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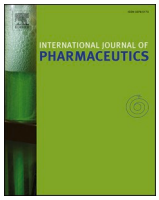

Review

Cell-derived membrane biomimetic nanocarriers for targeted therapy of pulmonary disease

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ABSTRACT

Pulmonary diseases are currently one of the major threats of human health, especially considering the recent COVID-19 pandemic. However, the current treatments are facing the challenges like insufficient local drug concentrations, the fast lung clearance and risks to induce unexpected inflammation. Cell-derived membrane biomimetic nanocarriers are recently emerged delivery strategy, showing advantages of long circulation time, excellent biocompatibility and immune escape ability. In this review, applications of using cell-derived membrane biomimetic nanocarriers from diverse cell sources for the targeted therapy of pulmonary disease were summarized. In addition, improvements of the cell-derived membrane biomimetic nanocarriers for augmented therapeutic ability against different kinds of pulmonary diseases were introduced. This review is expected to provide a general guideline for the potential applications of cell-derived membrane biomimetic nanocarriers to treat pulmonary diseases.

1. Introduction

Pulmonary diseases, including lung infection, acute lung injury, lung cancers, asthma, cystic fibrosis, etc., are currently one of the major threats of human health, especially considering the recent COVID-19 pandemic (Britto et al., 2017; Mao et al., 2016; Zhu et al., 2020). The traditional medical treatments for pulmonary disease are hindered by insufficient drug concentrations in pathological lesions (Deng et al., 2021; Xu et al., 2014). Therefore, lung-targeted drug delivery system (LTDDS) was then emerged to concentrate the therapeutic agents in pathological lung tissues, which has shown significant benefits in the treatments against diverse pulmonary diseases (Wei and Zhao, 2014). Thus far, dry powder preparation and atomized suspension inhaled through trachea (Abdelaziz et al., 2018; Muralidharan et al., 2015), and microparticles, liposomes and nanoparticles administered intravenously (Vidyadevi et al., 2021; Wei and Zhao, 2014) are the most applied strategies for lung-targeted delivery. However, no matter for inhalation strategy or injection approach, certain barriers exist. For instance, in the inhalation, nanoparticles would be easily blocked by mucus layer, bronchoalveolar fluid and phagocytes in conducting airways and alveoli (Liu et al., 2022; Ruge et al., 2013). Meanwhile, for intravenous injection, the first pass metabolism and clearance of kidney, intestine and liver would reduce the concentration of nanoparticles in local lungs (Alexescu et al., 2019; Zhao et al., 2020). Generally, nanoparticles with a particle size over 7 μm can rapidly aggregate in the lung through pulmonary capillary filtration (Azarmi et al., 2008; Dhand et al., 2014). Nevertheless, these exogenous nanoparticle carriers would soon be phagocytized by the reticuloendothelial system. Moreover, the dispersed nanoparticles tend to adsorb various proteins and construct protein crowns on their superficial coat, which reduces the targeting ability of nanoparticles. Of note, high doses of nanoparticles would induce lung epithelial damage and active the immune system, resulting in lung inflammation. Even worse, the injury of lung epithelial cells would recruit neutrophils to flood into the alveolar area (Aarbiou et al., 2002; Braakhuis et al., 2014).

During the past years, pulmonary drug delivery system relying on living cells has attracted increasing attentions, showing the advantages of prominently reducing the risks of immunogenicity and other

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undesirable side-effects. These cellular vehicles include red blood cells (RBCs), mesenchymal stem cells (MSCs), macrophages, etc. (Dai et al., 2021; Klyachko et al., 2017; Masterson et al., 2020) RBCs can be applied as carriers by encapsulating drugs inside the cells (intracellular coating) or by carrying on drugs on the cell surfaces (extracellular adsorption) (Bush et al., 2021; Koleva et al., 2020). For example, RBCs were applied to deliver dexamethasone for the treatment of patients with chronic pulmonary obstruction, which could remain in the circulation for 7 days (Rossi et al., 2001). MSCs were also reported as targeted carriers for lung tumor treatment, due to their inherent tumor homing ability (Zhang et al., 2021a) and the ability to resist lung clearance (Su et al., 2021; Zhang et al., 2021a). Macrophages were investigated as another type of 'Trojan horse' cells: protecting drugs from immune system clearance and targeting pulmonary inflammation (Novak et al., 2018). However, there are still some problems during the applications of living cells for lung targeted delivery. For example, although RBCs are endowed with long blood circulation, the preparation strategy of the carriers has not been standardized (Bush et al., 2021). MSCs can effectively target to lung tumors, but they are easy to cause pulmonary embolism (Wu et al., 2019b). In addition, MSCs were reported to bear the risks of promoting tumor growth and metastasis in some cases (Lazennec, 2011). Macrophages are ideal vehicles for targeting inflammatory lungs, but the uncontrolled release of drugs may cause inevitable side effects and affect their targeting ability. These limitations of cellular vehicles are hindering their further applications in the targeted therapy of pulmonary diseases.

To overcome the above-mentioned limitations, cell membrane biomimetic carrier was then proposed as a potential delivery strategy (Hu et al., 2011). The complete cell membranes are collected from natural cells (RBCs, platelets, cancer cells, stem cells, immune cells, bacteria, etc.) and then camouflage nanoparticles by coating their surfaces. In this delivery strategy, the inherent targeting ability of certain cells benefits the directional transport of core-nanoparticles without additional considerations of their characteristics. The constructed cell membrane coated nanoparticles retain various properties of the core-nanoparticles and inherent targeting ability. Meanwhile, natural cell membranes prevent the loss of integrity and function of nanoparticles in the process of drug preparation and delivery. Moreover, in inhalation approach, traditional nanoparticles are easier to be adsorbed by lung surfactants, leading to the inhibition of normal function of the lung (Liu et al., 2022). By using membrane biomimetic carriers, such absorption may be avoided. To sum up, cell-derived membrane biomimetic system possesses the superiorities of long circulation time, good biocompatibility and immune escape ability, which may provide a potential delivery strategy to overcome the current dilemma in the targeted treatment of pulmonary disease.

2. Designs and preparations

2.1. The basic principles of membrane biomimetic preparations

The lung targeting performance of cell-derived membrane biomimetic nanocarriers is closely related to design parameters. The particle size, shape and surface charge of membrane biomimetic carriers are crucial factors in determining the transmission and *in vivo* fate of nanoparticles.

Size plays a significant role in proper encapsulation of drugs, prolonging blood circulation and improving lung targeting. Nanoparticles below 5 nm are usually cleared by the kidney after intravenous injection, while nanoparticles over 200 nm are filtered through the spleen (Liu et al., 2019a). Therefore, nanoparticles, as well as cell-derived membrane biomimetic nanocarriers, with a range of 20–200 nm are considered suitable. At present, the particle size of membrane biomimetic agents used for lung targeting is commonly in the size from 100 nm to 300 nm.

The shapes of nanoparticles include spherical, disk, ellipsoid, rod, etc., have significant impacts on distribution, circulation and cellular uptake. For instance, disk-shaped nanoparticles tend to distribute in the lung and spleen (Rampersaud et al., 2016). Erythrocyte membrane coated nanoparticles with prolate ellipsoidal shape showed longer half-life than the ones with spherical shape. The half-life of prolate ellipsoidal shape is 171.6 min, while for spherical particles is 64.8 min (Ben-Akiva et al., 2020). Nanoparticles coated with cancer cell membrane with rod shapes showed higher cellular uptake efficiency compared to spherical-shaped biomimetic nanoparticles (Zhang et al., 2019b).

The surface charge of membrane biomimetic carriers also affects the properties of nanoparticles. Positively charged nanoparticles are more likely to cause internal safety risks and are quickly eliminated from the blood circulation. Negatively charged nanoparticles, on the other side, usually have a longer circulation and a lower systemic toxicity. Nevertheless, the distribution of negatively charged nanoparticles in the lungs is relatively low (Arvizo et al., 2011).

2.2. Preparation process

Several methods had been developed to prepare membrane biomimetic nanoparticles, such as membrane extraction, and fusion of cell membrane and core-nanoparticles (Liu et al., 2019b). Details of these methods are introduced below:

2.2.1. Cell membrane extraction

The extraction of anuclear cell membranes (RBCs and platelets) is usually through repeated freezing and thawing or dissolution with hypotonic solution. To obtain the cell membranes, RBCs or platelets are firstly isolated from plasma through centrifugation (e.g., 700 g, 10 min for RBCs), following with cell lysing by hypotonic treatment or repeated freeze-thaw processes, and cell membranes are purified from the mixture by centrifugation (e.g., 20,000 g, 10 min for RBCs). In order to maintain the biological activity of membrane proteins, protease inhibitors are usually added to the extracted cell membranes and stored at 4 °C (Li et al., 2019b; Liu et al., 2018a).

It is more complex to harvest the cell membranes from eukaryotic cells, such as cancer cells, stem cells and immune cells, partly due to the prerequisite of removing cell nuclei and some biomacromolecules. First of all, a sufficient number of cells must be collected for concentrating and purifying cell membranes, which are disrupted by incubation in hypotonic lysate or repeated freeze-thaw treatments. Nuclei and intracellular biomacromolecules are removed by discontinuous sucrose gradient centrifugation or differential centrifugation. The membrane-rich fraction was then washed with plasma buffer, and sonicated or extruded through a porous membrane to obtain cell membrane vesicles (Meng et al., 2018; Wu et al., 2020).

2.2.2. Fusion of cell membranes and core-nanoparticles

Major methods to fuse cell membranes and core-nanoparticles include membrane extrusion, ultrasonic treatment and microfluidic electroporation.

Membrane extrusion is a method to encapsulate nanoparticles in cell membranes by applying mechanical pressure to facilitate the penetration of nanoparticles to across the phospholipid bilayer of the cell membrane. The mixture is repeatedly extruded through porous membranes in different sizes according to the nanoparticle size, which allows the membranes to reconstitute on the nanoparticles (Saha et al., 2021).

Ultrasonic method is another major way to prepare the membrane biomimetic nanoparticles, in which cell membranes and nanoparticles self-assemble to form core-shell nanostructures under the destructive force provided by ultrasonic energy. This method possesses advantages of less material loss comparing to the physical extrusion (Yang et al., 2021).

Microfluidic electroporation is a recently developed technology to fabricate the membrane biomimetic nanoparticles, showing potentials as a platform technology for controllable, tunable, and scalable

preparations. In this method, nanoparticles and cell membrane vesicles are mixed in a microfluidic chip and then flow through the electroporation zone. Electric pulses between the two electrodes can effectively promote the entry of nanoparticles into cell membrane vesicles (Rao et al., 2017).

3. Cell sources for preparing biomimetic membrane carriers

The properties of membrane biomimetic preparation are largely determined by the functional proteins on the cell membrane, such as their quantity and type. Different kinds of cells had been studied to prepare biomimetic membrane carriers, such as RBCs, platelets, cancer cells, stem cells, immune cells, and bacteria.

3.1. RBCs

RBCs are the most abundant blood cells in the human body (i.e., 5 million cell/mm3 blood in a man) and are responsible for providing oxygen for cells and tissues and transport carbon dioxide to the lungs (Hamidi and Tajerzadeh, 2003). Because of the convenience to separate RBCs from blood and the anuclear characteristic, RBCs are the first type of cells being used to prepare membrane biomimetic carriers in 2011 (Hu et al., 2011). The self-recognition protein CD47 expressed on the membrane of RBC (RBCm), which is recognized by reticuloendothelial system, allows RBCm to possess advantages of a long circulation time: about 40 days in mice and 3 months in humans (Hu et al., 2012, Sun et al., 2019).

Thus far, RBCm has been extensively applied in the treatment of pulmonary diseases, because of its splendid biocompatibility and long-term blood circulation (Castro et al., 2021). For example, RBCm biomimetic carrier is frequently used for the treatment of lung cancer. Chen et al. fabricated RBCm-coated obatoclax mesylate (OM)-loaded poly (lactide-co-glycolide) (PLGA) nanoparticles, showing improved lung tumor inhibition with good biocompatibility. Compared with the naked nanoparticles, RBCm-coated nanoparticles showed more powerful cytotoxicity to non-small cell lung cancer (NSCLC) cells but exerted no significant toxicity to normal cells (Chen et al., 2020). In addition, polymer nanoparticles coated with RBCm were also reported to be applied as nanosponge for absorbing and neutralizing bacterial toxins in the treatment of bacterial infections. Chen et al. had designed a bacterial toxin nanosponge composed of PLGA core and wrapped RBCm. The RBCm shell provides a substrate simulation that can absorb various bacterial toxins, and the internal polymer core is used to stabilize the RBCm shell to achieve long-term systemic circulation. This nanosponge has been proved to effectively protect the pulmonary vascular barrier (Chen et al., 2019).

However, as a drug carrier, the major weakness of RBCm is their poor targeting ability. The modifications of RBCm with improved lung targeting ability is a potential solution, but facing the challenges of altering the lipid bilayer and membrane protein, which may adversely affect their biocompatibility.

3.2. Platelets

Platelets, which derive from mature megakaryocytes in bone marrow, are disc-shaped and changeable with the functions of coagulation and hemostasis (Italiano and Shivdasani, 2003). Platelets can escape immunity through CD47 mediated macrophage uptake and activation, thereby prolonging the circulation time in blood stream (Wang et al., 2020). Additionally, P-selectin expressed on platelets can specifically bind to up-regulated CD44 in cancer cells, which enables their tumor targeting ability (Merten and Thiagarajan, 2004; Naor et al., 2002).

Compared with RBCm, platelet membrane coated nanoparticles possess the targeting ability towards tumor and damaged blood vessels adhesion. For example, the platelet membrane coated nanoparticles (PM/PLGA/DTX) was used for lung cancer therapy. Compared with membrane-free nanoparticles, the platelet membrane coating significantly reduced the toxicity of antitumor chemotherapy drugs and inhibited the growth of lung tumors (Chi et al., 2019). Furthermore, platelet membrane coated nanoparticles were also applied in immunotherapy of lung cancer. Baharak et al. designed a small molecule immunomodulator R848 coated by platelet membranes for intratumorally local immune activation, which could inhibit lung metastasis (Bahmani et al., 2021).

Because of the specific adhesion of platelets to damaged blood vessels, thrombolytic drugs coated on platelet membranes can be delivered to target pulmonary artery thrombosis, thereby realizing a sustained drug release for improved treatment of pulmonary embolism (Yang et al., 2018b).

Moreover, the platelet membrane coating benefits the treatment of pulmonary inflammation, due to the inflammatory targeting ability. Jin et al. developed platelet membrane (PM) coated nanoparticles system (PM/Ber) for delivering berberine (Ber) to the inflammatory lung. PM/Ber successfully targeted to the inflammatory lung at two hours after intravenous injection, and released Ber slowly from 2 h to 48 h, thus reducing allergic asthma (Jin et al., 2021).

Although platelet membranes have showed the advantages of immune escape and inflammatory tropism in the treatment of lung tumor and pulmonary inflammation. There are still some problems to be overcome. Platelets are very sensitive, so the construction of platelet membranes as drug carriers may lead to unnecessary thrombosis or bleeding. In addition, platelets are easy to aggregate *in vitro*, making the stability of platelet membrane coated nanoparticles as a major challenge (Lu et al., 2019).

3.3. Cancer cells

The indefinite proliferation and fast *in vitro* expansion of cancer cells make the possibility of isolating cell membranes in a large number (Li et al., 2021a). Cancer cell membranes are rich in various functional proteins, including membrane proteins mediating homologous binding (selectins, integrins, etc.), biomarkers of self-recognition and immune escape (CD47, etc.), and immune activation-related tumor antigens (tumor-associated Thomsen-Friedenreich glycoantigen, etc.) (Khaldoyanidi et al., 2003). Therefore, cancer cell-derived biomimetic strategies are considered as a promising option due to their ability to escape immune surveillance and homologous tumor targeting (Jin and Bhujwalla, 2019; Pereira-Silva et al., 2020).

Wu et al. developed a biomimetic nanocarrier loaded with doxorubicin and icotinib, which was coated by cell membranes isolated from lung cancer cell line H975. This biomimetic nanocarrier was successfully applied to treat chemotherapeutic drug-resistant non-small cell lung cancer (NSCLC). Comparing with membrane-free nanoparticles, the biomimetic nanoparticles showed advantages of high stability and efficient tumor inhibition, killing 87.56% tumor cells (Wu et al., 2019c). In addition, nanoparticles coated with 4T-1 cell membranes significantly enhanced the distribution of nanoparticles in lung tumors, showing significant suppression on lung metastasis of breast cancer (Sun et al., 2016).

Nevertheless, the safety concerns regarding to the potential risks of inducing tumorigenesis using cancer cells-derived membrane restrict the clinical applications of this delivery strategy (Lei et al., 2022).

3.4. Stem cells

Some stem cells, like MSCs, embryonic stem cells and neural stem cells, are multi-potential differentiated cells that have an ability to self-replicate (Fu et al., 2021). In addition, stem cells have homing ability, which navigates stem cells to target to injured organs through combining chemokines, adhesion molecules and growth factors released by target organs with corresponding receptors expressed on the surface

Table 1
Applications of diverse sources cell membrane in pulmonary diseases.

Sources	Core-nanoparticles	Effects/Diseases	Ref.
RBCs	PGSC-PTX	NSCLC	(Gao et al., 2017)
	PLGA	Neutralize bacterial toxins and protect the pulmonary vascular barrier	(Chen et al., 2019)
	OM/PLGA	NSCLC	(Chen et al., 2020)
	PXTK, dPPA	Breast cancer with lung metastasis	(Yu et al., 2019)
Platelets	uPA	Pulmonary embolism	(Yang et al., 2018b)
	rt-PA	Pulmonary embolism	(Xu et al., 2020)
	DTX/PLGA	Lung cancer	(Chi et al., 2019)
	R848	Metastatic carcinoma of lung	(Bahmani et al., 2021)
	Berberine	Allergic asthma	(Jin et al., 2021)
Cancer cells	Doxorubicin and icotinib	NSCLC	(Wu et al., 2019c)
	PTX	Metastatic carcinoma of lung	(Sun et al., 2016)
MSCs	DOX/PLGA	Lung cancer	(Yang et al., 2018a)
	Ng/Ce6	Lung cancer	(Feng et al., 2020)
	Cyp-PMAA-Fe	NSCLC	(Yin et al., 2021)
Macrophages	Emtansine Liposome	Metastatic carcinoma of lung	(Cao et al., 2016)
	Quercetin, Bi2Se3	Lung metastasis of breast cancer	(Zhao et al., 2018)
	LPV/PLGA	Pneumonia	(Tan et al., 2021)
Neutrophils	SPX/PCL-PEG	Pneumonia	(Wang et al., 2020a)
	GOx/CPO	Metastatic carcinoma of lung	(Zhang et al., 2019a)
Bacteria	/	Klebsiella pneumoniae	(Li et al., 2021c)
	/	SARS-CoV-2	(Yang et al., 2021b)

Abbreviations: Red blood cell (RBC); Poly(l-γ-glutamylcarbocistein) (PGSC); Paclitaxel (PTX); Non-small cell lung cancer (NSCLC); Poly(lactic-co-glycolic acid) (PLGA); Cinnamaldehyde and thioacetal based paclitaxel dimer (PTXK); Anti-programmed cell death-ligand 1 peptide (dPPA); Urokinase plasminogen activator (uPA); Recombinant tissue plasminogen activator (rt-PA); Resiquimod (R848); Doxorubicin (DOX); Mesenchymal stem cells (MSCs); Chlorin e6 loaded gelatin nanogels (Ng/Ce6); Polymethacrylic acid nanoparticles loaded with Fe (III) and cypate (Cyp-PMAA-Fe); Lopinavir (LPV); sparfloxacin (SPX); Polycaprolactone-poly(ethylene glycol) (PCL-PEG); Glucose oxidase (GOx); Chloroperoxidase (CPO); Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

of stem cells (Cui and Madeddu, 2011; Tao et al., 2018). In particular, MSCs have showed inherent capability of potent tumor homing and inflammation induced migration, which is closely related to their expression of homing receptors, such as CXC motif chemokine receptor (CXCR) 4, CXCR2, cluster of differentiation 74 (CD74), in response to the corresponding cytokines expressed in tumor sites or injured tissues, such as stromal cell-derived factor 1 (Zhang et al., 2021). Most of the intravenous administrated MSCs are initially intercepted in the lung due to the filtration function of pulmonary vascular system and then migrate to the injured area in the lung (Nystedt et al., 2013). This property endows MSCs with advantages of excellent lung targeting ability and is extremely suitable for the targeted pulmonary diseases therapy. However, the administration of MSCs was reported to have potential risks of inducing pulmonary micro embolism (Wu et al., 2019a).

In this regard, the biomimetic nanoparticles using MSC membranes coating are developed as an alternative option to take the advantages of inflammatory homing while avoiding the potential risks of directly using MSCs. For example, Yang et al. showed the advantages of coating PLGA nanoparticles with MSCs membranes for targeted lung tumor treatment. The MSCs membrane coating effectively improved the cellular uptake by tumor cells, as well as the tumor targeting of PLGA nanoparticles, resulting in an efficient tumor cell killing (Yang et al., 2018a). In addition, Yin et al. utilized MSCs membranes to coat polymethacrylic acid (PMAA), which was loaded with iron and cypate, to structure Cyp-PMAA-Fe@MSCs. This carrier not only had high stability and good tumor accumulation, but also had excellent photothermal conversion efficiency, which was used in photothermal therapy of lung cancer (Yin et al., 2021).

Although MSC membrane coating has the advantages of tumor and inflammation targeting, its circulation time in the blood is shorter than that of RBCm. In addition, the acquisition of MSCs in a large number is relative inconvenient compared to RBCs (Liang et al., 2018).

3.5. Immune cells

Immune cell membrane biomimetic carriers also possess the ability of active targeting and immune escape, thus showing the potential as a vector for the targeting treatment against lung inflammation and lung tumor (Li et al., 2018). Currently, membranes harvested from macrophages and neutrophils are the most applied immune cell membranes for lung-targeted delivery.

3.5.1. Macrophages

Macrophages are the most population among immune cells, playing a crucial role during the immune response (Liang et al., 2021; Zhang et al., 2020). There are several superiorities of using macrophages to treat inflammatory diseases. Firstly, the inherent phagocytosis ability enables them to phagocytize diverse bacteria, viruses, injured cells and aging cells in nonspecific immunity. Additionally, macrophages are important antigen-presenting cells, which express antigen peptide major histocompatibility complex (MHC) and trigger subsequent immune response. Moreover, macrophages can mediate inflammatory response through the interaction between corresponding receptors on the surface of macrophage membrane and chemokines (Monocyte chemoattractant protein-1, etc.) at inflammatory sites (Zhang et al., 2020).

It has been revealed that macrophages have close interaction with lung tumor cells through the binding of $\alpha 4$ integrins on macrophages to vascular cell adhesion molecule-1 (VCAM-1), which is overexpressed in tumor cells (Chen et al., 2011). Such interaction between macrophages and tumor cells provides a potential application of using macrophage membranes for lung tumor-targeting delivery. For example, Cao et al. prepared macrophages membranes coated liposomes for targeting delivery of emtansine to lung metastases, achieving significant inhibition of tumor progression (Cao et al., 2016). Moreover, secretion of C-C chemokine ligand 2 (CCL2) from tumors was shown to promote the recruitment of CCR2-expressing macrophages, particularly notable for the preferential recruitment of macrophages in lung metastases (Bonapace et al., 2014). Exploiting the characteristics of the CCL2/CCR2 chemokine axis to actively recruit macrophages, Zhao et al. developed macrophage membrane coated nanoparticles for effective photothermal therapy of lung metastasis, which exhibited obvious aggregation in breast cancer lung metastasis (Zhao et al., 2018).

In addition to the tumor targeting ability, macrophage biomimetic nanocarriers further showed the potential of anti-inflammatory and anti-virus. Nanoparticles coated by alveolar macrophage membranes demonstrated the ability as decoys to prevent coronavirus from entering host cells, absorbing a variety of pro-inflammatory cytokines, thereby reducing lung injury and inflammation (Li et al., 2021b).

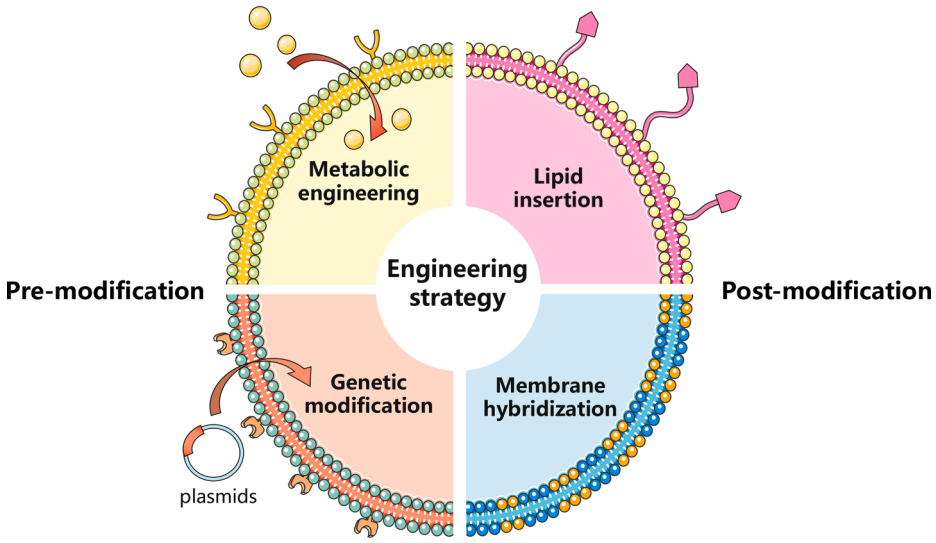

Fig. 1. Engineering strategies of biomimetic membrane: metabolic engineering, lipid insertion, membrane hybridization, and genetic modification.

3.5.2. *Neutrophils*

Neutrophils, as the most common white blood cells, participate in various inflammatory responses in vivo. The outbreak of inflammation leads to an increase of neutrophils, which serve as the first line to defend against pathogens in tissue infection or damage.

Inspired by the targeting property of neutrophil to inflammatory tissue, Wang et al. wrapped sparfloxacin (SPX) nanoparticles on the neutrophil membranes to treat lung inflammation. Compared with nanodrugs, neutrophil membrane coated nanoparticles showed superiority in accurate lung inflammation targeting (Wang et al., 2020a). An artificial super neutrophil, which has good inflammatory targeting and the ability to generate hypochlorous acid (HClO), has been developed to target and eliminate malignant tumor cells and pathogens. The experimental results showed that the artificial super neutrophil had good targeting and antitumor activity in the early lung premetastatic niche, as well as the already formed lung metastasis (Zhang et al., 2019a).

Presently, the major limitation of using immune cell-derived membranes is their immunogenicity. Because the major histocompatibility complex expressed in immune cells is high probabilistically inherited by their membranes (Oroojalian et al., 2021a).

3.6. *Bacteria*

Since the mutual recognition between biomolecules on bacterial membranes and host cells is the first step for bacteria adhesion and entry into target cells, bacterial membranes have become a novel drug-targeted delivery vehicle (Pizarro-Cerdá and Cossart, 2006; Yang et al., 2019). In particular, bacterial outer membrane vesicles (OMVs) extracted from the Gram-negative bacteria, which contains high levels of immunogenic proteins and adjuvants, is an alternative option to activate pathogen-associated innate and adaptive immune responses (Anwar et al., 2021). For example, bacterial OMVs are admitted as ideal components of bacterial vaccines, due to their rich in intact antigens, non-infectious characters, and the nanostructure (Anand and Chaudhuri, 2016; Kaparakis-Liaskos and Ferrero, 2015). These properties make OMVs with good ability to modulate the immune response. Li et al. used high mechanical pressure to drive Klebsiella bacteria through small gaps for inducing artificial budding and producing self-assembled bacterial biomimetic vesicles, which showed dual functions of stimulating humoral and cellular immune responses against antibiotic-resistant bacteria. These bacterial biomimetic vesicles using OMVs then induced potent defenses against drug resistant-Klebsiella pneumoniae infection in mice models (Li et al., 2021).

OMVs take significant advantages in large-scale production, partly due to their easy expansion *in vitro*. In addition, the relative ease to genetic engineer bacterial facilities the specifical designing and production of OMVs with desired functions. However, OMVs may cause excessive immune activation and lead to biosafety issues, because OMVs contain lipopolysaccharide and virulence factors on their surface (Naskar et al., 2021).

In conclusion, diverse cell-derived membrane biomimetic nanocarriers have been applied for the targeting treatments of pulmonary diseases, including pneumonia, asthma, primary, metastatic lung cancer, etc., showing the potentials for targeting delivery with good therapeutic outcomes. More examples of using membrane biomimetic nanocarriers for the targeted therapy of pulmonary disease were summarized in Table 1.

4. Engineering of biomimetic membrane for improved drug delivery

In order to overcome some limitations of natural cell membrane and to enhance the properties of membrane biomimetic carriers, cell membrane modifications were recently developed as a promising strategy (Yan et al., 2019), partly because the function of nanoparticles endowed by cell membrane mainly depends on its surface functional proteins (Guo et al., 2021). The cell membrane modification is carried out before destroying the natural cells (pre-modification), or introducing exogenous components into cell membranes after separation (post-modification). Presently, pre-modification includes genetic modification and metabolic engineering, while cell membrane post-modification includes lipid insertion and membrane hybridization (Fig. 1).

4.1. *Lipid insertion*

Lipid insertion is a method of binding targeting ligands to membrane coated nanoparticles through lipid anchors. In this strategy, the targeting part is first connected to the lipid molecule and then inserted into the cell membranes. The fluidity of the membrane bilayer allows the lipid chain to be inserted into the membrane coating by ultrasonic or physical extrusion (Luk and Zhang, 2015).

This strategy has been applied to anchor different ligands to the cell membrane to achieve specific targeting. For example, to enhance the specifical targeting ability to non-small cell lung cancer cells (A549) with high expression of CD44, hyaluronic acid (HA), the receptor of CD44, was applied to insert into RBCm. (Zhang et al., 2021c).

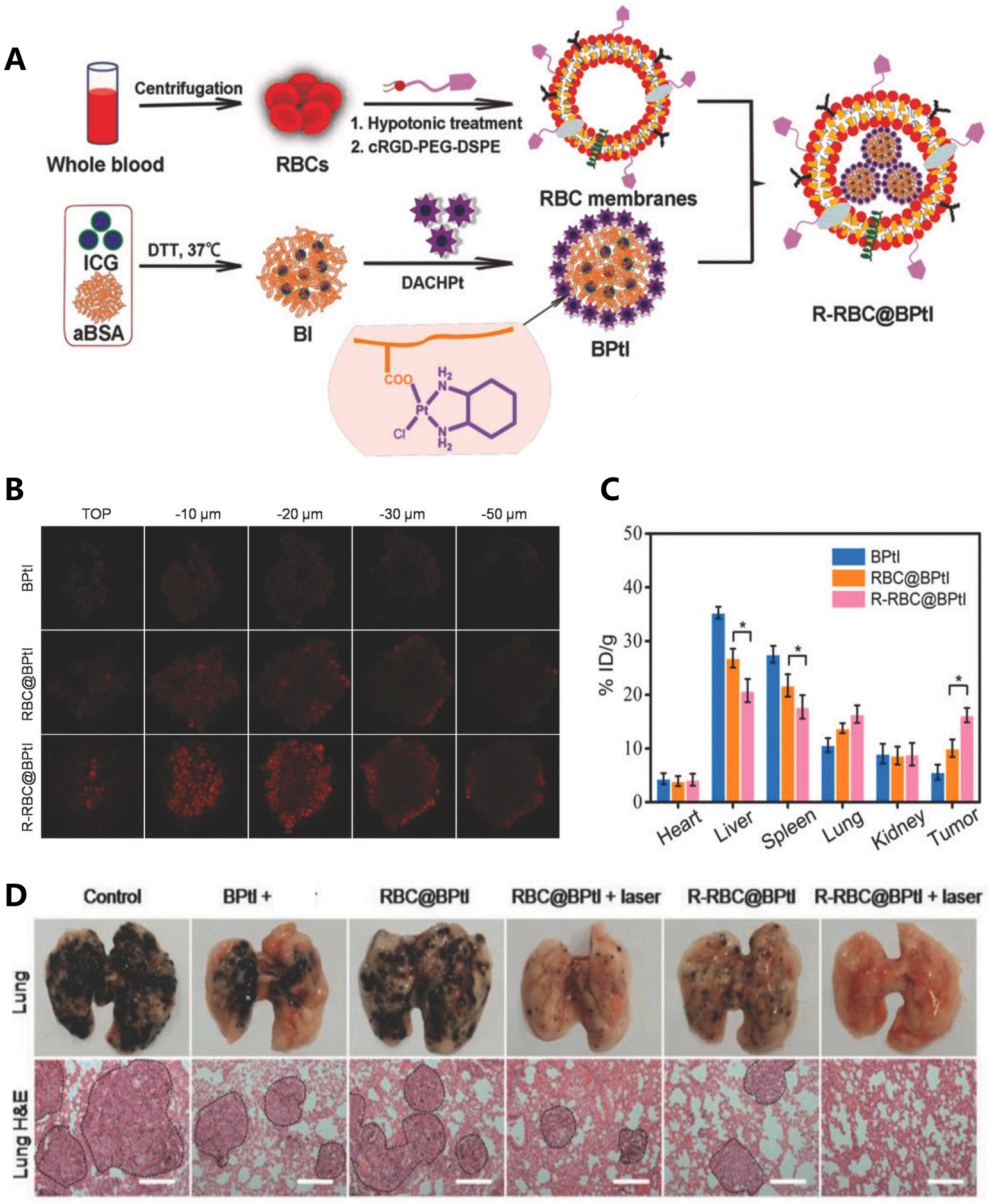

Fig. 2. Tumor penetration, biodistribution and therapeutic effect of membrane biomimetic nanocarriers constructed by lipid insertion. A) Schematic diagram of arginyl-glycyl-aspartate (RGD) peptide modified red blood cell membrane (RBCm) biomimetic carrier. B) Penetration ability in B16F10 tumor cell spheres. C) Biodistribution of different carriers after 24 h. D) Lung and hematoxylin-eosin (H & E) staining images after different treatments. (Scale bar = 100 μm) (Liu et al., 2018b). Copyright 2018, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In addition to polysaccharide ligands, lipid insertion has been utilized to anchor polypeptides. For example, in order to obtain higher tumor targeting ability, Arginyl-glycyl-aspartate (RGD) peptide was used to insert the RBCm, which can specifically recognize the overexpressed integrin receptor-like $\alpha v\beta 3$ in tumor cells (Chai et al., 2019; Fan et al., 2020; Huang et al., 2021; Zhang et al., 2018; Zhong et al., 2021). Wu et al. developed RBC camouflaged nanoparticles (RBC@BPtI), which coloaded photosensitizer indocyanine green (ICG) and 1,2-diaminocyclohexane-platinum (II) (DACHPt) to treat melanoma lung metastasis. The targeting ability of RGD enhanced tumor-specific cellular uptake and tumor penetration (Fig. 2B). In the melanoma lung metastasis model, the modified membrane biomimetic carrier showed better lung targeting (Fig. 2C) and antitumor effects (Fig. 2D) (Liu et al., 2018b).

In addition, some lipophilic molecules themselves also have the function of altering the properties of cell membrane after insertion. For example, Su et al. inserted the 1,1′- octadecyl-3,3,3′,3′- tetramethylindole tricarbocyanine iodide (DiR) into the RBC membrane. The DiR on the membrane can be converted into heat by near infrared light radiation for photothermal treatment of lung metastasis (Su et al., 2016).

Lipid insertion is a simple and efficient method, which provides a promising possibility for the functionalization of cell membrane biomimetic carriers. Lipids can not only act as anchors, but also carry specific functions, including photothermal conversion, pH response and the like.

4.2. *Membrane hybridization*

Membrane coating endows nanoparticles with specific biological functions. However, a single type of membrane packaging may not satisfy the complex practical applications. For example, RBCm has long blood circulation, but lacks targeting ability. Cancer cell membrane has the advantage of homologous targeting, but its immune escape ability is limited. Therefore, the combination of different cell membranes may provide multiple functions. For example, Peng et al. camouflaged the nanoparticles with a mixed membranes of RBCs and metastatic NCI-H1299 lung cancer cells (HRPD), which not only prolonged the circulation time, but also enhanced targeting ability (Peng et al., 2021). Another example is the fusion of membranes from RAW264.7 and 4T1 cells. The hybrid membrane coated with doxorubicin (DOX) loaded PLGA nanoparticles were prepared for the treatment of lung metastases

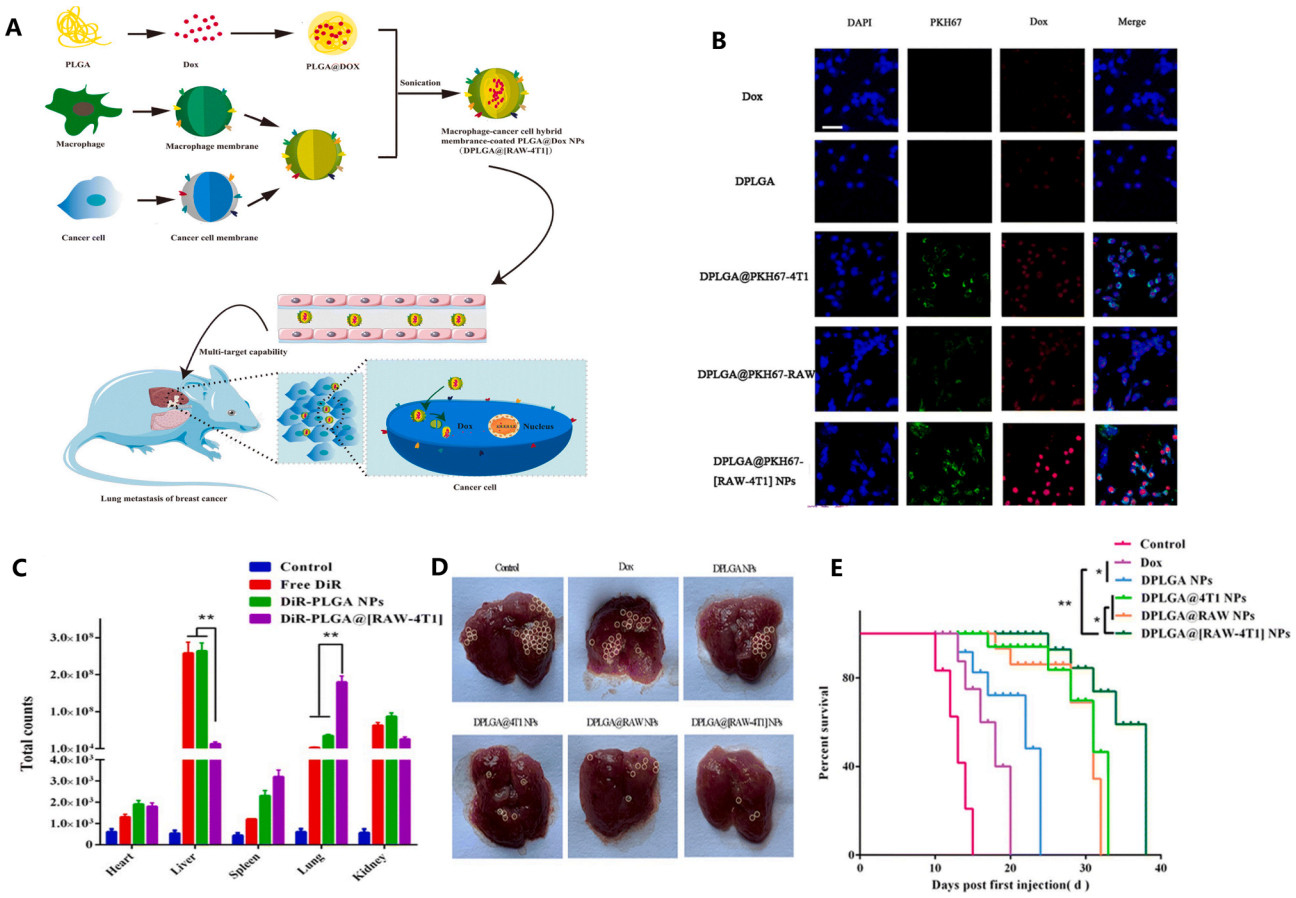

Fig. 3. The cellular uptake efficiency, biodistribution and therapeutic effects of membrane biomimetic nanocarriers constructed by membrane hybridization. A) Schematic illustration of hybrid membrane coated nanoparticles. B) Confocal laser scanning microscope (CLSM) fluorescence images of cell uptake. (Scale bar = 50 μm). C) Organ uptake of different carriers. D) Images of lung tumor nodules. E) Mean survival period after different treatments (Gong et al., 2020). Copyright 2022, BioMed Central Ltd.

from breast cancer. This membrane biomimetic preparation hybridized by macrophages and cancer cells has advantages of higher uptake capacity by tumor cells (Fig. 3B), increased distribution in the lung (Fig. 3C) and effective treatment against lung tumor metastasis (Fig. 3D and E) (Gong et al., 2020).

4.3. Metabolic engineering

Metabolic engineering is a method to change cell characteristics by regulating the natural biosynthetic pathway of cells. Metabolic substrates are first combined with functional parts and then cultured with cells for uptake and metabolism. These unnatural conjugates participate in related cellular metabolic processes by hijacking natural biosynthetic pathways, and then anchor on the cell surface (Han et al., 2019). Metabolic engineering includes sugar engineering and lipid engineering. Sugar engineering relies on the production of oligosaccharides and sugar conjugates (Biz et al., 2019; Lee et al., 2012). And lipid engineering utilizes natural lipid synthesis, such as cell membrane modified cytidine 5′- Diphosphate Choline pathway, some of which are usually metabolized in combination with choline analogues. Various functions have been obtained on the surface of the membrane, especially through the orthogonal connection of the membrane (Paper et al., 2018; Ricks et al., 2019; Tamura et al., 2020).

4.4. Genetic modification

Genetic modification refers to regulate the functional protein expression levels on the cell membrane by gene transfection for enhancing or obtaining specific functions. It has been reported that inflammatory endothelial cells recruit immune cells by up regulating the expression of VCAM-1, such as leukocytes expressing homologous ligand very advanced antigen-4 (VLA-4) (Nourshargh and Alon, 2014). To take advantage of this interaction, Zhang et al. gene transfected wild-type C1498 cell to overexpress VLA-4 and extracted the genetic modified membrane coated polymer nanoparticle core loaded with dexamethasone (DEX) for the treatment of pulmonary inflammation. The produced cell membrane biomimetic preparation showed higher affinity for target cells overexpressing VCAM-1 in *in vitro* experiment. Notably, compared with WT-NP, the accumulation of VLA-NP in the lung was significantly increased and it can effectively eliminate lung inflammation (Fig. 4) (Park et al., 2021).

Cell membrane modification methods of lipid insertion, membrane hybridization, metabolic engineering, genetic modification enrich the function of cell membrane gifted by their initial cells, making it great promising for a more efficient lung targeting drug delivery, especially in the complex internal environment. Applications of these membrane modification methods for lung targeting were summarized in Table 2. It is believed that these methods will provide more inspiration for promoting the application of cell membrane coating technology in the treatment of pulmonary diseases.

5. Challenges and prospects

Generally, the cell-derived membrane biomimetic nanocarriers possess several advantages including excellent biocompatibility, long-term internal circulation, immune escape, and inflammation/tumor

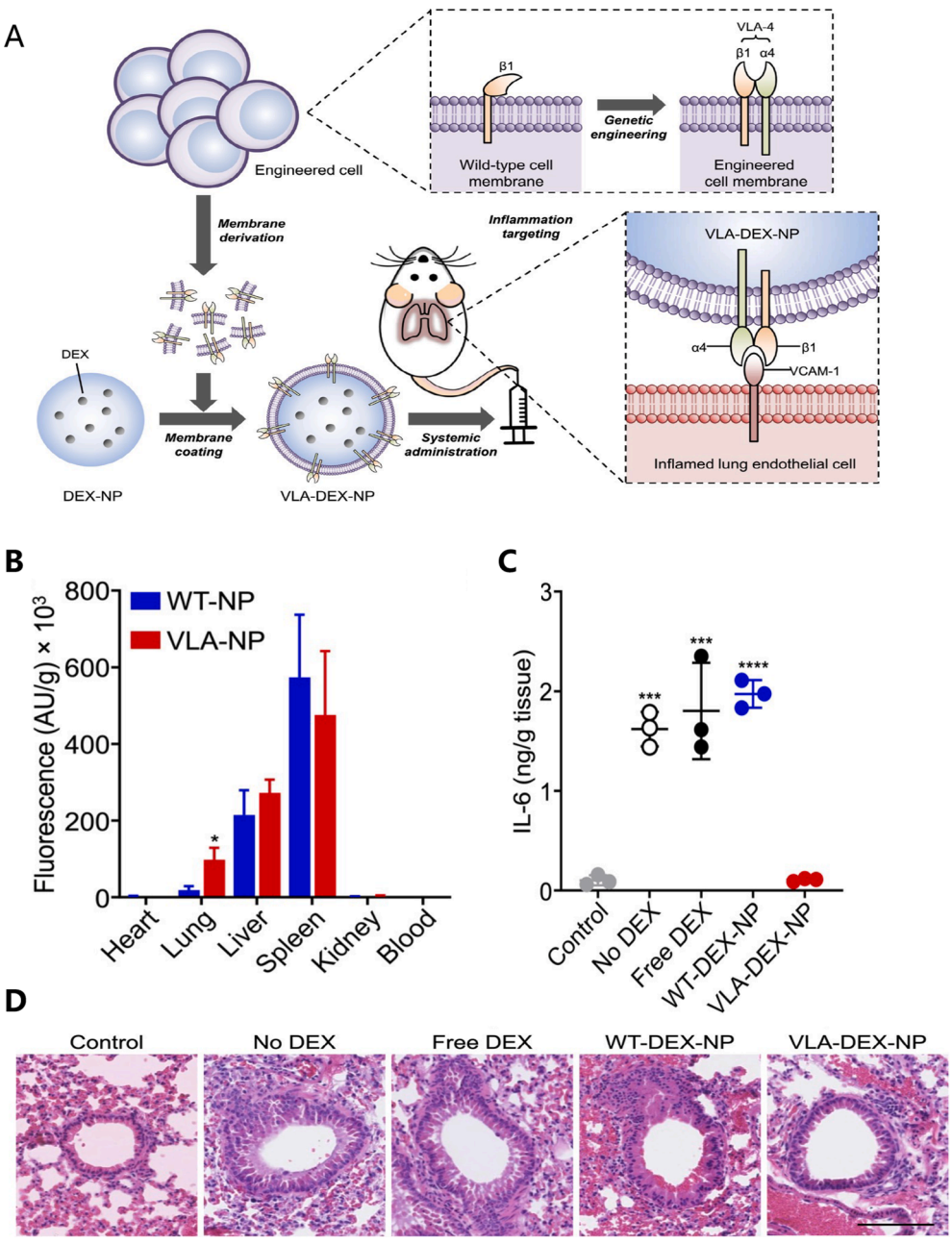

Fig. 4. The biodistribution and pulmonary inflammation elimination effects of membrane biomimetic nanocarriers constructed by genetic modification. A) Diagram of genetically engineered cell membrane coated nanoparticles with overexpression of very late antigen-4 (VLA-4) for inflammatory lung targeting. B) Biodistribution of membrane biomimetic carriers with or without genetic modification after intravenous injection. C) Interleukin 6 (IL-6) concentration in pulmonary sites after different treatments. D) H & E staining images in lung tissue after different treatments (Park et al., 2021). Copyright 2021, AAAS.

targeting, which endow bright potential as an efficient and biocompatible delivery strategy for the targeted therapy of diverse pulmonary diseases, such as lung cancer, pneumonia, asthma, pulmonary embolism and so on. Some advantages and limitations of cell membranes from diverse cell sources were summarized in Table 3.

However, limitations of this novel delivery strategy require further optimizations. Firstly, functional surface proteins are often inactivated under various *in vitro* conditions, making the applications of cell membrane camouflage nanocarriers being hindered by large-scale production. Moreover, despite of the good biocompatibility of these cell membranes coated nanoparticles, the biological behavior in long-term circulation is so far not fully understood. Therefore, the biosafety of membrane biomimetic preparations is worth of further study.

Another challenge is translating this delivery strategy to clinical application. Good manufacturing practice (GMP) is required to generate pure cell membrane with high yield, scalability, and reproducibility, which is a major challenge in the production of cell agents. In addition, most of the current studies are carried out on mice. However, the heterogeneous of the cell membrane proteins between mice and human beings may adversely impact the effectiveness and safety of this strategy when applied to human beings.

6. Conclusion

In conclusion, cell-derived membrane biomimetic nanocarriers have provided a promising way for the targeted treatment of pulmonary disease with high effectiveness and good biocompatibility. Although several limitations or weaknesses of this delivery strategy remain to be resolved, the outstanding advantages of cell-derived membrane coating have opened up a whole new way for the targeted treatment of pulmonary disease. Further studies focused on the cell membrane modifications for improved delivery ability and the large-scale production of cell membrane coated nanovehicles will further promote their applications.

Table 2
Engineering strategy of biomimetic membrane carriers for lung targeting.

Strategies	Cell membranes	Modifiers	Nanoparticles	Effects	Ref.
Lipid insertion	RBC	HA-DOPE	PTX, IR780	Actively targeting A549 cells	(Zhang et al., 2021c)
	RBC	RGD-PEG-DSPE	CS-6, DOX	Actively targeting TNBC cells	(Fan et al., 2020)
	RBC	RGD-PEG-DSPE	Black phosphorus	Improving tumor targeting by specifically recognizing $\alpha v\beta 3$	(Zhong et al., 2021)
	RBC	cRGD-PEG-DSPE	DACHPt, ICG	Actively targeting cancer tissues, enhancing tumor-specific cellular uptake	(Liu et al., 2018b)
	RAW 264.7	T7-PEG-DSPE	Saikosaponin D/ PLGA	Targeting ligands transfer ferritin receptors overexpressed in tumor cells	(Sun et al., 2020)
	RBC	DIR	PTX-PN	Providing powerful heat energy and promoting the release of core drugs under laser irradiation	(Su et al., 2016)
	A549	Liposome with MMP-9-sensitive peptide	PC@CO-LC	Promoting tumor cell penetration, pH triggered membrane rupture and drug release	(Zhang et al., 2021b)
Membrane hybridization	RBC	NCI-H1299 lung cancer cell	PLGA/DOTAP/ SAHA	Prolonging blood circulation time and homotype targeting of metastatic cells	(Peng et al., 2021)
	4T1	RAW 264.7	DOX/PLGA	Accumulating at inflammation sites and targeting specific metastasis	(Gong et al., 2020)
Metabolic engineering	4T1	Azide-cho, anti-CD205	MNCs	Preferentially recognized by CD8+ dendritic cells	(Li et al., 2019a)
Genetic modification	Wild-type C1498 cell	pQCXIP-$\alpha 4$	DEX	Targeting cells overexpressing VCAM-1	(Park et al., 2021)
	4T1-Fluc cancer cell	mem-KR	/	Expressing KR protein and producing cytotoxic ROS under laser irradiation.	(Kim et al., 2019)

Abbreviations: Hyaluronic acid conjugated dioleoyl phosphoethanolamine (HA-DOPE); Human non-small cell lung cancer cells (A549); Gamabufotalin (CS-6); Triple negative breast cancer (TNBC); Arginyl-glycyl-aspartate (RGD); 1,2-distearoyl-snglycero-3-phosphoe-thanolamine-N-ployethyleneglycol (DSPE-PEG); 1,2-diaminocyclohexane-platinum (II) (DACHPt); Indocyanine green (ICG); Mouse macrophage model cells (RAW 264.7); 1,1′- octadecyl-3,3,3′,3′- tetramethylindole tricarbocyanine iodide (DiR); Matrix metallopeptidase 9 (MMP-9); Citraconic anhydride-grafted poly-L-lysine (PC); Lipoic acid-modified polypeptide (LC); 1,2-dioleoyloxy-3-(trimethylammonium) propane (DOTAP); Suberoylanilide hydroxamic acid (SAHA); Mouse breast cancer cells (4T-1); Magnetic nanoclusters (MNC); Dexamethasone (DEX); Vascular cell adhesion molecule-1 (VCAM-1); Killer Red (KR); Reactive oxygen species (ROS).

Table 3
Advantages and limitations of cell membranes derived from different kinds of cells.

Sources	Biomarkers	Advantages	Limitations	Ref.
RBCs	CD47	Long circulation time, simple techniques for membrane surface decoration	Lack targeting, low drug-loading capacity	(Xia et al., 2019)
Platelets	P-selectin, CD47	Inflammation targeting, immune escape	Limited assessment of immunogenic potential,	(Kunde and Wairkar, 2021)
Cancer cells	T antigen-galectin-3	Homologous targeting	Potential concerns regarding safety	(Harris et al., 2019)
MSCs	CXCR4 and other chemokine receptors	Inherent tumor-tropic and inflammatory migratory	High preparation cost	(Wu et al., 2019b)
Immune cells	$\alpha 4$ integrins, CD45, CD47	Immune evasion, metastatic tumor targeting	Complex workflow to extract and purify membrane, immunogenicity	(Oroojalian et al., 2021b)
Bacteria	Virulence actors	Immune activation	Potential concerns regarding safety	(Anwar et al., 2021)

Abbreviations: Integrin-associated protein (CD47); CXC motif chemokine receptor 4 (CXCR4); Leukocyte common antigen (CD45).

Author contribution

Xixi Zheng: Writing - original draft. **Tianyuan Zhang:** Writing - review & editing. **Ting Huang:** Reviewing. **Yanjun Zhou:** Reviewing. **Jianqing Gao:** Conceptualization & Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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