing rapidly worldwide[1]. At present, delayed early diagnosis, the tendency of metastasis and recurrence, as well as the unresectable toxic side-effect of conventional chemo- and radio-therapy, make cancer treatment full of challenge[2]. Clinical studies have shown that chimeric antigen receptor T cell (CAR-T) therapy can effectively treat lymphoma and leukemia, and immune checkpoint blockade (ICB) inhibitors can regulate endogenous immunology for treating melanoma. The continuous progress of these innovative therapies has opened a new hot spot, namely cancer immunotherapy[2–4].

Cancer immunotherapy is a potential, low-toxic and effective therapy which can recognize and kill cancer cells through the autoimmune system. At present, cancer immunotherapies mainly include cancer vaccines, adoptive cellular immunotherapy, cytokine immunotherapy (interferon, interleukin) and immune checkpoint blockade inhibitors and so on. Although cancer immunotherapy has achieved certain curative effects in clinic, it still confronts many challenges that limit its effectiveness, such as cancer heterogeneity, immune cell disability, tumor immunosuppressive microenvironment, and concomitant systemic immune toxicity[5,6]. Besides, accurately delivering drug to tumor is one of the urgent problems to be solved, which can enhance immune response and reduce systemic immune toxicity[7].

Nanoparticles (NPs) have gradually become a promising generation of drug delivery systems because they have wonderful design flexibility, reduced toxic side-effects, and enhance efficacy *in vivo*[8,9]. Because of tumor enhanced permeability and retention (EPR) effect, nano delivery systems are widely used to deliver therapeutic agents for chemotherapy, radiotherapy, gene therapy and immunotherapy[10]. However, nanoparticles as exogenous substances can be effectively identified and removed due to the complex blood environment *in vivo*. The removal by the mononuclear phagocytic system (MPS) has become the main obstacle of nano drug delivery system[11–13]. Besides, the non-specific distribution of nanoparticles *in vivo* causes greater toxic side-effects. Engineering modified nanoparticles can improve the distribution of nanoparticles *in vivo*. For example, PEGylation nanoparticles can extend their blood circulation time *in vivo*. Antibodies and ligands modified nanoparticles can improve the targeting efficiency into lesion sites[14]. Nevertheless, repeated long-term administration of PEGylated nanoparticles can accelerate the elimination and induce a stronger immune response. Therefore, more effective solutions are needed[15–17].

In recent years, biomimetic designs based on cell membrane coating have gradually emerged. The first cell membrane-coated nanoparticles (CMCNs) were prepared by co-extruding erythrocyte membranes and polylactic acid-glycolic acid (PLGA) cores[18]. CMCNs can integrate advantages of the various proteins and molecules on cell membranes, which make them to have better biocompatibility and lower immunogenicity, escape the immune system clearance, target the tumor, and deeply penetrate the tumor[19–21]. Therefore, CMCNs are applied to precisely deliver drugs or directly promote the effect of cancer immunotherapy[22].

In the review, we emphasize the important role of biomimetic CMCNs in cancer immunotherapy, and summarize the latest research progress in biomimetic CMCNs for cancer immunotherapy. We outline several common cancer immunotherapies and their limitations in clinical applications. Besides, the functions and underlying molecular mechanisms of CMCNs and their applications in cancer immunotherapy are reviewed. Moreover, we analyze and discuss the challenges of their clinical translation.

2. Cancer immunotherapy

In the late 19th century, a strange phenomenon was found in clinical practice that when cancer patients developed epidermal infection with erysipelas, the cancer would undergo regression without anti-cancer intervention[23]. It ushered a new era for utilizing immune system to kill cancer. Later, William Coley, the "father of cancer immunotherapy", used Coley's toxin (a cocktail of heat-killed *Streptococcus pyogenes* and *Serratia marcescens*) with powerful immunostimulatory properties to alleviate various cancers progression[24]. Cancer immunotherapy made substantial progress in the 20th century. The hypothesis of "cancer immunosurveillance" was proposed which guessed that the autoimmune system can recognize tumor-associated neoantigens and suppress tumors[25,26]. With the development of cancer immunology, there is a more accurate and clear understanding of the cancer immune process.

In tumor microenvironment (TME), natural killer cells (NK cells) and neutrophils of the innate immune system directly identify and attack cancer cells. The adaptive immune system plays the main role of anti-cancer attack. The antigen presenting cells (APCs, *i.e.*, dendritic cells) in the TME capture the tumor antigen and present it in the form of major histocompatibility complex-I (MHC-I)-antigen peptide/MHC−II−antigen peptide complex on surface. Then, they transfer the MHC-antigen peptide complex to the secondary lymphoid organs[27]. For the next stage, $CD8^+$T cells and $CD4^+$T cells are activated through the interaction of T cell receptor (TCR) with MHC-antigen peptide complex on dendritic cells (DCs) in lymph nodes. And other corresponding receptor-ligands cross-interactions, including CD80/86−CD28, CD70−CD27, CD40−CD40L, etc., are also involved in the activation procedure. Ultimately, activated tumor-specific cytotoxic T lymphocytes (CTL) proliferate and migrate to tumor under the attraction of chemokines secreted in TME, where they recognize and further kill cancer cells[28].

Unfortunately, cancer cells have evolved a series of mechanisms to avoid the monitor of immune system and achieve immune escaping with disease progression, including antigen presentation defect, immunosuppressive signals upregulation, immunosuppressive cells recruitment and so on[29,30]. The current cancer immunological strategy is aiming at different stages of the cancer immune process, including the release of tumor-associated antigens (TAAs), effective antigen uptake of APCs, APCs activation and antigens presentation, effector T cell activation and proliferation, tumor-specific CTL trafficking and infiltrating in tumor, and activated T Cells recognizing and killing cancer cells. Cancer immunotherapies (such as cancer vaccines, adoptive cellular immunotherapy, cytokine immunotherapy, ICB inhibitors) can induce immune response in the cancer-immunity cycle, and have become effective cancer treatments following surgery, radiotherapy, and chemotherapy (Fig. 1).

2.1. Progress in cancer immunotherapy

At present, cancer immunotherapy which utilizes the autoimmune system to identify and kill cancer cells has been extensively studied, including cancer vaccines, adoptive cellular immunotherapy, cytokine immunotherapy, and ICB inhibitors. The details are summarized in the following parts.

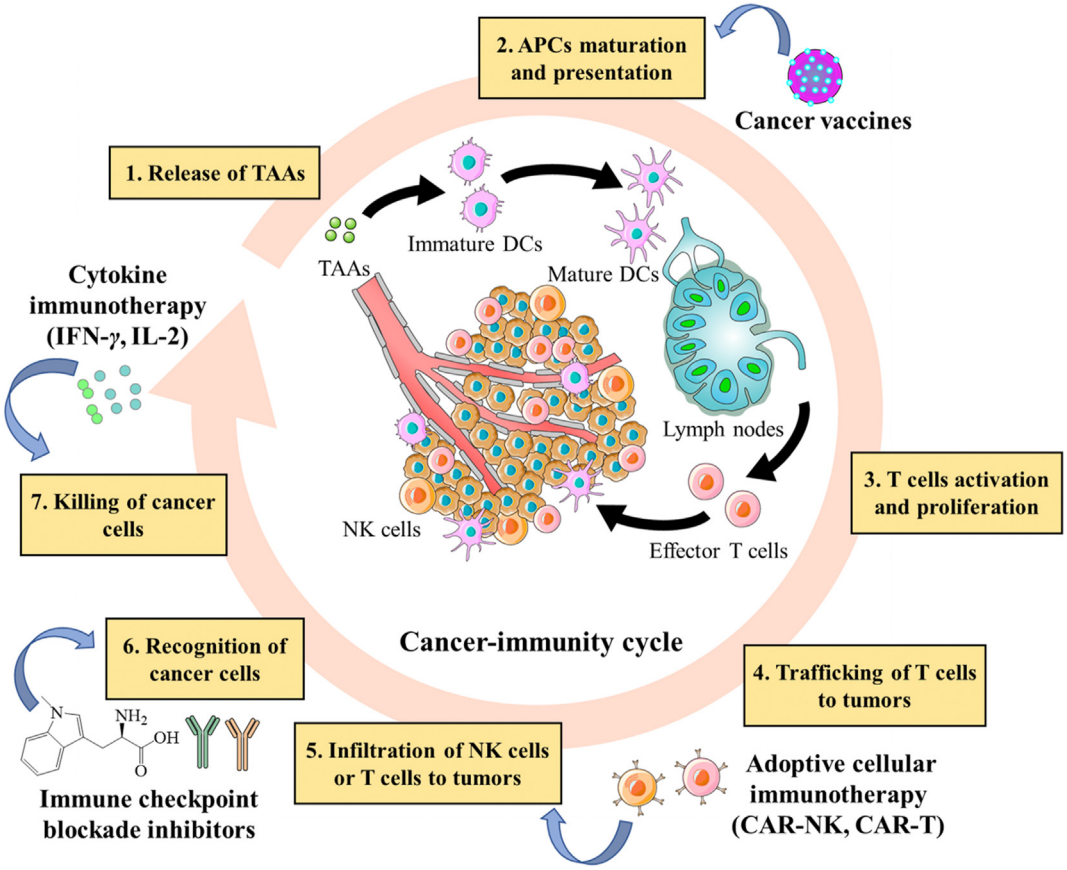

Figure 1 Schematic of several common cancer immunotherapies to induce immune response in the cancer-immunity cycle.

2.1.1. Cancer vaccines

Cancer vaccines exert anti-cancer effects through promoting the effective presentation of tumor-specific antigens (TSAs) by APCs to activate tumor-specific T lymphocytes. In 2010, FDA approved sipuleuce-T (Provenge; Dendreon) for treating metastatic castration-resistant prostate cancer, which is the only one therapeutic cancer vaccine and an active cellular immunotherapy. It is composed of autologous peripheral blood mononuclear cells (PBMCs) activated by a recombinant fusion protein (PA2024) *in vitro*. The cancer vaccine extends the patient's overall survival by 4.1 months[31]. With the development of antigen prediction technology, personalized cancer vaccines appeared on the stage[32], including DNA vaccines, RNA vaccines and peptide vaccines. Effective delivery of sufficient and high-quality antigens to DCs is the main principle for the success of cancer vaccines. Some studies have conducted explorations on the effects of tumor antigen vaccines with different delivery methods, including tumor antigen-specific DCs vaccines[33] and nano-vaccines[34]. They can effectively activate DCs to present tumor antigens, but the response rate of clinical patients is relatively low (11%−50%)[35,36]. It may be related to the complicated inhibitory network composed of cancer cells and other immunosuppressive cells in TME. Considering the above limitations, cancer vaccines may activate the effective anti-cancer immune response in combination with therapies acting on other stages of cancer immunity. These therapies include radiotherapy, chemotherapy that promote cancer cells immunogenic cell death (ICD) and kill immunosuppressive cells[37], and immune checkpoint blockade inhibitors that rejuvenate depleted tumor cytotoxic T cells[38].

2.1.2. Adoptive cellular immunotherapy

Adoptive cellular immunotherapy refers to infusion of immune cells edited *ex vivo* back into the patient to eliminate and control cancers, including non-tumor specific cells (NK cells, DCs, cytokine-induced killer cells, lymphocyte activated killer cells, tumor infiltrating lymphocyte), and tumor specific cells (CAR-T cells, T cell receptor-T cells, CAR-NK cells). The tumor specific cells have been modified to have stronger tumor antigen specificity and exert a stronger tumor recognition and killing effect. FDA has approved CAR-T drugs including Kymriah® and Yescarta®, which are used to treat relapsed or refractory adult large B-cell lymphoma and recurrent or refractory B-cell acute lymphoblastic leukemia[39]. However, compared with hematomas, the efficacy of CAR-T is quite restricted in solid tumors because of tumor antigens heterogeneity, insufficient infiltration, and the tumor immunosuppressive microenvironment. So far, improvements of CAR-T cells have been made in respect of cancer heterogeneity, including the construction of CAR-T cells expressing multiple CARs, the combined applications of multiple CAR-T cells[40], and the applications of CD133CAR-T cells targeting cancer stem cells that dominate the heterogeneity of solid tumors[41]. Intratumoral injection or combining with oncolytic virus that up-regulates the expression of chemokines in tumors was investigated for better CAR-T infiltration[42]. Aiming at the tumor immunosuppressive microenvironment, some studies focused on regulating the metabolism of CAR-T cells[43] and cytokine expression[44] to improve cell activity in harsh environments and enhance its tumor-killing activity. There are also researches on extracellular matrix (ECM) and cancer-associated fibroblasts in

the tumor immunosuppressive microenvironment. Fibroblast activation protein-specific CAR-T cells[45] showed great antitumor potential by killing immunosuppressive cells and degrading ECM. Although the various efforts made against solid tumors, CAR-T therapy still faces great challenges. CAR-T therapy combining with the complementary ICB therapy or cytokines that can effectively alleviate the tumor immunosuppressive microenvironment, may achieve better anti-cancer effects.

2.1.3. *Cytokine immunotherapy*

Cytokines are messenger molecules that are secreted in respond to cellular stress (such as infection, inflammation, cancer occurrence, etc.), and further coordinate the interaction and function of immune cells. Interleukin-2 (IL-2), interferon (IFN) and other cytokines enhance the anti-cancer immune effect by stimulating the maturation of DCs and enhancing the cytotoxicity of T cells[46]. In clinical practice, cytokine immunotherapy has played an effective anti-cancer effect, but it can cause nonnegligible toxicity, which limits its application as a monotherapy. At present, many researchers have conducted attempts to couple cytokines and adoptive T-cell immunotherapy[47], one of which coupled the reduction-sensitive IL-2 nanogel to the surface of the adoptive T-cell membrane. The lethal dose of IL-2 can be safely released at the tumor site during systemic administration, further effectively stimulated the adoptive T-cell in the tumor environment and enhanced its tumor killing effect. This study provides new insights into the combinational therapy for anti-cancer treatment.

2.1.4. *Immune checkpoint blockade inhibitors*

Immune checkpoints are a couple of molecules from co-suppress signal pathways, which are expressed in healthy tissue to maintain the body's immune balance. However, when cancers occur, cancer cells and immunosuppressive cells upregulate immune checkpoints expression to avoid immune surveillance. Blocking the co-inhibition signal pathway reactivates the anti-cancer immune response[48]. Extensive researches have shown multiple ICB targets, including indoleamine 2,3-dioxygenase (IDO), cytotoxic T lymphocyte-associated molecule-4 (CTLA-4)[49], programmed cell death receptor-1(PD-1) , programmed cell death ligand-1(PD-L1)[50], etc. Blocking the above receptor/ligand-mediated co-inhibition signaling pathways by specific antibodies has achieved good clinical anti-cancer effects[51−53]. However, in clinical applications, compared with the 80% effective rate for lymphoma, the effective rate for solid tumors drop to 10%−30%[54]. The low response rate has become a tough barrier for ICB inhibitors in the treatment of the most cancers, which may be related to the sophisticated immunosuppressive mechanisms in TME. Regarding these issues, development of new tumor co-suppressive molecules (such as Siglec-15)[55], application of two or more ICB inhibitors[56], or combination of ICB inhibitors with CAR-T or other immunotherapies to achieve a supplementary effect, can solve the immune escaping of cancer cells to a certain extent. Besides, the current clinical application of ICB inhibitors by systemic injection caused gastrointestinal toxicity, pulmonary toxicity, autoimmune complications[57], myocarditis[58] and other adverse reactions that cannot be ignored. Therefore, in addition to the combination with other therapies to improve the anti-cancer effect, specific delivery of ICB inhibitors into tumor tissue is an urgent need to be addressed.

By the retrospect of cancer immunotherapy, we found that an important development direction of cancer immunotherapy is specifically targeting tumor immunomodulatory targets to achieve precise delivery of immunotherapy drugs, which can enhance anti-cancer immunity, reduce the distribution of immunotherapy drugs in other tissues to lower adverse reactions in the meantime. Therefore, the development of the targeted delivery platform for cancer immune drugs with high biocompatibility is significant for achieving efficient and safe cancer immunotherapy. With the development of biomimetic nanotechnology, CMCNs with unique advantages have been gradually recognized and widely investigated in cancer immunotherapy.

3. Cell membrane-coated nanoparticles

In 2011, Hu and co-workers[59] prepared erythrocyte membrane-coated nanoparticles by co-extruding erythrocyte membranes and PLGA nanoparticles. This is the first report of cell membrane-coated nanoparticles. Subsequently, researchers explored various cell membrane-coated nanoparticles according to the required functions, and flexibly combined membrane materials from different source cells with different nanoparticle cores. In addition to erythrocyte membranes, various other cell membranes, including leukocytes, platelets, cancer cells, bacteria, mesenchymal stem cell membranes, brightly shined in the functional study of cell membrane coating. At the same time, researchers considered the diverse nanoparticle as an inner part for immunotherapeutic molecules loading and specific release, including biodegradable polyester (such as PLA, PLGA, PCL) nanoparticles, silica nanoparticles, metal nanoparticles (such as gold, Fe_3O_4), nanogels and MOF, etc (Fig. 2).

3.1. *Preparation of CMCNs*

The preparation of CMCNs mainly includes three steps: separation and preparation of cell membrane-derived vesicles (CMVs), synthesis of nanoparticle cores, and fusion of CMVs and nanoparticle cores.

3.1.1. *Separation and preparation of CMVs*

The extraction of cell membranes should be gentle to minimize the denaturation of membrane proteins, which usually includes cell lysis and membranes purification.

Erythrocytes and platelets are two types of non-nucleated cells. In order to obtain bioactive erythrocyte and platelet membranes, the cells are separated from whole blood by a blood separation kit and centrifugation. Then, the collected cells are lysed by hypotonic treatment or repeated freezing and thawing. The soluble proteins are removed to obtain purified membranes by centrifugation. Next, the purified membranes are extruded through polycarbonate porous membranes with nanopores to obtain nanovesicles[60,61]. Bacteria are enveloped by cell membranes and peptidoglycan, which makes the extraction of cell membranes more difficult. Fortunately, gram-negative bacteria can secrete outer membrane vesicles, that can be collected directly from the bacterial culture medium by ultrafiltration[62]. Compared with non-nucleated cells, it is more complicated to extract and purify cell membranes from eukaryotic cells (leukocytes, cancer cells, etc.)[20]. We need to collect the target cells from the culture medium, blood, or tissue. The cells are lysed using a combination of methods, including treatment with hypotonic solution, repeated freezing and thawing, and/or mechanical rupture (such as extrusion, ultrasound). Then, intracellular biological macromolecules, intracellular vesicles and cell nucleus are removed by using discontinuous sucrose gradient centrifugation to purify cell membranes[63].

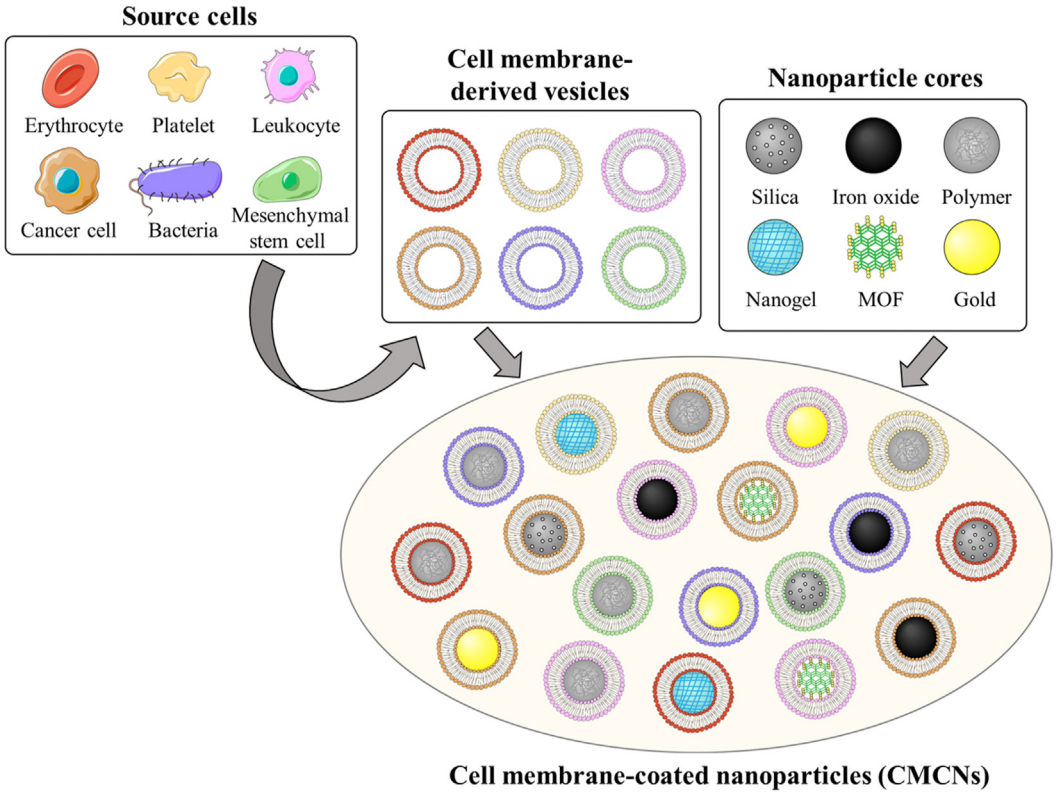

Figure 2 Schematic of sources and types of CMCNs.

3.1.2. Fusion of CMVs and nanoparticle cores

CMVs can be fused to synthetic nanoparticle cores by different methods. Extrusion, ultrasonic method, and microfluidic electroporation are the three main methods currently used.

3.1.2.1. Extrusion. Extrusion is the commonly used method for preparing CMCNs in the literature. The CMVs and nanoparticle cores are extruded through polycarbonate porous membranes with gradually decreasing pore diameters (from 400 nm to 100 nm). Due to the fluidity of the cell membrane, the extrusion generates the mechanical force which causes the NPs to pass through the phospholipid bilayer, resulting in membrane vesicle-nanoparticle fusion. The size of the obtained CMCNs basically depends on the diameter of the polycarbonate porous membranes pores, and the CMCNs are uniformly distributed. This method ensures the biological activity of membrane proteins to the great extent. However, it is a tedious and time-consuming process[64].

3.1.2.2. Ultrasonic method. Ultrasonic method is an effective alternative to the extrusion[65]. Ultrasound can destroy the membrane structure. When the NPs are incubated with cell membrane vesicles, the membranes around the NPs are reassembled due to ultrasonic waves. This method is convenient and time-saving. Nevertheless, we need to optimize parameters of ultrasonic treatment to ensure the efficiency of fusion while reducing protein denaturation, such as power, duration, and frequency. Moreover, the size distribution of the CMCNs obtained by this method may be uneven.

3.1.2.3. Microfluidic electroporation. Electromagnetic energy forms holes in cell membranes by a microfluidic chip. When core nanoparticles are mixed with cell membrane vesicles, these holes help the vesicles to coat the nanoparticles[66]. In the process, we also need to optimize parameters, including flow rate, duration, and pulse voltage. The CMCNs prepared by this method have a complete coating, uniform distribution, and high repeatability. But the cost of this technology is high.

The summary of the three methods is shown in Table 1[59,60,65–82]. The extrusion and ultrasonic method are more commonly used to prepare CMCNs in the laboratory. Microfluidic electroporation may be suitable for large-scale production due to its controllability.

3.2. Unique function and molecular mechanism of CMCNs

CMCNs inherit abundant source cell-relevant functions, including "self" markers, cross-talking with the immune system, biological targeting, and homing to specific regions. Most of these functions are related to cell membrane surface proteins or molecules.

3.2.1. Erythrocyte membranes

In the blood, erythrocytes are the most blood cells (more than 80%), and have a long circulation time (~115 days) to perform the oxygen transport function[83]. Some membrane proteins help erythrocytes to have a long circulation time. Among them, the most important protein is CD47. Specifically, a glycoprotein on the surface of phagocytes, signal-regulatory protein alpha (SIRPα), interacts with CD47 on erythrocytes, which is recognized as a "don't eat me" signal, and inhibiting immune phagocytes phagocytizing erythrocyte. Other membrane proteins on erythrocyte, such as complement receptor 1 (CR1), C8 binding protein (C8bp) and CD59 also play a role in defending against

Table 1 Fusion method of cell membrane vesicles and nanoparticle cores.

Method	Advantage	Disadvantage	Ref.
Extrusion	Protecting the biological activity of cell membranes; uniform size; the widest range of applications	Cumbersome steps; time-consuming; difficult to mass produce	59,67−76
Ultrasonic method	Convenient; time-saving	The size of CMCNs may be uneven; the parameters need to be adjusted	60,65,77−81
Microfluidic electroporation	High fusion efficiency; good reproducibility; uniform size	High cost; the parameters need to be adjusted	66,82

CMCNs, cell membrane-coated nanoparticles.

attack by the complement system. Therefore, these erythrocyte membrane surface proteins can help erythrocyte membrane-coated nanoparticles to have a prolonged systemic circulation time and weak immunogenicity, reduce the elimination of erythrocyte membrane-coated nanoparticles by the MPS, and increase the intratumoral distribution of nanoparticles through the EPR effect[84]. However, erythrocyte membranes are not tumor-targeting. Therefore, many researchers further use targeting peptides to modify erythrocyte membranes or fusion with other cell membranes to achieve tumor targeting[85,86].

3.2.2. *Leukocyte membranes*

Leukocytes can cross biological barriers, and reach target tissues, including macrophages, DCs, NK cells, etc. Tumor is a chronic inflammation tissue, and it secretes many cytokines and chemokines to attract and recruit leukocytes.

3.2.2.1. Macrophage membranes. Some specific receptors and adhesion molecules on macrophage membranes, such as C−C chemokine receptor 2 (CCR2), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) can guide macrophage membrane-coated nanoparticles to inflammatory sites, such as tumors[13,87]. In addition, the α4 and β1 integrins on macrophage membranes can interact with the VCAM-1 on cancer cell membranes, allowing macrophage membrane-coated nanoparticles to target cancer cells and cancer metastasis[88]. Besides, functional molecules such as CD45, CD11a and glycans on the macrophage membrane help to prevent the internalization/uptake of macrophage membrane-coated nanoparticles by phagocytes or venous endothelial cells, which promotes the nanoparticles smoothly gathering to tumors[9].

3.2.2.2. DC membranes. Mature dendritic cell membrane-coated nanoparticles have the antigen-presenting function of the entire DCs. Under this excellent advantage, they can specifically activate T cells because they have broad spectrum of peptide/MHC complexes on their membranes[89]. Moreover, adhesion molecules and costimulatory molecules, including ICAM-3, CD40, CD44, and integrins on DC membranes can mediate cell adhesion and promote the interaction between DCs and T cells[87]. In addition, the DC membrane coated-nanoparticles can also achieve lymph node targeting because of the lymph node homing molecule CCR7 receptor on DC membranes[90].

3.2.2.3. NK cell membranes. NK cells play a role in killing cancer cells and antibacterial by immune monitoring the abnormal expression of stress proteins and MHC-I on the cell surface. Although NK cells lack tumor antigen-specific cell surface receptors, they have many alternative receptors that can recognize cancer cells, including NKG2D, NKp44, NKp46, NKp30, and DNAM-1. For example, NKG2D is a disulfide bond-linked homodimer that can recognize several ligands commonly expressed on cancer cells, such as MHC class I chain-related gene A and UL16-binding protein[87,91]. Therefore, NK CMCNs have good biocompatibility, tumor targeting and tumor homing ability.

3.2.3. *Cancer cell membranes*

Due to a series of proteins on cancer cell membranes, cancer cell membrane-coated nanoparticles (CCMCNs) can have a prolonged systemic circulation, achieve immune escaping, and target homotypic tumors. CD47 molecules on cancer cells are very important for immune escaping, especially for certain breast cancer cell lines, including MCF-7, MDA-231 and 4T1[13]. Thomsen-Friedenreich antigens, Galectin-3, N-cadherin, epithelial cell adhesion molecule (EpCAM), and E-cadherin on cancer cell membranes are very important for targeting tumor, homotypic tumor cells and adhesion[74,92]. At present, the targeting mechanism of CCMCNs for homotypic tumor cells is not particularly clear. As an inflammatory site, tumor attracts CCMCNs due to the above-mentioned proteins on the surface of CCMCNs. Through the Thomsen-Friedenreich antigens-Galectin-3 interactions of CCMCNs and homotypic tumor cells, CCMCNs easily adhere homotypic tumor cells and are better ingested by homotypic tumor cells, which is conducive for drug specific delivery[92−101].

3.2.4. *Platelet membranes*

Platelets overexpress P-selectin which can specifically bind to the up-regulated CD44 receptor on cancer cells. Therefore, platelet membranes have been explored extensively for actively targeting tumors and circulating tumor cells[102]. CD47 molecules on platelet membranes can prevent macrophages uptake the platelet membrane-coated nanoparticles. In addition, other proteins on platelet membranes can inhibit the immune complement system attack, such as CD59 and CD55. These proteins contribute to prolong the circulation of platelet membrane-coated nanoparticles in blood vessels[13].

3.2.5. *Bacteria membranes*

Gram-negative bacteria produce outer membrane vesicles (OMVs) when they normally grow. OMVs are 20−250 nm spherical vesicles. They are composed of a lipid bilayer membrane and contain a variety of parent bacteria-derived components, which include bacteria-specific antigens, virulence factors, adhesin, enzymes and various pathogen-associated molecular patterns (PAMPs), including lipopolysaccharide (LPS), peptidoglycan, RNA, DNA, lipoprotein, etc.[103]. Because of a variety of PAMPs and bacteria-derived antigens, bacteria membranes can be developed as a bacterial vaccine, which produces strong cellular and humoral

Table 2 The unique function and molecular mechanism of CMCNs.

Type of cell membranes	Functional protein or molecule	Function	Ref.
Erythrocyte membranes	CD47, C8bp, CR1, and CD59	Biocompatibility, "self" mark, immune escaping, long circulation	59,84
Macrophage membranes	CCR2, VCAM-1, ICAM-1, CD45, CD11a, glycans, α4 and β1 integrins	Biocompatibility, long circulation, targeting tumors and tumor metastases	9,13,87,88
DC membranes	broad spectrum of peptide/MHC complexes, ICAM-3, CD40, CD44, integrins, and CCR7	Biocompatibility, long circulation, activating T cells, cell adhesion, targeting lymph nodes	87,89,90
NK cell membranes	DNAM-1, NKG2D, NKp44, NKp46, and NKp30	Biocompatibility, long circulation, targeting tumors	87,91
Cancer membranes	CD47, E-cadherin, Thomsen-Friedenreich antigens, galectin-3, N-cadherin, and EpCAM	Biocompatibility, long circulation, cell adhesion, targeting homotypic tumors	13,74,92–94
Platelet membranes	CD47, CD55, CD59, and P-selectin	Biocompatibility, long circulation, targeting tumors and circulating tumor cells	13,102
Bacteria membranes	PAMPs (LPS, lipoprotein, DNA, RNA)	Immune adjuvant	62,103,107
Mesenchymal stem cell membranes	CXCR1, CXCR2, CXCR4, CXCR5, CCR9, TGF-β, E-selectins, and P-selectins	Biocompatibility, long circulation, targeting tumors	105,106

C8bp, C8 binding protein; CCR2, C–C chemokine receptor 2; CR1, complement receptor 1; EpCAM, epithelial cell adhesion molecule; ICAM-1, intercellular adhesion molecule-1; LPS, lipopolysaccharide; PAMPs, pathogen-associated molecular patterns; VCAM-1, vascular cell adhesion molecule-1.

immune responses against its parent bacteria. The various PAMPs allow bacteria membranes to be used as an adjuvant, which can enhance and regulate specific immune responses to antigens expressed on bacteria membranes or mixed with bacteria membranes. Besides, some bacterial strains have tumor-targeting capabilities and can be used for tumor targeting delivery of drug, such as *Salmonella typhimurium*, *Bifidobacterium bifidum*, and *Clostridium beijerinckii*[104].

3.2.6. *Mesenchymal stem cell membranes*

Mesenchymal stem cell (MSC) is a pluripotent stem cell with the potential of self-renewal and multidirectional differentiation. Stem cell therapy has been applied to the routine treatment of many diseases around the world[105]. Similarly, mesenchymal stem cell membrane-coated nanoparticles (MSCMCNs) have also attracted more and more attention. A variety of chemokine receptors (including CXCR1, CXCR2, CXCR4, CXCR5, CCR9, etc.) on the MSC membranes respond to ligand molecules in tumor (including CXCL8 (IL-8), CXCL8 (IL-8), CXCL12 (SDF-1), CXCL13, CCL25), which induces MSCs migrate to the tumor. In addition, TGF-β, E-selectins, P-selectins, etc. on the MSC membranes also affect the tumor tropism of MSCs[105,106]. Due to the natural proteins and molecules, MSCMCNs have good biocompatibility, a prolonged systemic circulation, and tumor targeting ability.

The unique functions and molecular mechanisms of various CMCNs are summarized in Table 2[9,13,59,62,74,84,87–94,102,103,105–107]. Researchers can choose appropriate CMCNs to achieve better treatment effects.

4. Application of CMCNs in cancer immunotherapy

Due to the unique advantages, CMCNs have been used in cancer immunotherapy (Fig. 3). For instance, they can be applied to deliver immunotherapy drug and immunomodulators to tumors, or directly enhance the efficacy of cancer immunotherapy by their own characteristics. Next, we introduce the application of various CMCNs in cancer vaccines, adoptive cellular immunotherapy, regulation of tumor immunosuppressive microenvironment, and combined therapy related to cancer immunotherapy.

4.1. *Cancer vaccines*

Tumor immunosuppressive microenvironment and antigen exhibiting low immunogenicity are the two main obstacles which limit the effectiveness of cancer vaccine. In the tumor immunosuppressive microenvironment, DC cells are disabled and cannot effectively present antigens. The high expression of IDO, PD-L1, etc. makes the downstream T cells unable to be effectively activated[108]. What's more, it is difficult to select effective tumor-specific antigens, and the selected specific antigens may have low expression on tumor cells[108,109], which makes cancer vaccine treatment restricted. In view of these problems, CMCNs can make a difference[110]. For example, cancer cell membrane-coated nanoparticles can achieve personalized treatment through membrane surface antigens[111]. DCs can be activated *in vitro*, and highly express costimulatory molecules and MHC-antigen complexes on the cell membrane surface, which stimulates downstream signaling pathways[112]. In addition, platelet membranes, bacterial membranes and hybrid membranes-coated nanoparticles also play a role in cancer vaccines. Next, we discuss the application of these CMCNs in cancer vaccines.

4.1.1. *Cancer cell membrane-coated nanoparticles*

Clinically, the expression of proteins in different patients is quite different. Therefore, single tumor specific antigen or tumor associated antigen is not suitable for all patients, and the therapeutic effects of cancer vaccines on different patients are different. What's more, due to the complex tumor immune escaping mechanism, cancer vaccines cannot induce an effective long-term immune response[108,113]. To solve these problems, different schemes are put forward, typically using cancer cell lysates. But cancer cell lysates have complex components and many of them are endogenous non-tumor-related antigenic substances, which induce low tumor immune response efficiency and poor therapeutic effect[114]. Conversely, a variety of tumor-associated antigens are presented on the cell membrane surface, which can discard a large amount of useless cell contents and efficiently improve tumor-specific immune responses. Moreover, CCMCNs can also avoid phagocytosis of macrophages and target homotypic

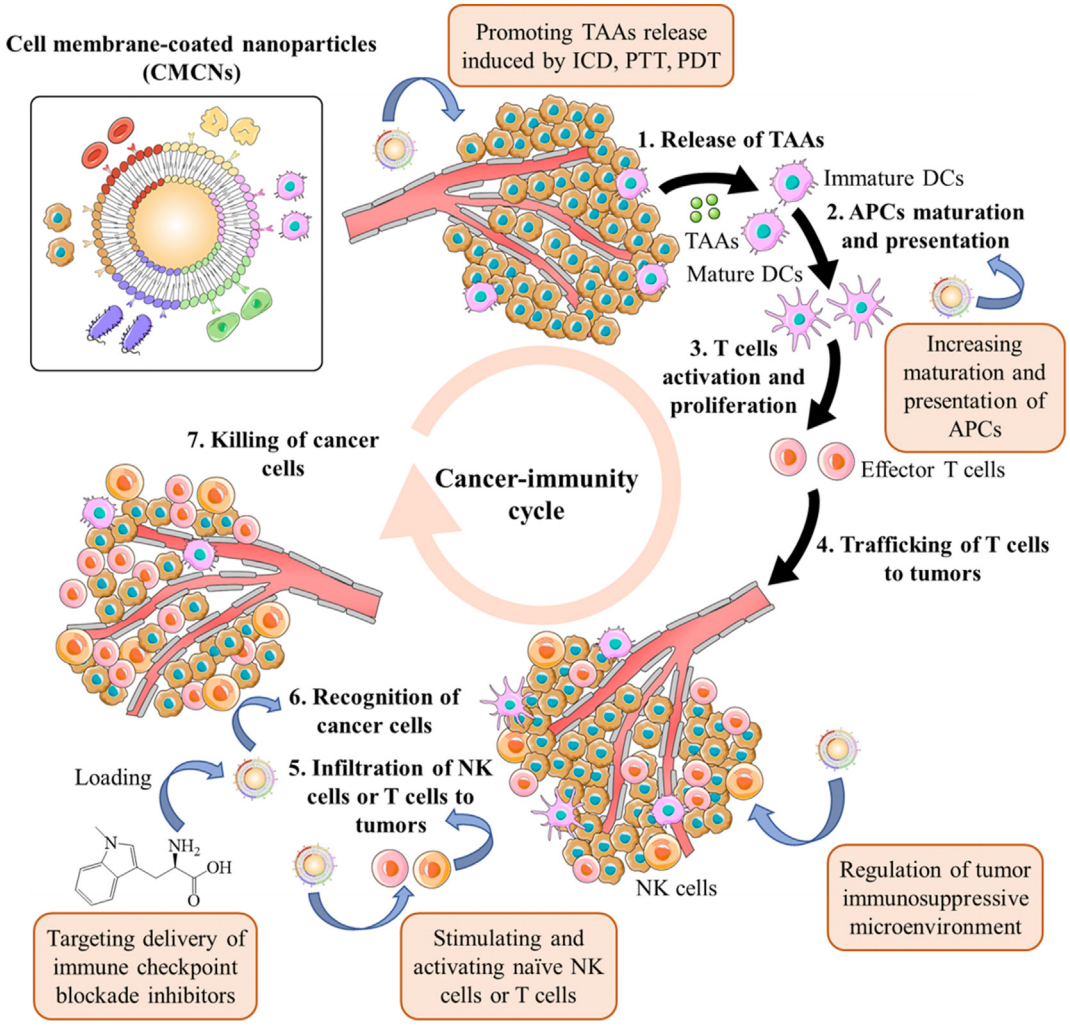

Figure 3 Schematic of CMCNs promoting anti-cancer immunotherapy in the cancer-immunity cycle. Due to a series of proteins and molecules on cell membranes, the CMCNs possess the unique functions. The CMCNs (leukocyte membrane, cancer cell membrane, platelet membrane, mesenchymal stem cell membrane-coated nanoparticles and so on) can target the delivery of immunotherapeutic drugs or immunomodulators (such as immune checkpoint blockade inhibitors) to tumors which can enhance immune response and reduce systemic immune toxicity. The CMCNs can promote the release of TAAs by combining cancer immunotherapy with chemotherapy, PDT or PTT which contribute to the ICD effect of cancer cells. DC membrane, cancer cell membrane, platelet membrane, bacterial membrane and hybrid membrane-coated nanoparticles play a major role in cancer vaccines which promote DCs maturation and TAAs presentation of APCs. In addition, the CMCNs can reverse the tumor immunosuppressive microenvironment into the immune support microenvironment, which enhance the anti-cancer immune response. Besides, the CMCNs can activate T cells and NK cells, which improves T cells and NK cells adoptive therapy. In conclusion, the cell membrane-coated nanoparticles greatly enhance the effects of cancer immunotherapy through sundry mechanisms.

tumor cells by related functional proteins on cancer cell membranes[93,115,116].

Therefore, in a 2014 study by Fang et al.[95], the CCMCNs were constructed using cancer cell membranes and PLGA nanoparticles. Benefiting from the tumor-associated antigens and homologous targeting binding proteins on cancer cell membranes, the CCMCNs can effectively target tumors, and be used as a vaccine to effectively present antigen and improve the maturation of DCs. As reported by Yang et al.[117] in 2018, mannose was used to modify cancer cell membranes for effective DCs uptake. The membranes-coated PLGA nanoparticles loaded toll-like receptor-7 (TLR-7) agonist R837 as adjuvant (NP-R@M-M), and used B16−F10 melanoma cell membrane as antigen. NP-R@M-M promoted the maturation of bone marrow-derived dendritic cells (BMDCs). NP-R@M-M combined with anti-PD-1 antibody has excellent anti-cancer effect *in vivo*. Gan et al.[118] reported that B16F10 tumor cell membranes were coated with CpG-loaded aluminum phosphate nanoparticles (APMC) as a vaccine. Subcutaneous injection of APMC increased the co-uptake of tumor antigens and CpG by DCs, promoted the maturation of DCs, triggered powerful cellular and humoral immunity, and exhibited good effects in tumor prevention and treatment (Fig. 4[118]). Fig. 4B and C shows that the cancer cell membrane-coated nanoparticle group (APMC) had a better promotion of DCs maturation, tumor treatment efficacy, and longer survival time of mice than the cancer cell membrane vesicle group (FM). Compared with cell membrane vesicles, cell membrane-coated nanoparticles can more easily deliver multiple drugs at the same time, and are easier to carry out multi-functional design, thereby having more application and better anti-cancer immunotherapy effects.

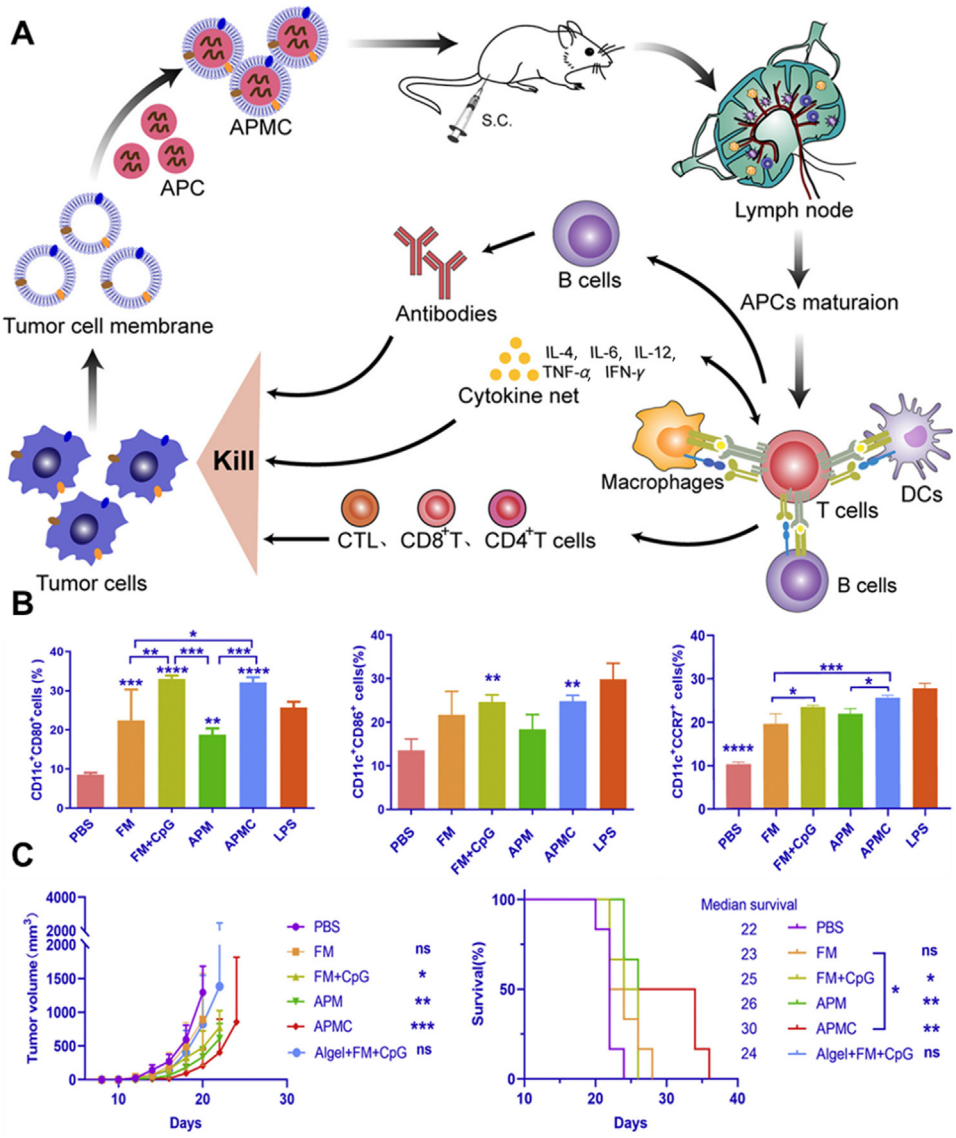

Figure 4 (A) Schematic of APMC activated the anti-cancer immune response as a nano-vaccine; (B) The mature ratio of BMDCs; (C) Anti-cancer efficacy of APMC *in vivo*. *P* values were calculated by Log-rank (Mantel-Cox) test. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, and ns means no significance. Reprinted with the permission from Ref. 118. Copyright © 2020 Elsevier B.V.

Tumor-associated antigens, MHC-I, and CD80 or CD86 co-stimulatory molecules are required to activate tumor-specific T cells. MHC-I and tumor-associated antigens already exist in cancer cells. By gene engineering technology to express costimulatory molecules on the surface of cancer cells, the cancer cells can directly activate T cells without DCs to achieve artificial antigen presentation. Jiang et al.[119], engineered wild-type B16-F10 cancer cells to express co-stimulatory marker CD80, and extracted the engineered cancer cell membrane to prepare cell membrane-coated nanoparticles. Combined with the natural MHC-I and tumor-associated antigens on the membrane, the biomimetic artificial antigen presentation nanoparticles can directly activate T cells and promote tumor antigen-specific immune responses.

4.1.2. DC membrane-coated nanoparticles

As the most important APCs, DCs can activate helper T cells, natural T cells and memory T cells to kill cancer cells. Disabled DCs induce cancer cells to evade immune surveillance[87]. Therefore, improving the effectiveness of cancer vaccines is inseparable from the effective antigen presentation function of DCs[120].

When DCs are activated by TAAs *in vitro*, the surface of mature DCs will express the corresponding MHC/antigen complexes and costimulatory molecules. Using these cell membranes to prepare DC membrane-coated nanoparticles will also retain these proteins and corresponding functional properties. Cheng et al.[89] extracted the cell membranes from DCs which were activated by lysate of ovarian cancer cells. The DC membranes were further coated on PLGA nanoparticles loaded with IL-2. Because of the functional proteins (such as MHC, CD86 and CD40) on these DC membranes, the DC membrane-coated nanoparticles can mimic DC's antigen presentation ability, thereby activating T cells and eliciting effective anti-tumor immune responses. These DC cell membrane-coated nanoparticles can be regarded as a kind of activated mini DCs for artificial antigen presentation. After injecting the DC cell membrane-coated

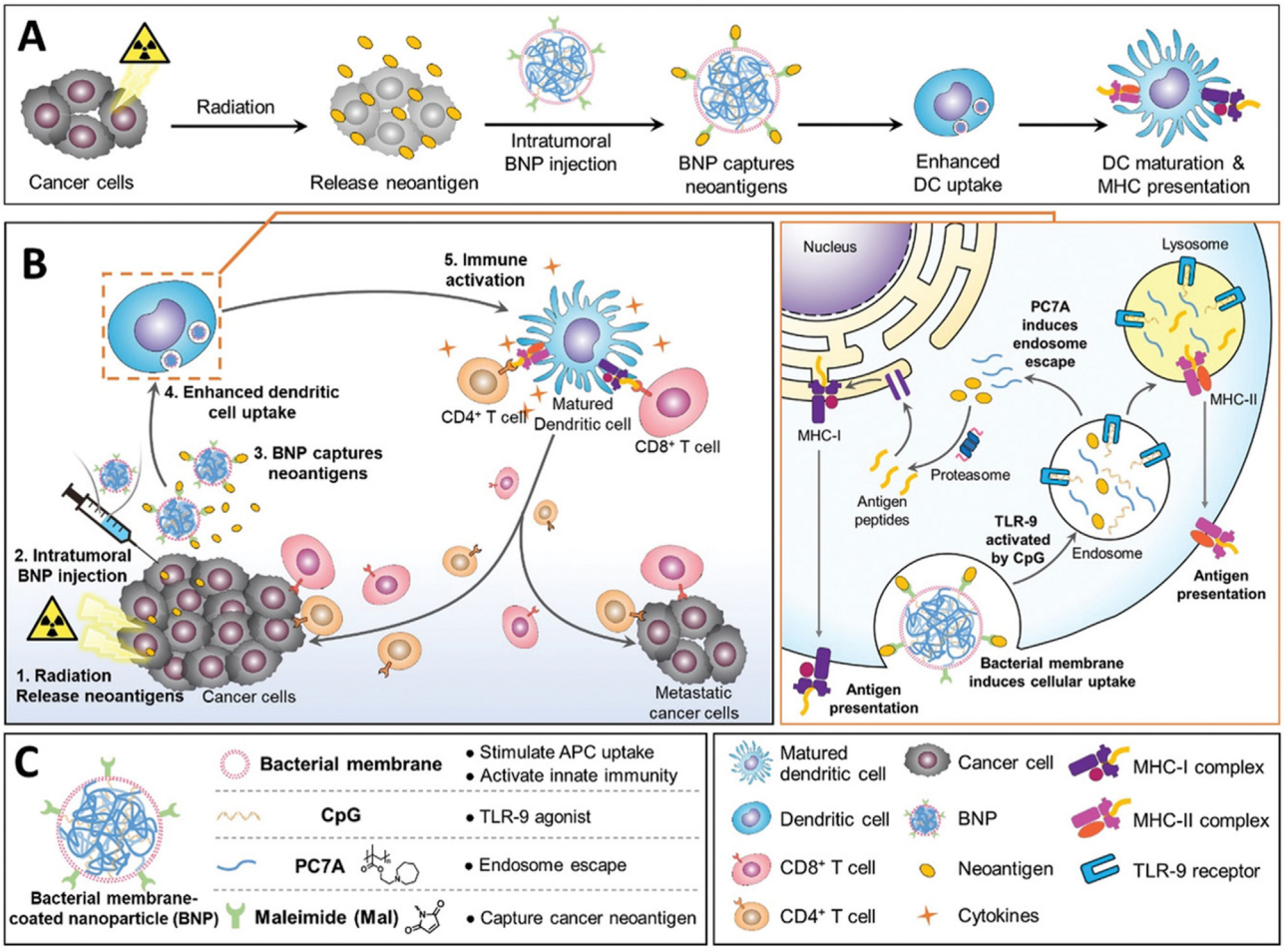

Figure 5 Schematic of the anti-cancer effect induced by RT + BNP. (A) BNP enhancing APCs uptake and activation; (B) The anti-cancer immune response induced by RT + BNP; (C) Composition of the BNP. Reprinted with the permission from Ref. 107. Copyright © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

nanoparticles *in vivo*, T cells can be directly activated without going through the process of activating DCs in the body, which can reduce immune tolerance because of the inability of DCs in the body.

In the study of Yang et al.[121], in addition to having stronger antigen delivery value, DC membrane-coated nanoparticles can target lymph nodes. They prepared DC membranes (DCM)/histidine-modified stearic acid-grafted chitosan (HCtSA)/ovalbumin (OVA) micelles (DCM/HCtSA/OVA micelles) which can target lymph nodes and induce anti-cancer immune responses. The micelles had a pH-dependent antigen release behavior and the ability to effectively escape from DCs lysosomes. In the lymph nodes, the accumulation and retention of the micelles ensured the efficient uptake by DCs and induced an effective T cell immune response.

4.1.3. Platelet membrane-coated nanoparticles

Some proteins on platelet membranes give platelets a variety of properties, such as selective targeting of tumors and selective adhesion to cells in the tumor microenvironment[60]. Bahmani and co-workers[122] prepared platelet membrane-coated nanoparticles (PNP-R848) to locally deliver toll-like receptor agonists resiquimod (R848, as an adjuvant). Platelet membrane coating was conducive to the effective delivery and retention of immunostimulants in tumors, also enhanced the interaction between nanoparticles and tumor microenvironment cells, thereby maximizing the activity of R848. Intratumoral injection of PNP-R848 can greatly enhance local immune activation, lead to complete cancer regression, and result in long-term anti-cancer immunity, so that all surviving mice can resist subsequent re-attack in colorectal cancer models. The effective activity of the preparation was further confirmed, and metastasis was significantly reduced in the triple-negative breast cancer mouse model.

4.1.4. Bacterial membrane-coated nanoparticles

Traditional cancer vaccines are composed of antigens and adjuvants. Adjuvants are important for enhancing the effectiveness of tumor antigens. Bacterial membranes contain various PAMPs[103], which can be used as adjuvants to stimulate immune responses. Researchers have explored the potential use of bacterial membranes in anti-cancer treatment[123]. Patel and co-workers[107] developed bacterial membrane-coated nanoparticles (BNP) as an *in situ* anti-cancer vaccine. In BNP, immune activating PC7A/CpG polyplex cores were coated with imide groups and bacterial membranes. Following radiotherapy (RT), BNP captured cancer neoantigens, enhanced their uptake and cross presentation by DCs

and activated T cells to kill cancer cells (Fig. 5[107]). Treatment with BNP + RT can activate DCs and effector T cells, inhibit tumor growth and generate anti-cancer immune memory in the melanoma and neuroblastoma mouse model.

4.1.5. *Hybrid membrane-coated nanoparticles*

Different cell membrane coating has various functions. Combining the functions of multiple cell membranes into one nanoparticle may maximize the function. Therefore, hybrid membranes have outstanding advantages in cancer vaccine applications.

In the study of Li et al.[124], hybrid membrane-coated nanoparticles were prepared by the fusion of cancer cell membranes and bacterial membranes, as mimic cancer vaccines. Cancer cell membranes contain many different tumor antigens, and bacterial membranes contain a variety of immunostimulatory PAMPs, which are effective adjuvants. The hybrid membrane coating enhanced the nanoparticles uptake by DCs, facilitated cross presentation, and promoted the maturation of DCs. Hybrid membrane-coated nanoparticles induced stronger tumor immunity and were effective in tumor prevention and treatment.

Because cancer cell membranes can provide numerous tumor antigens, and DC membranes can provide costimulatory molecules, Ma et al.[125] used dendritic cell-cancer cell fusion cell membranes to prepare the CMCNs. In addition to the above examples, Liu et al.[126] also developed dendritic cell-cancer cell fusion cell membrane-coated nanoparticles (MOF@FM) as cancer vaccine, which effectively inspired APCs to stimulate T cell activation, and induced an effective anti-cancer immune response *in vivo* (Fig. 6[126]).

4.2. *Adoptive cellular immunotherapy*

Adoptive cellular immunotherapy refers to infusing autologous or allogeneic immune effector cells activated *in vitro* into patients to kill cancer cells. Among them, CAR-T is an emerging therapy. In solid tumors, poor infiltration and off-target effects limit the application of CAR-T. Besides, activating T cells requires the assistance of a variety of cells[127]. Compared with CAR-T, NK cells are more capable of targeting cancer cells by the inhibitory and activated receptors on their membranes, and they kill cancer cells without other stimulation[128]. However, the limitation of NK cell adoptive therapy lies in the activation and expansion after isolation. Using effective methods to activate naïve NK cells is the key to enhance its anti-cancer efficacy. In the study of Wu et al.[129], cancer cell membranes were used to coat Fe_3O_4@SiO_2 nanoparticles (CM-Fe_3O_4@SiO_2, CMNP), and effectively activated naïve NK cells through tumor-specific antigens on the cancer cell membranes, which up-regulated NK cell surface activation receptors, and stimulated the secretion of cytotoxic components (granzyme, perforin, etc.) (Fig. 7[129]). The CCMCNs improved NK cell adoptive therapy.

4.3. *Regulation of tumor immunosuppressive microenvironment*

At present, tumor immunosuppressive microenvironment astricts the efficacy of cancer immunotherapies, including cancer vaccines, ICB inhibitors, and so on[130]. A large proportion of tumor-associated macrophages (TAMs) is a main element for tumor immunosuppressive microenvironment. TAMs can responsively

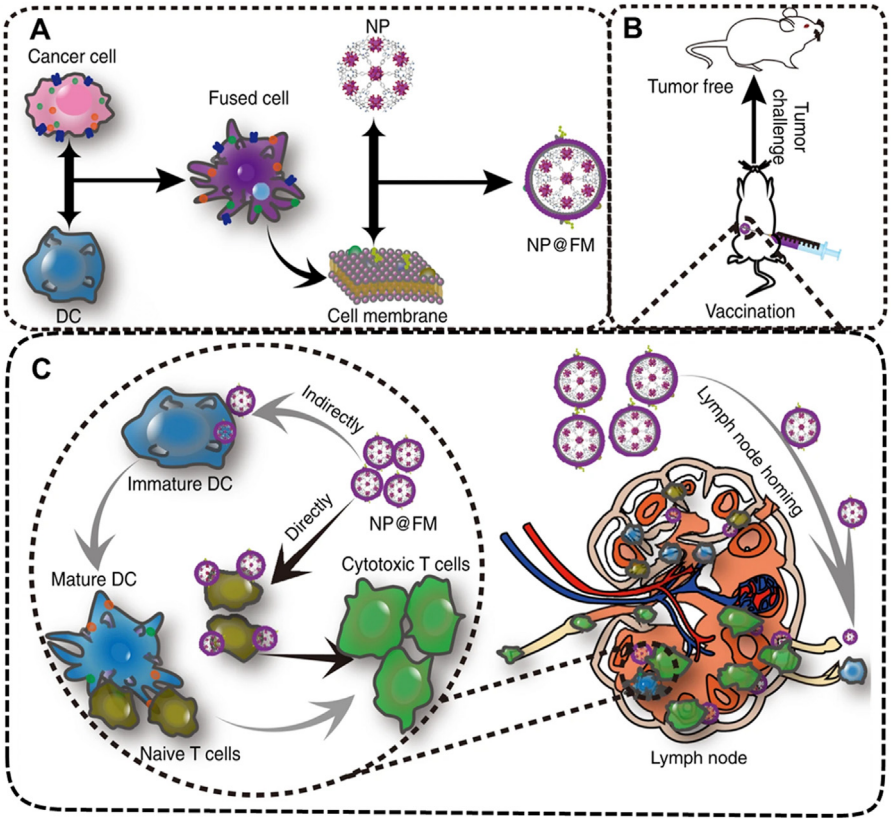

Figure 6 Schematic of MOF@FM used to inhibit tumor growth. (A, B) Preparation of MOF@FM used as cancer vaccines; (C) The mechanism of MOF@FM inducing anti-cancer immune response. Reprinted with the permission from Ref. 126. Copyright © 2019 The Author(s).

polarize into M2 immunosuppressive cells to promote tumor growth, invasion, and metastasis[131,132]. It is worth noting that TAMs have a certain degree of plasticity and can be trans-differentiated into M1 type under the regulation of inflammatory factors[133]. Liu et al.[134] developed macrophage membrane-coated nanoparticles, biomimetic polymer magnetic nanocarriers (PLGA-ION-R837@M (PIR@M)) for selective targeting the tumor microenvironment, and polarizing TAMs. The core of the nanocarrier adopted Fe_3O_4 magnetic nanoparticles to encapsulate the TLR-7 agonist imiquimod (R837), and the outer layer adopted LPS-induced macrophage membrane coating to achieve effective targeting of TAMs. After TAMs ingested the nanoparticles, the nanoparticles can induce TAMs to switch from immunosuppressive M2 subtype to anti-cancer M1 subtype under the synergistic effect of Fe_3O_4 magnetic nanoparticles through iron ion activation of IRF5 signaling pathway and R837 activation of NF-κB signaling pathway. PIR@M nanoparticles can increase the ratio of tumor M1 type from 11.27% to 29.44%. There was a similar effect in the spleen (Fig. 8[134]).

4.4. *Combination therapy*

Cancer is a disease caused by multiple complex factors. The complex tumor microenvironments make it challenging to treat multiple types of cancer by a single therapy[135,136]. It suggests that combination therapy is one of the future trends of cancer therapy. The combination of radiotherapy, chemotherapy, phototherapy (photothermal therapy and photodynamic therapy) or other therapies with immunotherapy (cancer vaccines, immune checkpoint blockade inhibitors, etc.) is the main combination therapy. CMCNs occupy a certain position in the development of combination therapy due to their unique advantages. Next, we mainly introduce the application of erythrocyte membrane, cancer cell membrane, macrophage membrane, NK cell membrane and mesenchymal stem cell membrane-coated nanoparticles in combination therapy related to cancer immunotherapy.

4.4.1. *Erythrocyte membrane-coated nanoparticles*

Erythrocyte membrane-coated nanoparticles have a prolonged circulation and good biocompatibility, so erythrocyte membrane-

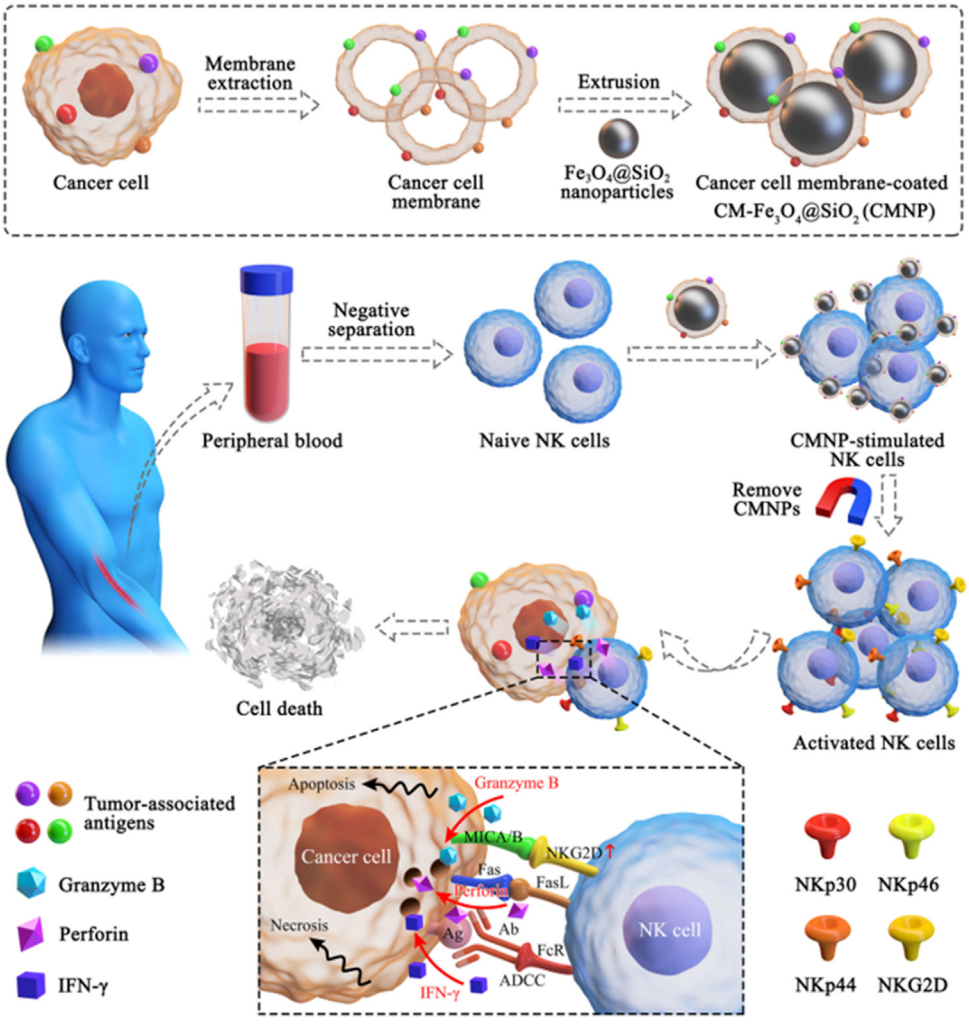

Figure 7 Systematic schematic of the synthesis of CMNP and the mechanism of activating naïve NK cells to enhance anti-cancer killing. Reprinted with the permission from Ref. 129. Copyright © 2020 Elsevier Inc.

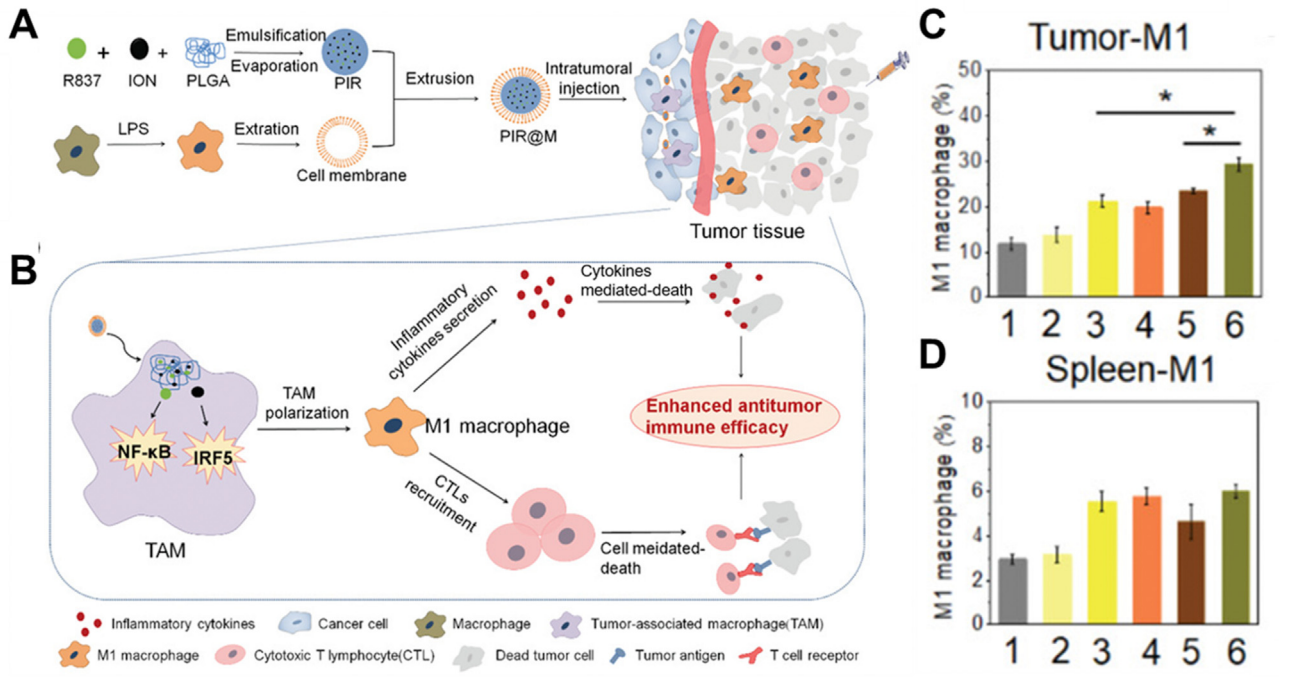

Figure 8 (A) Schematic of preparing M1 macrophage membrane-coated nanoparticles (PIR@M); (B) Intratumor injection of PIR@M NPs stimulated the polarization of TAMs into the M1 subtype by activating the NF-κB signaling pathway and the IPF5 signaling pathway. After polarization into the M1 subtype, the secretion of inflammatory cytokines that induced tumor apoptosis can be increased, and the suppressed cytotoxic T lymphocytes can regain their function. Increasing cytotoxic T lymphocytes infiltration and inflammatory factors at the tumor can enhance the efficacy of cancer immunotherapy; (C, D) The ratio of tumor, spleen M1 type cells, and 1−6 were the saline groups, P@M, PI@M, Vc + PI@M, PR@M, and PIR@M groups. Reprinted with the permission from Ref. 134. Copyright © 2020 Wiley-VCH GmbH.

coated nanoparticles are widely used in cancer immunotherapy. Feng and co-workers[137] used the nitrite reductase activity of hypoxic hemoglobin (Hb) and RRx-001 to enhance the properties of deoxy Hb to catalyze the formation of reactive nitrogen species (RNS) from nitrite. They prepared a hollow TiO_2 nanoparticles filled with deoxyhemoglobin-dependent RRx-001, which were modified with hemoglobin on their surface, and finally coated with erythrocyte membranes into RBC@Hb-TiO_2/RRx-001 (R@HTR). The results showed that erythrocyte membrane coating can effectively avoid macrophage damage during the circulation process. The conditioning effect significantly increased the enrichment of nanoparticles at the tumor. At the hypoxic tumor, hemoglobin released oxygen molecules. After activation by ultrasound, TiO_2 nanoparticles transferred energy to oxygen molecules which generated ROS; meanwhile, hemoglobin gradually deoxidized. The nitrite reductase activity of deoxy Hb was greatly enhanced by the covalent binding of β-Cys93and RRx-001 which increased the level of NO production. In tumor hypoxic microenvironment, ROS and NO were cascaded to produce RNS with stronger cytotoxicity in the cell. Further research found that R@HTR can significantly increase the M1 type transformation of M2 macrophages and the infiltration of mature DCs and CTLs. While reducing the intratumoral infiltration of Tregs and bone marrow-derived suppressor cells, they effectively reversed the tumor immunosuppressive microenvironment, and enhanced tumor killing of the immune system. Finally, they significantly enhanced the cancer suppression effect and effectively prolonged the survival time of tumor-bearing mice.

4.4.2. *Cancer cell membrane-coated nanoparticles*

CCMCNs have unique tumor antigens and tumor homologous targeting, and are always the main choice for their wide application in tumor vaccines and other therapies. Here we mainly introduced CCMCNs for combined photothermal therapy (PTT) and ICB therapy.

ICB is currently a significant leap made in clinical cancer treatment, but its application is limited due to the complex tumor immunosuppressive microenvironment. For example, since only 20% of triple negative breast cancer (TNBC) patients express PD-L1, anti-PD-1/PD-L1 ICB therapy is only suitable for a small number of patients. Therefore, combining multiple immune activation mechanisms is an effective solution for TNBC, and how to reduce systemic immune toxicity is also one of the keys[138]. PTT can induce ICD effects and induce cells to release tumor-associated antigens. Combining these antigens with immune adjuvants can produce cancer vaccine-like effects in the tumor, which displays great potential in inhibiting tumor growth and metastasis by remodeling TME when combining ICB inhibitors[114]. Cheng et al.[139] used cancer cell membranes to coat dendritic mesoporous silicon nanoparticles. The core of mesoporous silicon nanoparticles loaded with immune adjuvant resiquimod (R848) and light-to-heat conversing CuS nanoparticles. Cancer cell membranes were modified with anti-PD-1 polypeptide AUNP-12. The cancer cell membrane-coated nanoparticles (AM@DLMSN@CuS/R848) combined with photothermal therapy, cancer vaccine and ICB therapy can effectively competitively inhibit the binding of PD-1 antibodies and PD-1 on splenic lymphocytes *in vitro*. A positive rate of

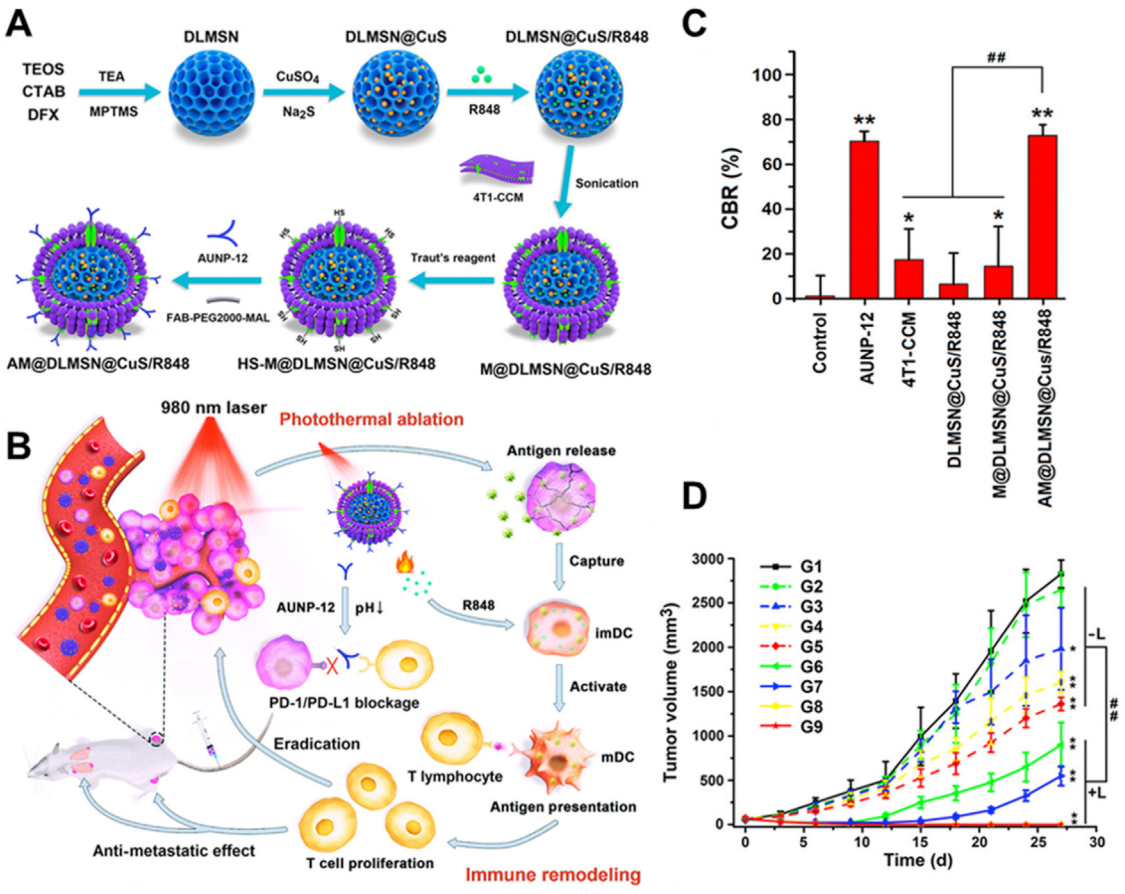

Figure 9 (A) The synthesis and preparation schematic of AM@DLMSN@Cus/R848; (B) The mechanism of AM@DLMSN@Cus/R848 combined with photothermal therapy and immune remodeling to treat TNBC; (C) The competitive binding rate of splenic lymphocytes with anti-PD-1-FITC antibody after incubation with different preparations. $^{*}P < 0.05$ and $^{**}P < 0.01$, compared with the control group; $^{\#\#}P < 0.01$, comparison between two treatment groups; (D) Tumor inhibition curves of primary tumors, and G1-G9 are control, DLMSN@CuS, DLMSN@Cus/R848, M@DLMSN@Cus/R848, AM@ DLMSN@Cus/R848, DLMSN@CuS + L, DLMSN@Cus/R848 + L, M@ DLMSN@Cus/R848 + L, AM@ DLMSN@Cus/R848 + L. Reprinted with the permission from Ref. 139. Copyright © 2020 American Chemical Society.

34.5% was showed in the control group combined with anti-PD-1 -FITC antibody, while adding AM@DLMSN@Cus/R848, the positive rate dropped to 9.79%. The competitive binding rate (CBR) of AM@DLMSN@CuS/R848 was higher than 70%, which showed their wonderful ability to block the PD-1/PD-L1 interaction. Moreover, the CCMCNs had a good anti-cancer effect *in vivo* (Fig. 9[139]).

4.4.3. *Macrophage membrane-coated nanoparticles*

The combination of chemotherapy or/and phototherapy (PTT and photodynamic therapy) with immunotherapy is one of the current effective treatments for cancers. Certain chemotherapeutic drugs such as oxaliplatin and doxorubicin can effectively induce ICD. Phototherapy can locally kill cancer cells and release TAAs. The combined application of chemotherapy or/and phototherapy with immune checkpoint blockade inhibitors can convert cold tumors into hot tumors which effectively enhance tumor immune response. Hu et al.[140], used M1 type macrophage membranes to coat polymer nanoparticles loaded with DOX (chemotherapeutic drug), Ce6 (photosensitizer) and indoximode (I) (IND, IDO-1 inhibitor) ((C/I)BP@B-A(D)&M1m). M1 macrophage coating enhanced tumor targeting and accumulation. The inner stimulus-responsive NPs can enhance the tumor permeability by changing the surface potential, morphology, size, and other physical and chemical properties. They combined chemotherapy, photodynamic therapy (PDT) and immune checkpoint inhibitors to effectively inhibit the growth and metastasis of primary tumors, and prevent tumor recurrence (Fig. 10[140]).

4.4.4. *NK cell membrane-coated nanoparticles*

The complexity and heterogeneity of cancers, the differences between patients, and the systemic immunotoxicity make traditional immunotherapy clinically limited. Therefore, it is always a challenge to develop effective, long-lasting, tumor-specific immunotherapy[71,141]. NK CMCNs can retain functional proteins on NK cell membranes, with good biocompatibility, a prolonged circulation, strong tumor targeting and homing[142,143]. Moreover, NK CMCNs surface proteins can also promote the differentiation of macrophages into M1 subtypes[144]. PDT is widely used for cancer therapy. PDT can generate reactive oxygen species (ROS) through laser radiation. Furthermore, it can induce the ICD effects and stimulate the secretion of damage-related molecular pattern proteins (DAMPs). However, PDT cannot induce an effective and long-lasting immune response[145,146]. Combining NK cell membrane immunotherapy with PDT can effectively enhance the anti-cancer immune effect. Deng et al.[91] prepared NK cell membrane-

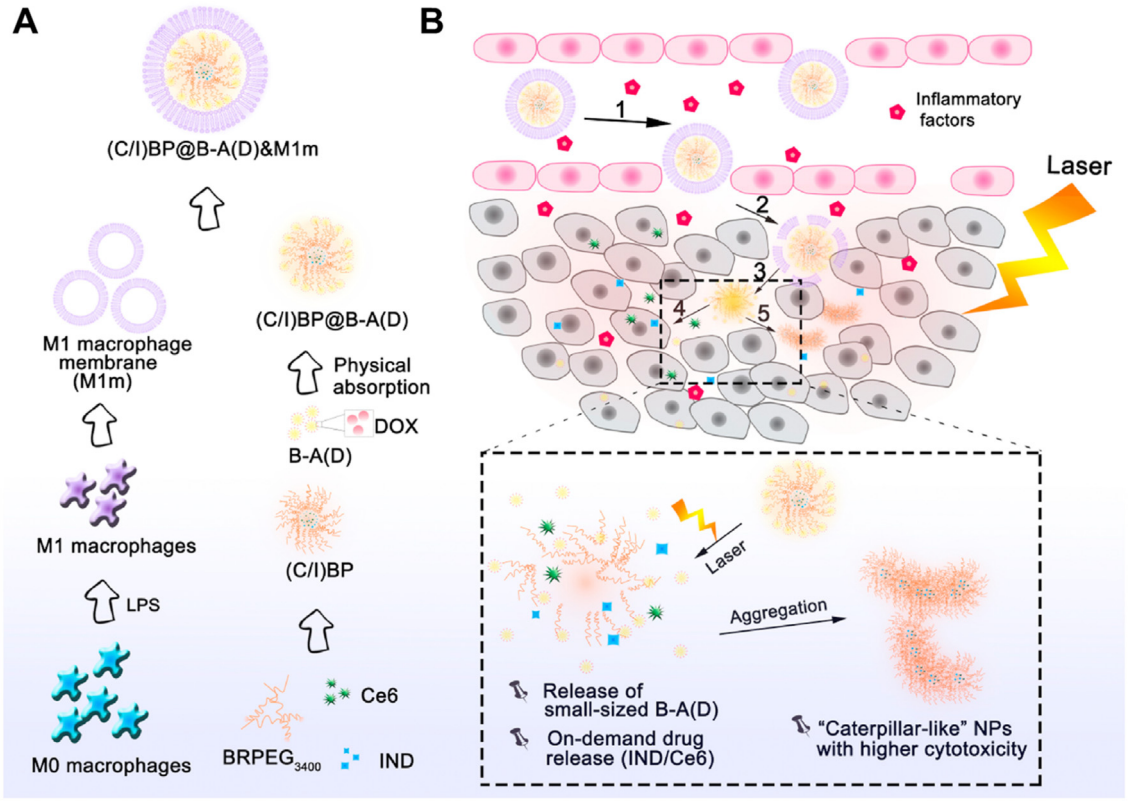

Figure 10 (A) Preparation of (C/I)BP@B-A(D)&M1m; (B) Tumor-targeted combination therapy of (C/I)BP@B-A(D)&M1m. Reprinted with the permission from Ref. 140. Copyright © 2020 Elsevier Ltd.

coated 4,4′,4″,4‴-(porphine-5,10,15,20-tetrayl) tetrakis (benzoic acid) nanoparticles (TCPP). NK cell membrane coating can effectively achieve tumor targeting and induce macrophages to polarize into M1 type. TCPP NPs effectively induced ICD effects through PDT, and the combination can induce effective and long-lasting immune effects.

Du et al.[147]used the hydrophobic oxaliplatin and the small molecule IDO-1 inhibitor, 1-methyl-D-tryptophan (1-MT) to form an amphiphilic prodrug by using a PEG bridge, in which the ICD effect caused by oxaliplatin can further enhance the immunotherapy of the ICB inhibitor. Then it was coated with NK cell membrane which can target cancer cells, and enhance the immune response by inducing M1 type polarization of macrophages. The NK cell membrane-coated nanoparticles effectively realized multiple immune regulation functions, and effectively transformed the "cold" immune microenvironment of breast cancer into the "hot" tumor immune microenvironment.

4.4.5. Mesenchymal stem cell membrane-coated nanoparticles

Due to the chemokine receptors and selectins on MSCs membrane, MSCMCNs have a tropism for tumors and tumor metastases. Therefore, MSCMCNs have also received extensive attention from researchers. Mu et al.[148], applied the MSC membranes in coating DOX and PD-L1 siRNA polydopamine nanoparticles (PDA-DOX/siPD-L1@SCM). DOX can induce ICD in cancer cells, increase the release of tumor antigens, and improve the efficacy of PD-L1 immune checkpoint blocking. These MSCMCNs can have a prolonged circulation, target the tumor, accumulate in the tumor, and have superior anti-tumor effects.

This part is summarized in Table 3[62,79,89,91,95,107,117–119,121,122,124–126,129,134,137,139,140,147–164]. Due to discrepancies in proteins or molecules on different cell membranes, the functions of these membrane-derived cell membrane-coated nanoparticles are also different. Erythrocyte, macrophage, NK cell, cancer cell, platelet, and mesenchymal stem cell membrane-coated nanoparticles exhibit a prolonged circulating. Macrophage, NK cell, cancer cell, platelet, and mesenchymal stem cell membrane-coated nanoparticles have tumor targeting capabilities. Although erythrocyte membranes coating can improve the blood circulation of nanoparticles, the natural erythrocyte membranes lack tumor targeting. A couple of modifications of erythrocyte membranes to obtain the tumor targeting ability, including tumor targeting peptide modification or fusion with other tumor targeting cell membranes have been documented. In addition, because of TAAs on the cancer cell membranes, immunostimulatory molecules on the DC membranes and PAMPs (as adjuvants) on the bacteria membranes, these membrane-coated nanoparticles are often used in tumor vaccines. Macrophages are divided into pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. M1 macrophages can engulf cancer cells, while anti-inflammatory M2 macrophages such as tumor-associated macrophages promote tumor growth and invasion. M2 macrophages express immunosuppressive signal molecules (such as PD-L1) on macrophage membranes, which participate in tumor immune escape. Therefore, M1 macrophage membrane-coated nanoparticles are usually used to improve the efficacy of cancer immunotherapy instead of M2 macrophage membrane-coated nanoparticles. Normally, there are immunosuppressive molecules such as PD-L1 and PD-L2 in natural cancer cell membranes and tumor-associated macrophages

Table 3 Application of CMCNs in cancer immunotherapy.

Cancer immunotherapy	Type of cell membrane-coated nanoparticles	Application	Ref.
Cancer vaccines	Cancer cell membrane-coated nanoparticles	Targeting tumors and accurately delivering drugs, effectively stimulating the maturation of DCs and enhancing anti-cancer immunity.	79,95,117−119
	DC membrane-coated nanoparticles	Providing costimulatory molecules or/and MHC/antigen complexes to effectively activate T cells; targeting lymph nodes to induce stronger anti-cancer immune responses.	89,121
	Platelet membrane-coated nanoparticles	Selectively adhering to cells in TME, enhancing the effective delivery and retention of immunostimulants in tumors, enhancing the interaction of nanoparticles with cells in TME, and maximizing the activity of R848.	122
	Bacterial membrane-coated nanoparticles	As adjuvants, promoting antigen cross-presentation and stimulating anti-cancer immune response.	62,107
	Hybrid membrane-coated nanoparticles	Hybrid membranes of cancer cell membranes and bacterial membranes: the cancer cell membranes provide tumor antigens, and the bacterial membranes act as an adjuvant. This hybrid membrane can induce stronger anti-cancer immunity;	124
		Hybrid membranes of DC membranes and cancer cell membranes: the cancer cell membranes provide tumor antigens, and DC membranes provide costimulatory molecules, which effectively inspires APCs to stimulate T cell immune responses.	125,126
Adoptive cellular immunotherapy	Cancer cell membrane-coated nanoparticles	Tumor-specific antigens on tumor cell membranes effectively stimulated NK cells, up-regulated NK cells surface activation receptors, stimulated the secretion of cytotoxic components, and effectively enhanced the efficacy of NK cell adoptive immunotherapy.	129
Regulation of tumor immunosuppressive microenvironment	Macrophage membrane-coated nanoparticles	Targeting tumors, accurately delivering immunomodulators, and inducing TAMs to polarize from immunosuppressive M2 type into anti-tumor M1 type.	134
Combination therapy	Erythrocyte membrane-coated nanoparticles	RNS therapy was combined with the regulation of the tumor immunosuppressive microenvironment, and erythrocyte membrane coating gave the nanoparticles long-circulation characteristics and better biocompatibility.	137
		The combination of chemotherapy or/and phototherapy (PTT and PDT) with immunotherapy; erythrocyte membrane coating gave the nanoparticles long-circulation characteristics and better biocompatibility.	149−151
	Cancer cell membrane-coated nanoparticles	The combination of chemotherapy or/and phototherapy (PTT and PDT) with immunotherapy; tumor cell membrane coating can provide tumor antigens and make nanoparticles have prolonged blood circulation and tumor targeting ability.	139,152−155
	Macrophage membrane-coated nanoparticles	The combination of chemotherapy or/and phototherapy (PTT and PDT) with immunotherapy; macrophage membrane coating can make nanoparticles have prolonged blood circulation and tumor targeting ability.	140,156−158
	NK cell membrane-coated nanoparticles	The combination of chemotherapy or/and PDT with immunotherapy; NK cell membrane coating can effectively achieve tumor targeting and induce macrophages to polarize into M1 type.	91,147
	Platelet membrane-coated nanoparticles	Ferroptosis induced mild immunogenicity and polarized macrophage into M1 type to improve the efficacy of PD-1 immune checkpoint blocking therapy. Platelet membrane coating can effectively achieve tumor targeting.	159
		Combination of phototherapy with other methods to reshape the tumor immune microenvironment; Platelet membrane coating can improve the tumor targeting ability of nanoparticles.	160,161
	Bacterial membrane-coated nanoparticles	Combination of PTT and ICB inhibitors; Bacterial membrane as an adjuvant.	162

Table 3 (*continued*)

Cancer immunotherapy	Type of cell membrane-coated nanoparticles	Application	Ref.
	Mesenchymal stem cell membrane-coated nanoparticles	Combination of chemotherapy and ICB inhibitors; Mesenchymal stem cell membrane coating can make nanoparticles have a prolonged blood circulation and tumor targeting ability.	148
	Hybrid membrane-coated nanoparticles	The combination of chemotherapy or/and phototherapy (PTT and PDT) with immunotherapy; Hybrid membrane coating can make nanoparticles have a prolonged blood circulation and tumor targeting ability; Hybrid membranes can provide tumor antigens, costimulatory molecules, or PAMPs.	163,164

APCs, antigen presenting cells; DCs, dendritic cells; ICB, immune checkpoint blockade; ICD, immunogenic cell death; IDO, indoleamine 2,3-dioxygenase; NK, natural killer; PAMPs, pathogen-associated molecular patterns; PDT, Photodynamic therapy; PTT, photothermal therapy; PD-1, programmed cell death receptor-1; RNS, reactive nitrogen species; TAMs, tumor-associated macrophages.

to inhibit CTL function and achieve immune escape. At present, the consideration was lacked when these membrane-coated nanoparticles were used in cancer therapy. It may be possible to use gene engineering technology to reduce the expression of the immunosuppressive molecules on the cell membranes. The modified engineered membranes are extracted to prepare cell membrane-coated nanoparticles which can reduce the hidden immunosuppression defects caused by the natural cell membranes and achieve better immunotherapy effects. Therefore, researchers can select appropriate types of cell membrane-coated nanoparticles according to their research purposes to obtain more excellent cancer immunotherapy efficacy.

5. Conclusions and challenges

CMCNs inherit abundant source cell-relevant functions, including "self" markers, cross-talking with the immune system, biological targeting, and homing to specific regions, which endow CMCNs with ideal characteristics, including better biological compatibility, disguising as self-components, weak immunogenicity, escaping the clearance of the immune system, a prolonged circulation, targeting tumor, as well as accumulating and deeply penetrating the tumor. Benefiting from these advantages, the CMCNs can deliver immunotherapeutic drugs or immunomodulators to tumors, regulate the tumor immunosuppressive microenvironment to the immune support microenvironment, induce ICD, promote the release of TAAs, promote DCs maturation and tumor antigen presentation, and activate NK cells and T cells, etc., which significantly enhance the effect of cancer immunotherapy.

In recent years, biomimetic carriers such as cell membrane vesicles and exosomes have also been continuously used. Compared with CMCNs, cell membrane vesicles and exosomes have similar functions in biocompatibility and targeting. However, these biomimetic carriers have some shortcomings. They are difficult to deliver hydrophobic drugs, co-deliver drugs with different properties, and achieve specific controlled release. In addition, the cell membrane yield is much higher than exosomes[99]. CMCNs not only have the natural and various characteristics of the source cells, but also have the efficient drug delivery and specific drug release function of nanoparticle cores, making it easier to carry out multi-functional design and meet more functional requirements. But it's worth noting that the more complicated design may make CMCNs more difficult to achieve the clinical translation.

Although the advantage of cell membrane coating nanotechnology has promoted the continuous development of cancer immunotherapy, the clinical translation of CMCNs still faces many challenges. Firstly, the problem of large-scale production needs to be solved. Large-scale production is one of the main obstacles to the clinical transformation of nanomedicine. In order to enable nanomedicine to be produced at an industrial level, a simple and reliable method is required. Currently, the extrusion method commonly used in the laboratory has low production efficiency which is difficult to scale up in industrial manufacture. In addition, the methods and technologies used in industrial production need good reproducibility, and the preparation processes of different cell membrane-coated nanoparticles require certain stable technical parameters.

Secondly, the extraction steps of the entire cell membrane mainly include cell lysis, removal of cell contents, and cell membranes purification. Current researches used differential centrifugation methods to remove cytoplasmic components, which may not remove all cytoplasmic components completely, and may also result in the loss of membrane fragments. Some residues of cytoplasmic components will cause the immune system to recognize them as foreign bodies, and trigger an immune response against endogenous antigens leading safety risks. In addition, the process of extrusion and fusion may also result in the loss of film fragments. The loss of membrane fragments is uncertain and may affect its effectiveness. Moreover, since the functional proteins on the cell membrane are easily inactivated, the cell membrane needs to be carefully extracted. How to extract complete and high-purity cell membrane components to ensure the effectiveness, safety, and biocompatibility of CMCNs is worth continuing to study.

In addition, the preparation of CMCNs requires nanoparticle cores. The preparation of nanoparticle cores should be qualified to apply in clinically translate easily. In order to prepare safe and highly reproducible nanoparticles, materials (such as PLGA) approved by the FDA having less toxicity in the body are required.

Besides, cancer heterogeneity is a common challenge faced by current cancer therapies. Improving the efficacy of personalized treatment of CMCNs may be an effective mean to address this issue. As the clinical translation of CMCNs currently lacks clear regulations, policies, and safety evaluation guidelines, the clinical translation of CMCNs is inseparable from the multi-party cooperation of research institutions, medical institutions, enterprises, and regulatory agencies.

Although CMCNs still face many challenges to achieve clinical translation, it is undeniable that CMCNs have natural advantages and enormous potency for cancer immunotherapy.

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Author contributions

Fuqiang Hu conceived and revised the review. Yingping Zeng completed the research and sorting of related literatures, the production and modification of related figures, and the writing and revision of the manuscript; Sufen Li and Shufen Zhang completed the research and sorting of related literatures and the modification of the manuscript; Li Wang made some sketches of the figures; Hong Yuan revised the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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