Cell membrane-coated nanoparticles: a novel multifunctional biomimetic drug delivery system

Hui Liu1 · Yu-Yan Su1 · Xin-Chi Jiang1,2 · Jian-Qing Gao1,2,3

Abstract

Recently, nanoparticle-based drug delivery systems have been widely used for the treatment, prevention, and detection of diseases. Improving the targeted delivery ability of nanoparticles has emerged as a critical issue that must be addressed as soon as possible. The bionic cell membrane coating technology has become a novel concept for the design of nanoparticles. The diverse biological roles of cell membrane surface proteins endow nanoparticles with several functions, such as immune escape, long circulation time, and targeted delivery; therefore, these proteins are being extensively studied in the fields of drug delivery, detoxification, and cancer treatment. Furthermore, hybrid cell membrane-coated nanoparticles enhance the beneficial effects of monotypic cell membranes, resulting in multifunctional and efficient delivery carriers. This review focuses on the synthesis, development, and application of the cell membrane coating technology and discusses the function and mechanism of monotypic/hybrid cell membrane-modified nanoparticles in detail. Moreover, it summarizes the applications of cell membranes from different sources and discusses the challenges that may be faced during the clinical application of bionic carriers, including their production, mechanism, and quality control. We hope this review will attract more scholars toward bionic cell membrane carriers and provide certain ideas and directions for solving the existing problems.

Keywords Nanoparticle · Drug delivery systems · Cell membrane · Applications · Challenges and prospects

Abbreviations

| Acronym | Full Form |
|---------|-----------|
| DDSs    | Drug delivery systems |
| NP      | Nanoparticle |
| EPR     | Enhanced permeability and retention |
| RES     | Reticuloendothelial system |
| ABC     | Accelerated blood clearance phenomenon |
| PEG     | Polyethylene glycol |
| GRAS    | Generally recognized as safe |
| FDA     | Food and Drug Administration |
| CMC-NPs | Cell membrane-coated nanoparticles |
| RBC     | Red blood cell |
| HCMNs   | Hybrid cell membrane-coated nanoparticles |
| PLGA    | Poly(lactic-co-glycolic acid) |
| PTT     | Photothermal therapy |
| SPIO    | Superparamagnetic iron oxide |
| PDT     | Photodynamic therapy |
| MRI     | Magnetic resonance imaging |
| RBC-MNs | RBC membrane-capped magnetic nanoparticles |
| NPID    | Noninvasive pregnant diagnostics |
| WB      | Western blot |
| SDS-PAGE| Sodium dodecyl sulfate polyacrylamide gel electrophoresis |
| TEM     | Transmission electron microscopy |
| FRET    | Förster resonance energy transfer |
| CD47    | A cluster of differentiated 47 |
| SIRPα   | Signal-regulatory protein alpha |
| DAF     | Decay-accelerating factor |
| CR1     | Complement receptor 1 |
| DOX     | Doxorubicin |

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SGNPs  Supramolecular gelatin nanoparticles  
Ru–SeNPs  Ru complex-modified selenium nanoparticles  
PMNPs  Platelet membrane-coated nanoparticles  
ICG  Indocyanine green  
CCNPs  Cancer cell membrane-coated nanoparticles  
CCAMs  Cancer cell adhesion molecules  
TF-Ag  Thomsen–Friedenreich glycoantigen  
Ig-SF  Immunoglobulin superfamily  
MNPs  Macrophage membrane-coated nanoparticles  
LPS  Lipopolysaccharide  
PRR  Pattern recognition receptor  
ICB  Immune checkpoint blockade  
EpCAM  Epithelial cell adhesion molecule  
PFTs  Pore-forming toxins  
LCM  Leukocyte–cancer cell HCMN  
CTCs  Circulating tumor cells  
DLS  Dynamic light scattering  
GMP  Good manufacturing practice

Introduction

Nanotechnology is defined as a branch of science, engineering, and technology that involves molecules at the nanoscale (1–100 nm). To date, nanotechnology has contributed to several scientific fields, such as chemistry, physics, biology, and medicine. In particular, in biomedicine [1], many novel and promising nanoparticle (NP)-based drug delivery systems (DDSs) have been used for the safe and efficient transport of drugs or therapeutic genes in vivo [2]. Controlled distribution and drug release of NPs due to their nanoscale properties could improve bioavailability in vivo [2]. For example, because of their enhanced permeability and retention (EPR) effect [3–6], NPs can highly accumulate in tumor tissues. Even if NP delivery systems can achieve passive targeting, problems such as interaction with the reticuloendothelial system (RES), formation of a protein crown, accelerated blood clearance (ABC), and poor targeting ability toward specific cells remain unresolved [7–11]. Polyethylene glycol (PEG), designated as generally recognized as safe (GRAS) by the Food and Drug Administration (FDA), is widely used for the surface modification of NPs in order to extend their blood circulation time and enhance their targeting capabilities [12]. The PEG chains form a flexible polymer brush layer and create steric hindrance, which can cover up the NP surface charge [13, 14]. This significantly inhibits the adsorption of serum proteins, thereby reducing the recognition of macrophages and minimizing complement activation [15]. However, recent clinical research has indicated the existence of anti-PEG immunity, suggesting that PEGylation can also lead to the ABC phenomenon [16–19]. Therefore, more modification strategies for NPs should be considered.

Fig. 1 Timeline of CMC-NPs development
The membrane coating technology provides a novel solution to the aforementioned problems. The timeline of CMC-NPs development is presented in Fig. 1. In 2011, Zhang et al. developed a top–down biomimetic approach in which they utilized natural erythrocyte membranes to coat polymeric NPs in order to reduce macrophage uptake and systemic clearance for the first time [20]. Later, Tasciotti et al. expanded the selection of membranes from non-nucleated cells to nucleated cells and used leukocytes as the raw material for membrane coating. In 2015, Zhang L et al. enriched the source of membrane material, shifting the focus from human cells to bacterial cells. They again explored the cell membrane biomimetic field and identified mitochondria as a membrane source in 2021. In the past decade, various cell membranes were utilized to design biomimetic systems; these include red blood cells (RBCs) [20], platelets [21], cancer cells [22], and macrophages [23]. Some CMC-NPs are already being considered for clinical application.

To further integrate multiple functions, the hybrid cell membrane-coated nanoparticle (HCMN) strategy has been designed [24–26]. This strategy was first proposed by Zhang et al. in 2017. The RBC–platelet HCMN DDS preserves proteins from RBCs and platelets, combining their unique functions. Subsequently, increasing numbers of differentiated cells are combined to modify NPs, e.g., cancer cells–RBCs [27], macrophages–cancer cells [28], and bacterial vesicles–cancer cells [29]. Double cell membrane NPs are the most common particles in HCMNs. Few studies have used a mixture of three or more membrane

![Fig. 2 A schematic diagram of preparing monotypic cell membrane-coated nanoparticles. Step 1 includes two processes of harvesting cell membrane fragments; step 2 requires cautious selection and fabrication of the inner core according to the purpose; step 3 is the final step to coat the cell membrane onto a template. Created with BioRender.com](image)

| Methods          | Advantages | Disadvantages                                           | Examples   | Ref      |
|------------------|------------|---------------------------------------------------------|------------|---------|
| Hypotonic lysis  | Simple     | Low cell fragmentation efficiency                       | Erythrocyte| [20, 32, 33] |
| Freeze–thaw      | Simple     | Partly affect protein activity, influence the recovery of active protein | Platelet   | [34, 35]  |
| Ultrasonic       | Efficient  | Generate a lot of heat, hard to be used in factory-scale | NK-92, cancer cell | [43, 44]  |
| Homogenizer      | Efficient and broad scope of application, suitable for large-scale industry | Large energy consumption, require an enormous maintenance workload, not suitable for high viscosity samples as well | Neutrophil, cancer cell, mitochondria | [22, 40–42] |
types because the preparation and inspection processes are complex and expensive. Hence, it can be difficult for membrane proteins to function effectively [26, 30].

This review introduces various types of monotypic CMC-NPs and HCMNs with double cell membranes and discusses their manufacturing techniques, benefits, and therapeutic uses. Moreover, it covers the difficulties in clinical application and the advantages of membrane-coated biomimetic NPs.

Methods for preparing cell membrane-coated NPs

Monotypic cell membrane-coated NP preparation methods

The preparation of CMC-NPs usually involves three steps (Fig. 2), namely cell membrane extraction (step 1), NP inner core fabrication (step 2), and cell membrane coating (step 3).

Cell membrane extraction

The first step involves cell membrane isolation and membrane purification, both of which need to be performed gently to preserve the structure and composition of the membrane [31]. Pure and intact cell membranes facilitate maximal functional replication on the inner core surface and result in minimal adverse reactions. Methods widely used for membrane isolation are listed in Table 1; these include hypotonic lysis, freeze-thawing, use of ultrasonic waves, and homogenization.

The principle of hypotonic lysis is that cells can become swollen and rupture under low osmotic pressure. Hypotonic lysis is widely used in erythrocyte membrane extraction but is not commonly used in the extraction of other cells because of its low efficiency [20, 32, 33].

In freeze-thawing, cells are frozen at low temperatures and repeatedly thawed at room temperature. This is a relatively simple method commonly used during platelet membrane extraction [34, 35]. However, freezing and thawing can partially affect protein activity.

Ultrasonic waves cause cell breakage as a result of vast shock waves and shear forces. This method is efficient and suitable for crushing most microorganisms but generates large amounts of heat. Hence, the sensitivity of membrane proteins to heat should be considered when choosing this method. Corresponding cooling measures also should be taken. This may restrict the use of ultrasonic waves in large-scale apparatuses [36].

Homogenization can shear cells into smaller pieces and disperse them. Depending on the pressure setting, a homogenizer may function at pressures up to 2000 bar and can accept a variety of sample volumes (0.05–50 L/h) [37, 38]. In a study conducted by Van Hee et al., cell rupture results remained consistent for different biomass concentrations from 0.06 to 115 g/L in high-pressure homogenizers, indicating potential application in large-scale industries [39]. Previous research has revealed that homogenization is suitable for the fragmentation of various cell types, including neutrophils, cancer cells, and even mitochondria [22, 40–42]. A recent report also revealed that homogenization separates mitochondria from the mouse liver and membrane from mitochondria, indicating that it is a practical method for intracellular organelles [42]. However, the use of a homogenizer is energy intensive and causes a heavy maintenance workload. In addition, it is poorly suited for samples with high viscosity.

The combined use of these methods can yield satisfactory results. For example, B16-F10 mouse melanoma cells were first treated by hypotonic lysis and later treated using a Dounce homogenizer. Consequently, the cancer antigens were preserved and the NPs were successfully functionalized [22].

The next stage involves the purification of cell membranes. Several methods have been developed, including differential ultracentrifugation, density gradient centrifugation, and ultrafiltration [24, 45, 46].

Differential ultracentrifugation adopts a gradual increase in centrifugal speed, which is suitable for cell lysates with significantly different sedimentation coefficients. Density gradient centrifugation requires the formation of a continuous or discontinuous density gradient in the centrifuge tube. The cell suspension or homogenate at the top of the medium can be stratified and separated by gravity or centrifugal force fields. This method is suitable for separating materials with different densities [47]. By contrast, ultrafiltration requires no phase change, no heat release, low energy consumption, and no chemical reagents. It is an energy-saving and eco-friendly separation technology; however, it is greatly limited by sample volume [48].

In summary, cell characteristics determine the method of membrane extraction. For non-nuclear cells, simpler extraction methods, such as hypotonic lysis and freeze-thawing, can be used. For nuclear cells, other methods, such as the use of ultrasonic waves and homogenization, are more suitable [24, 49]. In industrial-scale production, homogenization combined with centrifugation is extensively used [37, 38, 49].

Principal types of NP templates

Different inner cores endow CMC-NPs with different properties. There are two main types of inner cores: organic and inorganic. Core selection according to the subsequent application is necessary.

Organic inner cores have better biocompatibility and biodegradability [50, 51]. The US FDA has approved the clinical application of gelatin, liposome, and poly(lactic-co-glycolic
Among all inner cores, PLGA is the most commonly used in the preparation of membrane biomimetic carriers and holds great promise for clinical applications [52]. Various membranes, including platelet membranes [21, 53], cancer cell membranes [22, 54], macrophage membranes [55], and stem cell membranes [56], can be modified on PLGA particles to prevent the formation of agglomerates on NPs and achieve better delivery efficiency. Another widely used inorganic inner core is a liposome, which resembles the cell membrane [57, 58]. Liposomes are biodegradable colloids capable of containing hydrophobic or hydrophilic pharmaceuticals [59, 60]. Moreover, they can penetrate in vivo barriers as they are flexible [60]. Cell membrane coating improves the stability of phospholipid membranes and achieves a longer circulation time without affecting the drug loading capacity [61, 62].

The stability of inorganic NPs and their resistance to enzymatic degradation are unmatched [63]. Moreover, by manipulating the form, size, composition, and surface qualities of inorganic NPs, their inherent electrical, optical, and magnetic capabilities can be enhanced to achieve full therapeutic potential [63]. For example, an innovative class of nanophotothermal transduction agents, Fe₃O₄ NPs, can be designed for use in photothermal therapy (PTT) [28]. Macrophage membrane-coated Fe₃O₄ NPs can specifically target cancer cells and selectively kill cells by increasing the ambient temperature when exposed to laser light [64]. Another example is the use of stem cell membrane-camouflaged superparamagnetic iron oxide (SPIO) NPs for thermomagnetic therapy. SPIO NPs can rapidly change their magnetic moments and thus generate heat under a high-frequency alternating magnetic field for hyperthermia therapy applications [65]. When using inorganic nanocarriers, toxicity and biodistribution continue to be key concerns. Changing the particle size is one solution [66]. For instance, micron-sized CuO could result in safe delivery; however, CuO NPs could cause DNA damage [66–68]. In the case of SiO₂, an increase in particle size (from 30–40 to 100–150 nm) could significantly reduce cytotoxicity [69]. In addition, cell membrane coating is a persuasive strategy. By blending with the cell membrane, NPs achieve higher biocompatibility and avoid direct contact with the internal environment, indicating a high potential for use in safe and effective therapy [8].

In conclusion, different inner cores have different characteristics and perform multiple functions. Organic inner cores are safer carriers with strong loading capacity, while inorganic inner cores have more unique functions in photodynamic therapy (PDT), PTT, fluorescence imaging, and magnetic resonance imaging (MRI), among others.

**Construction of cell membrane-coated NPs**

Several methods are commonly used to coat the cell membrane onto the inner core; these include physical extrusion, sonication, and microfluidic electroporation. When selecting the coating method, membrane coverage, right-side-out ratio, uniformity, size dispersity, and protein loss are important factors that need to be considered.

Extrusion refers to the production of uniformly sized particles without sacrificing the membranes by pushing the material through nanoporous membranes; it is also known as nonsacrificing template synthesis [70]. The obtained cell membrane fragments can form uniform cell membrane-derived vesicles by extrusion (Fig. 3a). These vesicles are re-extruded with solid NPs (inner core) in the nanopore channel, thereby fusing to form core–shell CMC-NPs [71]. The efficiency of cell membrane coating by extrusion can be determined based on two factors: membrane-to-polymer ratio and surface charge of the inner core. These factors influence the membrane coverage of NPs and the right-side-out ratio [72]. Compared with conventional methods, extrusion results in better uniformity and smaller size dispersity [73]. In addition, extrusion significantly improves the membrane sidedness with a “right-side-out” orientation ratio of over 80% [71]. In 2011, erythrocyte membrane-camouflaged polymeric NPs,

![Fig. 3](image_url)  
Fig. 3  
Fig. 3  
(a) Schematic illustration of the vesicle extrusion process for liposome preparation. Reproduced with permission [70]. Copyright 2005, Small.  
(b) Schematic illustration of the camouflage of cell membrane to nanoparticles by sonication.  
(c) Microfluidic electroporation facilitates the synthesis of RBC membrane-capped magnetic nanoparticles (RBC-MNs). Reproduced with permission [78]. Copyright 2017, ACS Nano.
the first membrane-coated NPs, were constructed through extrusion [20]. Since then, extrusion has been one of the most commonly used methods as it is straightforward and can be flexibly applied to coat NPs of different sizes, ranging from 65 to 340 nm [42]. The primary drawback of using this method for mass manufacture is the substantial sample waste resulting from the buildup of material on the porous membrane [24].

The sonication method generates a dispersed cell membrane layer via sonic energy. The cell membrane and template are brought back together to produce a membrane-coated NP through noncovalent interactions (Fig. 3b). This technique has been used for constructing CMC-NPs by several groups. For example, RBC membrane-coated NPs (RBCNPs) were constructed by sonication. Anti-RBC polyclonal IgG was successfully bound and neutralized by these NPs, indicating that the function of membrane protein was not affected by ultrasound waves [74]. In recent research, sonication was used to coat the mitochondrial membrane. Subsequent experiments revealed that mitochondrial membrane-coated NPs exhibited a competitive right-side-out ratio [42]. Unlike extrusion, sonication prevents material loss during the coating process and yields the possibility of a high degree of dispersion [63]. However, this method may cause uniformity and an uneven size [75, 76]. Moreover, limitations on the soft inner core will be imposed because the cavitation caused by ultrasound exposure will shrink and modify the surface of nanomaterials [77].

Microfluidic electroporation successfully enhances the entrance of the inner core into membrane vesicles by generating temporary hydrophilic holes through the cell membrane using quick high-voltage electric field pulses (Fig. 3c) [78]. The feasibility of CMC-NP manufacture using microfluidics was proven in 2017. Rao et al. coated RBC membrane-derived vesicles onto Fe3O4 magnetic NPs and constructed RBC-MNs through an S-shaped channel microfluidic chip [78]. The RBC-MNs showed improved colloidal stability, uniform size, and high efficacy in vivo. The benefits of this approach are its high throughput and quantitative format. This method may be used at the industry scale because of its scalability and storage capacity [24, 79]. However, problems such as the lack of specifications and standards for core technologies need to be addressed if industrial production is to be further advanced. To achieve high production efficiency, it is necessary to specify different standards of chip pipes,
applied voltages, and flow rate ratios for different cell membranes and NPs by reasonable investigation of the product’s physical and chemical properties (such as size, PDI, and surface charge) [80]. Moreover, the microfluidic electroporation chip must be manufactured in accordance with good manufacturing practice (GMP) standards while retaining batch-to-batch repeatability to get approved by the FDA [81].

HCMN preparation methods

Membranes from different cells can be fused to prepare HCMN before covering the NPs (Fig. 4a). Fusing two source cells by centrifugation or electrofusion is another method of obtaining hybrid membrane-derived vesicles (Fig. 4b) [26, 82, 83].

These two methods exhibit slight differences in terms of the stability of HCMNs, degree of membrane fusion, and expression of characteristic proteins. The second method may result in uncontrollable protein expression on the fused cells [26, 84]. More importantly, its preparation process is far more complex. Generating sufficient self-recognition markers on dendritic cells and 4T1 cells requires at least 6 days for fusion [84, 85]. Therefore, the first approach is more widely used to prepare a hybrid membrane [28, 52, 86].

Both ultrasound waves and extrusion can be used to mix already extracted membranes. Monodispersed uniform-sized membrane vesicles can be successfully prepared after sonication or extrusion through a polycarbonate membrane [25, 26]. Furthermore, numerous experiments have indicated that this fusion approach is applicable to both nucleated and nucleus-free cells (e.g., bacterial vesicle–cancer cell hybrid membranes [29] and macrophage–cancer cell hybrid membranes [87]). Most existing studies on HCMNs have utilized different membrane proportions and ultrasonic parameters to optimize the process ratio for hybrid membrane preparation, and most experimental results have indicated that 1:1 (w/w) is the preferable ratio to obtain the desired fusion effect.

Sonication, extrusion, PEG modification, and electrofusion are widely used for hybrid cell membrane synthesis [88]. These methods are quite different from those used to obtain monotypic membranes. In this section, the unique steps of preparing hybrid membrane-derived vesicles are described (Table 2).

Morphology, thickness, and biomarker characterization are key attributes for determining whether HCMNs are successfully fused. Most studies have performed western blot (WB) analysis and sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) to detect surface marker proteins in order to determine whether cell membranes are successfully mixed and wrapped to the inner core. As shown in Fig. 5, CD235a (an important RBCialoglycoprotein), CD41 (a surface glycoprotein on platelets), and the cluster of differentiation 47 (CD47, a “do not eat me” marker on RBCs and platelets) appeared on RBC–platelet membrane-coated NPs (RBC–PMNPs) [52, 91], verifying that the membranes of RBCs and platelets were successfully modified on NPs. Furthermore, transmission electron microscopy (TEM) allowed a more intuitive observation of a thicker layer of film structure outside the NPs and a larger particle size in HCMNs.

The uniformity of encapsulation is a significant factor when evaluating a hybrid cell membrane. Förster resonance energy transfer (FRET) can visualize the fusion process and uniformity [27, 92, 93]. For instance, during the preparation of RBC–platelet hybrid membranes [52, 91], the intensity of dye on platelets interacting with RBCs would increase on increasing the RBC input, whereas the intensity of dye interacting with platelets would decrease, indicating the dispersion and fusion of the two membrane materials.

Mechanisms and functions of monotypic CMC-NPs

RBCNPs

Most circulating blood cells are RBCs. They have several biological characteristics, including long-circulating half-life, biocompatibility, and biodegradability. The utilization of RBC membranes has gained considerable research interest since the initial attempt to isolate RBC vesicles by Gaudreault et al. in 1994 [94]. In 2011, Zhang et al. pioneered the use of erythrocyte membrane-camouflaged polymeric NPs as a bioinspired delivery system [20]. The past decade has witnessed the rapid progress of RBCNPs for various biomedical applications, including anticancer [95–97], antibacterial [98, 99], antiviral [100], imaging, and photoactivatable therapies [78, 101, 102], as well as their transition from preclinical to clinical stages.

RBCs have a long circulation time of approximately 120 days [103]. CD47 significantly contributes to the in vivo circulation of RBC membranes [104]. CD47 can interact with signal-regulatory protein alpha (SIRPα) glycoprotein, which is expressed on phagocytic cells [104]. When CD47 interacts with macrophage-expressed SIRP, SH2 domain-containing tyrosine phosphatases are activated. This prevents myosin IIA from accumulating in phagocytic synapses and promotes the release of “do not eat me” signals that block macrophage-related phagocytosis [105, 106]. Other RBC membrane proteins contribute to defense against complement system attacks; these include C8-binding protein (C8bp), complement receptor 1 (CR1), decay-accelerating factor (DAF), and CD59
| Membrane compositions       | Synthesis ways                        | Membrane proportion | Nanoparticles                                    | Advantages                                                                                      | Usage                                      | Ref |
|----------------------------|---------------------------------------|---------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------|-----|
| Erythrocyte–leukocyte      | Ultrasonication and extrusion         | 1:1 (w/w)           | Magnetic nanoparticles                            | Biocompatibility, significant efficiency, and purity                                          | Noninvasive pregnant diagnostics (NIPD)  | [89]|
| Leukocytes–tumor cells     | Sonication and extrusion              | 1:1 (w/w)           | Paclitaxel-loaded liposomal nanoparticles        | Prolonging circulation time, minimizing the MPS uptake, enhancing solid tumor targeting        | B16 melanoma                              | [28]|
| Erythrocyte–melanoma cells | Sonication                            | 5:1, 3:1, 1:1 (w/w) | Doxorubicin-loaded hollow copper sulfide nanoparticles | B16-F10 cell self-recognition capability, high photothermal conversion efficiency               | Photothermal/chemotherapy of melanoma     | [27]|
| Erythrocyte–4T1 cancer cells | Dialyzed, ultrasound and coextruding | 1:10 (w/w)          | Dextran-poly (histidine) copolymer incorporated BLZ-945 | Biocompatible and nonimmunogenic, tumor targeting capability                                  | Cancer immunotherapy                       | [90]|
| Erythrocyte–MCF-7 cells    | Magnetically stirring, centrifuging, wash buffer | 1:1 (w/w) | Melanin nanoparticles                            | Adding flexibility and controllability in nano-drug functionality, enhancing PTT efficacy, homotypic targeting, reducing the cellular uptake by macrophages | Tumor photothermal therapy                | [86]|
| Erythrocyte–platelet       | Sonicating, repeatedly extruding     | 1:1, 2:1, 1:2 (w/w) | Polypyrrole nanoparticles                        | Evading immune system attacks, extending blood retention times, improving the photothermal killing ability | Tumor photothermal therapy                | [91]|
| Macrophage–cancer cells    | Sonication                            | 5:1, 4:1, 3:1, 2:1, 1:1 (w/w) | Doxorubicin-loaded PLGA nanoparticles | Specific targeting 4T1 cell, enhancing anticancer effects, long-term survival, without overt cardiotoxicity | Lung metastasis in breast cancer therapy | [87]|
In vivo experiments by Hu et al. on male ICR mice suggested that the elimination half-life was 39.6 h for RBCNPs, being much longer than that for PEG-modified NPs (15.8 h) [20]. Another in vivo experiment revealed that RBCNPs had a longer half-life than uncoated particles (2.63-fold increase) [110]. These results indicate that the membrane coating technique outperforms PEG modification in extending the circulation time. Furthermore, as a natural substance, RBC membranes are highly biocompatible and biodegradable. These attributes are crucial for resolving material toxicity on bare materials, such as carbon nanotubes and iron NPs [111]. RBCNPs loaded with doxorubicin (DOX) could deliver toxic chemotherapy drugs to target sites and have a significantly prolonged survival time without eliciting immune reactions [96].

In conclusion, RBCNPs have long-term circulation and detoxification properties and have the potential to be used for mass production. All these advantages jointly support the clinical application of RBCNPs and open a window for advanced therapeutic use.

PMNPs

Platelets are derived from cytoplasmic lysis of mature megakaryocytes. The plasma membrane of platelets contains multifunctional membrane proteins and provides an essential biological basis for platelets to perform their physiological functions in blood hemostasis [117]. PMNPs inherit the natural properties of platelets and possess functionalized characteristics of immunocompatibility and selective adherence [21].

The ability of PMNPs to evade macrophage detection is also thought to be related to the CD47 receptor. Therefore, platelet membrane cloaking counteracts cellular uptake (approximately 0.55 times less cellular uptake by human THP-1 and macrophage-like cells) and prolongs circulation time, which are vital for more efficient drug delivery [21].

PMNPs can also selectively adhere to pathogens. Bacteria can attach to platelets via bacterial surface proteins or plasma-bridging molecules that join bacterial and platelet surface receptors [118]. Both in vivo and in vitro experiments have shown that PMNPs can utilize selective adhesion...
mechanisms for more effective targeting delivery and higher antimicrobial efficacy than bare NPs or RBCNPs [21].

Furthermore, platelets can selectively aggregate and adhere to damaged vasculatures and the inflamed endothelium via surface membrane proteins [119] such as GPIbα [120], GPIa/IIa, GPVI [121, 122], GPIIb/IIIa (αIIbβ3 integrin) [123, 124], P-selectin, and GpVII integrin [125, 126]. In addition, the membrane proteins α6β1, αIIbβ3, and P-selectin are proposed to be involved in platelet–tumor cell interaction and tumor metastasis [127]. Hence, PMNPs have the potential to adhere to damaged vasculatures, inflamed endothelia, and tumor tissues. Compared with free drug treatment, drug-loaded PMNP-directed delivery to diseased vasculatures was found to significantly reduce the intima-to-media ratio and luminal obliteration by more than four times [21]. PMNPs also adhere to intercellular collagen IV in vitro by interacting with collagen through GPVI. They have been reported to exhibit a satisfactory treatment effect in DBA/1 mice with collagen-induced arthritis [125]. Moreover, PMNPs can better deliver DOX and indocyanine green (ICG) to cancer cells and significantly inhibit breast cancer cells [128].

In summary, PMNPs specifically bind to pathogens and damaged vasculatures. Moreover, they can evade macrophage detection. All these characteristics offer fresh perspectives on the therapeutic uses of PMNPs in patients with cardiovascular disorders, ischemic stroke, cancers, autoimmune diseases, and infectious diseases. Although increasing PMNPs are being explored and developed, the challenges are still non-negligible. Pressing issues, such as maintaining the bioactivity of PMNPs and meeting the supplementation of platelet membranes during large-scale production in the event of blood donor shortage, remain unresolved [122, 129].

**Cancer cell membrane-coated NPs (CCNPs)**

CCNPs inherit natural immune escape and cancer-homing features from cancer cells [22, 130], providing fresh perspectives on the clinical application of DDSs for anticancer therapy and cancer immunotherapy.

The overexpression of CD47 on the cell membrane is regarded as the cause of immune escape [131]. The mechanism of homotypic response is highly dependent on cancer cell adhesion molecules (CCAMs) [132]. Membrane receptors, such as selectins, cadherins, integrins, the immunoglobulin superfamily (Ig-SF), and lymphocyte-homing receptors (such as CD44), are included in CCAMs [133]. The details are summarized in Table 3. Cell–cell adhesion, cell signaling, cell migration, and gene regulation are significantly influenced by cadherin [134]. Integrins play a role in both cell–cell and cell-extracellular membrane interactions, and they are required for cell proliferation, differentiation, and migration [135–137]. Apart from these CCAM proteins, tumor-associated Thomsen–Friedenreich glycoantigen (TF-Ag) with galectin-3 can mediate metastatic cell homotypic aggregation [137]. Thus, CCNPs use the innate homotypic targeting ability of cancer cell membranes to provide a special cancer targeting technique that may be used for anticancer drug delivery [138]. Compared with RBCNPs and bare PLGA cores, MDA–MB-435 membrane-coated NPs showed approximately 40-fold and 20-fold higher homologous cellular uptake in vitro, respectively [22]. In addition, compared with bare NPs, SGC7901 cell membrane-coated silica NPs showed reduced accumulation in the liver and kidney and increased homing to tumor tissues [139].

Moreover, CCNPs efficiently present tumor antigens and can thus be used for cancer immunotherapy [22, 130, 140]. Fontana et al. constructed CCNP-loaded acetylated dextran for cancer immunotherapy, resulting in decreased expression of co-stimulatory signals in the immortal cell lines and increased secretion of inflammatory factors [141].

In summary, CCNPs effectively induce phagocytosis and increase tumor-specific accumulation. By camouflaging the cancer membrane, these NPs prevent medications from being released into the bloodstream too soon and enable precision distribution, thereby reducing side effects and achieving precise delivery [142]. Thus, they provide a potential strategy for synergistic anticancer therapies [132]. Notably, CCNPs target both primary cancer cells and metastatic cancer cells [143]. Hence, this biomimetic site-specific delivery

| Table 3 | Selective key cancer cell membrane proteins in the adhesion of cancer cells [132] |
|-----------------------------|---------------------------------------------------------------|
| **Cancer cell membrane adhesion-related proteins** | **Selective proteins** |
| Cadherins, catenin | Cadherin-1, 2, 19; protocadherin; catenins-α, β, γ; desmoglein DSG2, DSG3; desmocollin DSC2, DSC3 |
| Integrins | αβ3, αβ5, αβ1, αβ4, αβ1, αβ6 |
| Ig-SF CAMs | ALCAM, contactin, ICAM, MCAM, NCAM |
| Tetraspanins | CD9, CD151, CD44 |
| Integrin-associated proteins | CD47 |
| G proteins and GPCRs | CXCR4, CD97 |
tool provides a potential treatment strategy for metastatic cancer cells, which is a great challenge at present [143]. Although the manufacturing costs, scale-up logistics, and quality control methods remain critical barriers [142, 144], CCNPs offer new insights into precise cancer treatment in the future [145, 146].
**Macrophage membrane-coated NPs (MNPs)**

Recently, MNPs have gained increased attention as they mimic the natural properties of macrophages, namely non-immunogenicity, tumor cell targeting, inflammatory site targeting, and pathogen adhesion [23, 147, 148].

MNPs can inhibit macrophage uptake and have a long circulation time (Fig. 6a). In a previous study, after 24 h of treatment, more than 30% of MNPs remained free, whereas uncoated NPs were almost phagocytosed (Fig. 6b) [23]. Consequently, tumor growth was successfully reduced by MNPs loaded with low doses of DOX in 4T1 tumor model mice [23].

MNPs also inherit the tumor endothelium recognition property [147] and can therefore lead to better tumor tropic accumulation than bare NPs, RBCNPs [149], or PEGylated NPs (Fig. 6a) [23]. In another recent study, MNP-mediated PDT therapy reduced the amount of CSF1 that tumor cells released and gathered specifically in the tumor microenvironment (Fig. 6c) [150]. This therapy also converted the protumoral M2-like phenotype to an antitumoral M1-like state, eliminating primary tumor growth and producing an abscopal effect to inhibit distant tumor growth. Thus, MNPs provide a solid foundation that could be used for several anticancer treatments following the inner cores [151, 152].

Macrophages can bind to and recognize pathogen-associated molecular patterns (Fig. 6a). During infection, macrophages release potent proinflammatory cytokines that help eliminate invading pathogens when the pathogen-associated molecular pattern CD14 recognizes lipopolysaccharide (LPS)-binding protein. All these important membrane proteins required for endotoxin binding are maintained by MNPs. A previous study revealed that MNPs could neutralize LPS and sequester cytokines by interacting with proinflammatory factors via the pattern recognition receptor (PRR) and cytokine receptor [55]. Thus, MNPs can serve as fake cytokine binders without triggering downstream inflammation cascades (pathological cytokine storm) [55], thereby avoiding pathological consequences, such as septic shock. In addition, inflammation often occurs during the recruitment of monocyte-derived macrophages because of the membrane proteins Mac-1 and CD44 [153]. Compared with bare NPs and RBCNPs, macrophage-derived microvesicle-coated NPs exhibited enhanced binding to inflamed vessels in a mouse model of collagen-induced arthritis (Fig. 6a, d) [154]. All these results suggest that MNPs are promising vehicles for anti-infectious and anti-inflammatory treatments.

In summary, macrophage membrane coating confers MNPs with properties of inflammatory tissues, cancer site targeting, and pathogen and inflammatory cytokine adhesion, providing exciting opportunities for advanced applications in anticancer therapies, anti-inflammatory therapies, and detoxification strategies.

The mechanism, benefits, and applications of four types of cell membrane carriers are introduced in this section. Researchers have used various membranes to treat various diseases as they have unique biological roles. The following Table 4 summarizes the types of cell membranes that can be selected for some common disease application scenarios, in addition to their advantages and mechanisms.

**Different combinations and biomimetic applications of HCMNs**

Some studies have incorporated ligand targeting and biomarker auxiliary modification in the multiple functions of CMC-NPs [30, 170], inspiring research on HCMN DDSs. RBCs were first used in the preparation of HCMNs because of their biocompatibility and immune clearance escape ability. Subsequently, increasing numbers of biological membranes were involved in the preparation and application of HCMNs.

**RBC–platelet HCMNs**

The combination of RBC and platelet cell membranes has distinct advantages in the field of DDSs as they both avoid immune clearance and target the inflammatory area [21, 52, 171]. The circulation half-life of RBC–platelet HCMNs was found to be 51.8 h, which was much longer than that of RBCNPs (42.4 h) and PMNPs (38.3 h) [52]. After the induction of multiple microthrombosis and inflammatory factors in tumor regions, RBC–platelet hybrid membranes coated with polypyrrole showed the longest circulation time and significantly better tumor targeting ability in vivo. These membranes resulted in higher temperatures during PTT than monotypic cell membrane-coated NPs and bare NPs, suggesting that RBC–platelet HCMNs can improve photothermal conversion efficiency and achieve better curative effects [81].

RBC membranes can also target bacteria and absorb PFTs [164] that are normally released in gram-positive bacterial infections. Meanwhile, platelet membrane proteins can interact with bacterial pathogens and adhere to them. Hence, several researchers have combined RBC and platelet membranes to remove toxins and pathogenic bacteria (e.g., *Staphylococcus aureus*) from the bloodstream [172].

In summary, RBC–platelet HCMNs enable the integration of cell membrane surface proteins, resulting in advantages, such as increased circulation time, payload accumulation in diseased tissues, and detoxification [52, 91, 172].
Table 4 Different cell membranes can be chosen in various diseases

| Disease conditions                                      | Mechanism                                                                 | Cell membrane type                  | Advantages                                                                 | Ref                  |
|--------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------|---------------------------------------------------------------------------|----------------------|
| Endotoxemia (LPS-related diseases such as obesity and diabetes) | The high affinity between membrane receptors (CD14, TLR-4) and LPS block the immune response and decrease the release of cytokines. | Macrophage, extracellular vesicles from immune cell | Avoid antibiotic resistance, biocompatible and efficient                    | [155–158]           |
| Cancer treatment                                       | Immune evasion ability through CD47, the innate inflammation directed chemotactic ability, activating anti-tumor immune response, intercellular homologous binding capability. | Immune cell, stem cell, cancer cell, platelet, RBC | Escaping the immune system and long circulation time, cancer targeting, or homologous targeting ability | [159–163]           |
| Cancer detection                                       | Achieving highly specific self-recognition of source cancer cell lines.    | Cancer cell                         | Display the diversity of antigens on the source cell surface to realize keen detection | [137]                |
| Bacterial infection                                    | Pore-forming toxins (PFTs) attack or LPS-induced activation of the immune system is the main virulence mechanism. Cell membranes can absorb various PFTs and reduce toxicity. Some cell membranes can capture LPS to block immune response. | Bacterial cell, platelet, RBC, macrophage | Improve detoxification ability and biosafety, and reduce antibiotic resistance | [164–166]           |
| Inflammatory arthritis (Autoimmune diseases)           | Combine with immunomodulatory molecules to exert anti-inflammatory effects. Stimulate the production of neutrophil chemokines in the region, and repair tissue damage. | Neutrophil                          | High efficiency, low toxicity, and safety. Overcome the complexity and heterogeneity of the inflammatory network of autoimmune diseases | [167]                |
| Vaccination                                            | The bio-membrane exerts its own function by activating the autoimmune system to effectively inhibit the disease process such as cancer and bacterial/viral infection. | Cancer cell, bacterial cell         | Targeting delivery, good biocompatibility, immunomodulation ability, long circulation time and avoiding antibiotic resistance | [22, 168, 169]      |
Erythrocyte–cancer cell HCMNs

Adhesion molecules on the surface of tumor cell membranes share homologous recognition and homing characteristics [173]. The preparation of monotypic cancer cell membrane vesicles may result in a loss of membrane protein integrity and fail to avoid immune surveillance completely [26]. However, combination with RBC membranes could realize the complementarity of long-term circulation. Hence, several studies have used erythrocyte–cancer cell HCMNs as an effective DDS in cancer therapy [27, 163, 164].

Compared with other types of HCMNs, erythrocyte–cancer cell HCMNs are more frequently combined with various cancer treatment methods, such as ICB therapy, PTT, and PDT. The latter two methods belong to phototherapy [175]. Phototherapy combined with erythrocyte–cancer cell HCMNs could greatly tackle the disadvantages of phototherapy agents, such as easy recognition, clearance by the immune system after injection, and less accumulation at the target location. ID8 ovarian cancer cell–erythrocyte HCMNs combined with PTT showed the highest photothermal conversion efficiency (Fig. 7) [176], tumor elimination rate, and tumor growth inhibition rate by prolonging the blood circulation time and improving cancer homotypic targeting. Thus, erythrocyte–cancer cell HCMNs are beneficial for cancer therapy.

Erythrocyte–cancer cell HCMNs also exhibit great advantages in the field of drug delivery. They mainly evade elimination, prolong the systemic circulation time in vivo, and exhibit a high degree of homologous tumor targeting. After 24 h post-administration, erythrocyte–cancer cell HCMNs get highly aggregated in tumor tissues, become less targeted to the liver, and exhibit reduced removal; these findings are attributed to the synergistic effect of homotypic binding and immune camouflaging abilities of the hybrid cell membrane [90].

In recent years, erythrocyte–cancer cell HCMNs have also been used in tumor vaccines. Tumor vaccines introduce different forms of tumor-derived antigens into patients, thus creating an adequate and long-lasting immunogenic context for effective treatments [166]. However, several trials have indicated that autologous tumor vaccines cannot totally suppress tumor recurrence because of their weak immunogenicity [177]. Senescent RBCs have the ability to target the splenic antigen-presenting cell; therefore, erythrocytes and cancer cell membrane-associated antigens are coated onto NPs [174]. They can successfully interact with splenic APCs and trigger T-cell immune responses, ensuring biosecurity without any unwanted by-products.

In summary, erythrocyte–cancer cell HCMNs exhibit the advantages of both cell membranes and can be widely used in multiple scenarios.

Leukocyte–cancer cell HCMNs (LCMs)

Various types of research have been conducted on LCMs to combine the immune escaping ability of leukocytes with tumor targeting ability. Compared with other hybrid membranes, LCMs were found to exhibit synergistic effects of cancer cells and leukocyte membranes on tumor targets in vivo. The tumor targeting ability could achieve therapeutic drug accumulation in tumor tissues, high tumor clearance...
rates, and positive therapeutic effects. To enhance solid tumor homing, Yang et al. composited leukocyte and cancer cell membranes. At 48 h post-administration, the biodistribution result of LCMs in tumor-bearing mice revealed that the fluorescence intensity was highly aggregated in the tumor region, being approximately 9.3-fold higher than that in the control group (Fig. 8) [28].

LCMs can also be used for cancer detection, playing an important role in cancer monitoring and diagnosis. Some existing detection methods are not sensitive and accurate enough for capturing and detecting circulating tumor cells (CTCs). They fail to predict tumor metastasis in advance because of the low concentration of CTCs and interference from leukocytes [178]. However, LCMs can reduce interference from homologous leukocytes and have the ability of tumor region targeting, which can improve CTC isolation and detection. For instance, Ding et al. successfully built a nanoplatform with LCMs for highly efficient cancer detection [171]. The purity of captured CTCs in the LCM-coated NPs group was 96.96%, which was much higher than that in the bare NPs and monotypic cell membrane-coated NPs groups.

In conclusion, LCMs can be extensively used for disease treatment, particularly in cancer therapy. Leukocytes have also been confirmed to be a precursor of tumor metastasis in human bodies. Therefore, some studies have focused on the regulation of epigenetic expression of the parent cell by LCMs and expression of a specific antigen profile for performing immunotherapy in order to enable efficient removal of tumor cells and cancer treatment [89].

This section reviews the characteristics and advantages of various types of HCMNs. More applications and experiments of HCMNs are presented in Table 2 for better understanding. In summary, several reports have indicated that different cell membrane combinations play unique roles in the treatment of specific diseases. HCMNs can have multiple applications, use in liquid biopsy and cancer vaccines, targeting disease regions, use in combination with other treatments, and detoxification.
Prospects and challenges

Cell membrane coating utilizes natural components at the source to directly transfer natural properties displayed by source cells, thereby recreating complex biological functions and integrating functions that cannot be achieved through synthesis. In this review, the drug delivery capabilities of CMC-NPs are highlighted. Biologically derived raw materials offer a longer blood circulation time, better immune escape, and stronger targeting ability than bare NPs. Undeniably, CMC-NPs still have drawbacks and pose obstacles. Their prospects and challenges will be the main topics of this section.

Quality control

As CMC-NP is a novel drug delivery platform, its quality control needs to be further explored. By referring to the existing standards and quality control specifications for cellular medicines [179, 180], the quality control of CMC-NPs can be divided into three parts.

Cell collection and isolation process control

In the case of cellular raw materials used for preparing CMC-NPs, cell identification, survival and growth activity assessment, foreign pathogen detection, and basic cell characteristic assessment are necessary. Cell characteristics include specific populations of cell surface markers, expression products, and differentiation potentials.

In addition, standard operation and management procedures for the collection and separation of different cells should be formulated and strictly implemented based on GMP requirements. Moreover, each cell type requires standardized and well-established cell culture protocols so that its phenotype and purity can be maintained during passaging [181].

Manufacturing process and storage ability

More consideration needs to be given to the fusion process. Careful calculation and control of the membrane-to-NP ratio are essential to ensure complete coverage and reduce loss of cell membrane. Moreover, the preparation of HCMNs is complex (e.g., determination of the ratio of the two cell membranes and the membrane mixing type), making it difficult to determine an optimal HCMN preparation method suitable for a particular disease [25]. Furthermore, producers are required to use standard biotechnological production and purification techniques. The entire production process should not lead to further impurities other than those originating from the active substance.

Sterilization is another important part of manufacturing process control. The currently accepted sterility assurance level (SAL) is $10^{-6}$ [182]. Quality control systems need to guarantee that pyrogens, bacteria, virus endotoxins, or LPS do not contaminate CMC-NPs. Filter sterilization is a widely used technique for sterilizing nanoformulations [183, 184]. Specific standards for sterility and endotoxin testing can be formulated according to national quality control regulations.

During the storage process, biological sample storage is usually performed using the freeze–drying method [185]. The potential influence of the lyophilization process on finished product quality results in product-derived impurities, which need to be controlled using the established analytical methods. In addition, the purity and coverage of the preparation process can impact the storage stability of different cell membrane coating systems [24, 31]. Therefore, numerous pre-experiments on screening conditions in the early stage of mass production are required to improve the storage stability of certain CMC-NPs.

Product control, batch analysis, and product stability

For analyzing the active substance quality in CMC-NPs, therapeutic activity, encapsulation rate, and drug release rate are assessed. The precise ingredients in each CMC-NP primarily vary in two areas: safety and efficacy.

To ensure batch-to-batch repeatability during mass production, process parameters must be examined to determine the variables that could harm the product. Process variables include ambient conditions (temperature, pH, and pressure), formulation variables (cell types, component ratios, and solvents utilized), and formulation processes (time, speed, flow conditions, and power) [186]. Short-, medium-, and long-term stability must also be assessed.

Consideration for clinical applications

Although massive studies have resulted in different membrane-coated NP formulations, little research has progressed to clinical practice. This section focuses on the challenges in the clinical translation of CMC-NPs and tries to provide reliable solutions.

First, the in vivo mechanisms of both hybrid and monotypic CMC-NPs remain unknown. One of the main reasons why it is challenging to perform clinical trials for membrane biomimetic carriers is the intricacy and unpredictability of the intermediate process results in vivo. It is risky to assume that the CMC or HCMN would deliver drugs via the theoretical route after entering the human body. To apply membrane coatings beyond the current black box approach [8], researchers need to elucidate more physiological mechanisms, such as internalized mechanisms, intracellular release mechanisms, and subcellular-level actions. This requires a more...
fundamental understanding of cell biology, which is becoming more prevalent. Therefore, it is imperative to study the in vivo mechanism of membrane biomimetic carrier DDSs, their route of delivery, and their process as soon as possible.

Second, there are issues related to actual benefits. In vivo and in vitro experiments on various types of HCMNs have revealed that HCMNs can indeed exhibit the functional advantages of both types of CMC-NPs. Several experiments, however, have revealed that the mixed benefits of HCMNs are not as high as the unique benefits of monotypic cell membranes in terms of certain functions, such as targeting ability [86, 87] or prolonged blood circulation time [8, 27]. In other words, while the new HCMN DDS verifies and realizes the possibility of $1 + 1$, this does not make it $> 2$.

Third, technical difficulties in acquiring source materials still exist. While cell membranes can be autologous, it may be more practical to obtain and store materials from types of matched donors [24]. However, heterologous cells may have toxicity, biological incompatibility, and immunogenicity. The optimization of protocols to remove unnecessary proteins and retain necessary ones remains to be explored. In addition, changes in membrane protein contents during storage remain another challenge [187, 188]. However, we believe that once a patient-specific cell membrane becomes available, precision medicine will dramatically advance. Addressing disease heterogeneity and establishing personalized therapeutics will then become an achievable goal.

Furthermore, cell membrane-coated platforms will encounter greater developmental opportunities through the integration of newer branches of science and biotechnology (e.g., synthetic biology and biomaterial science), leading to richer therapeutic possibilities. For instance, the use of CMC-NPs to develop vaccines is a novel method for the prevention and treatment of COVID-19, which has been continuously developed and transformed in recent years [189]. Moreover, a few studies have used the membrane from genetically engineered source cells. In these studies, the expression of specific surface markers has been induced or upregulated, optimizing the functionality for a given application [41, 190]. Although cell membranes are by far the main source of membrane coatings, more consideration could be given to other membrane sources, like organelle membranes [42].

**Conclusion**

Monotypic cell membrane coating or hybrid cell membrane coating confers unique biological properties to NPs, including immune escape, long circulation time, and targeted delivery, thereby enabling more efficient drug delivery. Consequently, cell membrane-coated DDSs have gradually become a novel research hotspot. However, more efforts are needed for the clinical transformation and application of CMC-NPs. Obstacles to the standard protocol, quality control, and large-scale production need to be overcome. Assessment of the mechanism and in vivo process will also guide further improvements in the design and preparation of biomimetic carriers.

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