Biomaterials Translational

Membrane-coated nanoparticles as a biomimetic targeted delivery system for tumour therapy

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biomimetic targeted delivery system; membrane-coated nanoparticles; membrane-coated technology; tumour therapy

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ABSTRACT

Drug therapy towards tumours often causes adverse effects because of their non-specific nature. Membrane-coated technology and membrane-coated nanoparticles provide an advanced and promising platform of targeted and safe delivery. By camouflaging the nanoparticles with natural derived or artificially modified cell membranes, the nano-payloads are bestowed with properties from cell membranes such as longer circulation, tumour or inflammation-targeting, immune stimulation, augmenting the performance of traditional therapeutics. In this review, we review the development of membrane coating technology, and summarise the technical details, physicochemical properties, and research status of membrane-coated nanoparticles from different sources in tumour treatment. Finally, we also look forward to the prospects and challenges of transforming membrane coating technology from experiment into clinical use. Taken together, membrane-coated nanoparticles are bound to become one of the most potential anti-tumour strategies in the future.

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Introduction

Nowadays, drug therapy is a vital component of medicine and widely used in clinical practice. However, the therapeutic efficacy of drugs often unable to meet the demands due to their non-specific nature and poor pharmaceutical performance. Once the drug is administrated systematically, only a small amount can be deposited in specific positions and fulfill its role.[1-3] To improve the penetration ability of the drugs towards the physiological barriers and optimise the therapeutic efficacy, the concept of nano-medicine is proposed. Nanoparticles (NPs) can be transported more specifically to position by either passive distribution or active targeting mechanisms.[1,4,5] Nevertheless, the nanodrugs are often recognised as foreign elements and cleared by the immune system rapidly before coming into effect. Besides, the off-targeting effect towards the normal tissues often leads to multiple adverse effects or systematic damages.[5] For decades scientists were exploring novel delivery methods to address the challenges. The ideal delivery system should have the following characteristics, high targeting abilities, high biological safety, and low influence to the delivered drugs.[6]

Membrane-coating technology is an advanced strategy that has shown great promise as a delivery system. By camouflaging the NPs or nanodrugs with several classes of biological membranes, membrane-coated NPs (MCNPs) have been endowed with the specific properties of the source cell such as prolonged circulation time, optimised biocompatibility, better immune evasion ability and improved targeting ability.[7-9] For drugs with poor stability, solubility, or difficulty to be coated directly with membranes (such as particles with positive charges on the surface), nanocarriers can be used to load the drugs before coated with membranes which enables the loaded drugs to exist stably in the body during circulation. Additionally, the coating membrane will not affect the physical and chemical properties of the inner cores as well as preserve the integrity of NPs from complex microenvironment.[7-9]

Cells are fundamental units of life, which tend to accumulate and reside in specific microenvironments through interactions between membrane receptors and the environment. In that case, some MCNPs can achieve similar effect and target specific niches.[1, 7-9] Nevertheless, the targeting ability of natural cell membranes is often unsatisfactory for direct biomedical application. To further enhance the targeting ability of the carrier, the outer membrane can be modified with chemical ligands with different functions to achieve engineered membrane-coated nanocarriers. Compared with traditional drug delivery strategies, MCNPs provide a hybrid delivery system exploiting both multifunctional advantages and biosafety nature, which provides a better option for future pharmaceutical development.[1, 4, 6-8]

In this review, the development history of membrane coating technology is reviewed. The preparation, characterisation, biomedical applications of MCNPs in different fields are updated. We classify the MCNPs into several types depending on the source of membranes and review their current research status, respectively. Finally, we review the future opportunities and challenges associated with MCNPs (**Figure 1**).

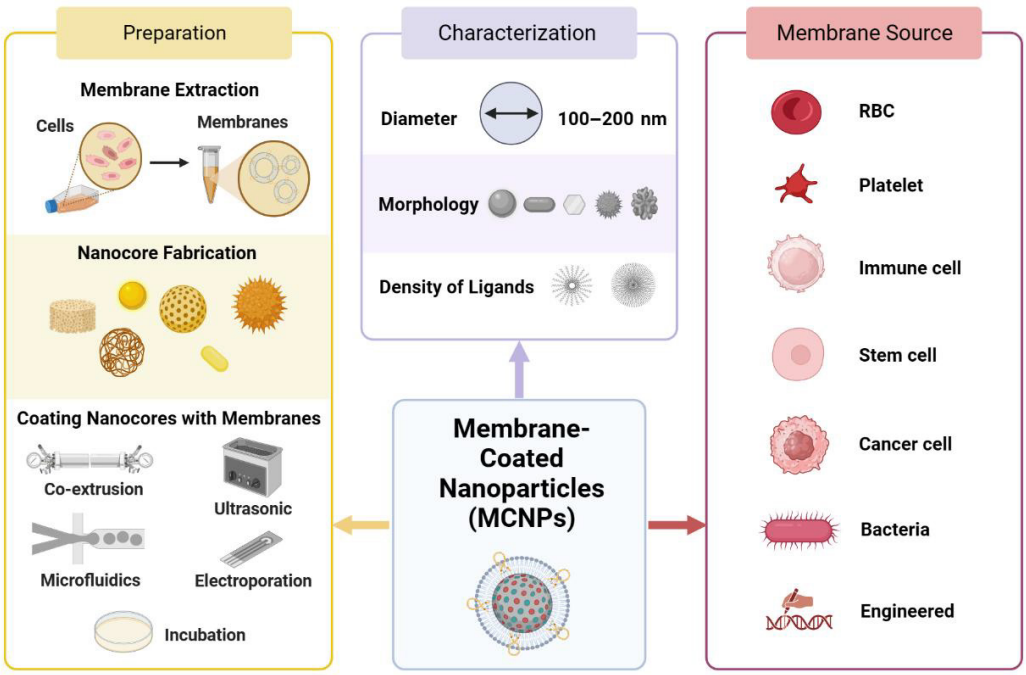

Figure 1. Schematic diagram of membrane-coated delivery system for targeted cancer therapy. The preparation, characterisation, and common membrane sources of membrane-coated nanoparticles in targeted cancer therapy. Created with BioRender.com. RBC: red blood cell.

Retrieval Methods

PubMed and Web of Science (WOS) core collection database were searched as search engines to find relevant publications and reports of MCNPs in tumour therapy. The search strategy or formula of our searching was "(membrane coated) OR (membrane coating) OR (membrane camouflaged) OR (membrane camouflaging) OR (membrane biomimetic) OR (membrane cloaked) OR (membrane mimicking)) AND ((tumour) OR (cancer)". The publication year duration was limited from 2015 to 2024. 3676 articles were retrieved on December 15, 2023 before being reviewed and selected. Relative research article and reviews were screened and saved in Endnote database.

Membrane-Coating Technology

The development of membrane-coating technology

The physiological barriers in human body often hinder the nanodrugs from transporting to specific positions. In addition, most of the conventional NPs are recognised as exogenous substances and rapidly cleared by reticuloendothelial system, leading to shorter circulation time and even toxic immune reactions.[1-3] To improve the performance of NPs, multiple

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attempts were made. Modifying the surface of NPs with chemical ligands such as poly(ethylene glycol) (PEG) molecules is a widely used technology. PEGylation could protect the NPs from non-specific protein absorption and shield the NPs from clearance, which improves their circulation time and biocompatibility.[10-12] Nevertheless, these nanocarriers exert their tumour-targeting ability via enhanced penetration and retention effect exclusively. Nowadays, more and more researchers are focusing on delivery systems with biomimetic active tumour-targeting strategies.[7]

Membrane-coating technology shows better performance for their cell-mimicking properties.[2, 5, 6] With The earliest report of MCNPs was in 2011, Hu et al.[13] designed a core-envelope structure NP via coating the poly(lactic-co-glycolic) acid (PLGA) particles with membranes extracted from red blood cells (RBCs) to improve the circulation time of NPs. Since then, the source of membranes has been expanded rapidly, from simple lipid membranes to engineered membranes.[14, 15] The disruptive advantages of membrane-coating technology are its natural derived nature, editability and functional scalability. The MCNPs borrow the envelope of the natural cell structure, which can interact with the complex microenvironment such as proteins, surrounding cells and extracellular matrix. These interactions bestow the MCNPs with high biocompatibility that avoid immune identification and clearance, and protect the encapsulated drug from being destroyed by enzymes in the blood circulation.[4, 7, 8, 15] Besides, to match different sizes of nanocores according to different needs, the size of membrane vesicles can be adjusted artificially within a certain range. Large number of functional proteins were presented on the surface of envelope membranes, endowing the MCNPs with specific capabilities like anti-phagocytosis ability, disease site-navigating ability, immune-presentation ability, which enrich the functions of nanocarriers.[1, 2, 6] To obtain advanced nanocarriers with all the functions researchers acquired, the membrane envelopes can be updated by several methods, such as surface chemical modification, gene editing, membrane fusion. The final engineered nanocarriers concentrate the advantages of natural membranes and artificial polishing, which has better prospects and development opportunities.[16, 17] Apart from coating nanodrugs with cell membranes, there are currently methods for transporting nanodrugs with living cells directly. Wu et al.[18] loaded magnetic mesoporous silicon NPs containing doxorubicin in active neutrophils to penetrate the blood-brain barrier, achieving better navigation and anti-glioma effects.

The preparation of membrane-coated nanoparticles

MCNPs are mainly composed of two components, the outer cellular membrane, and the inner synthetic nanocores. The preparation methods of MCNPs can be divided into three parts, extracting and purifying the membranes, designing and fabricating the nanocores, and finally, coating the nanocores with extracted membranes to obtain MCNPs (**Figure 2**).[8, 16]

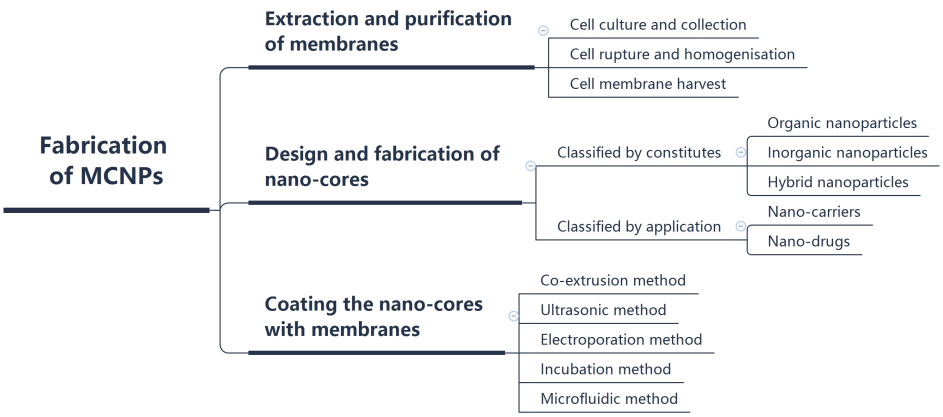

Figure 2. The fabrication of MCNPs. The fabrication of MCNPs contains three major process, extraction and purification of cell membranes, design and fabrication of nanocores, coating the nanocores with membranes. Created with Xmind Software. MCNP: membrane-coated nanoparticle.

Extraction and purification of membranes

To extract purified membranes from intact cells, three vital procedures should be finished. First comes cell culture and harvesting. During this phase, bacteria-free and gentle operation should be noticed. For cells extracted from blood, the resource is steady and the collection protocol is mature. Membranes derived from cell lines need to be cultured in the laboratory, while the source is stable and researchers can obtain sufficient quantities of cells depending on their demands.[16, 17] Cells are harvested by differential centrifugation before ruptured or homogenised. Depending on the nature of different cells, the rupture protocols are dissimilar. For anucleate cells such as RBCs and platelets (PLTs), hypotonic solutions are widely used to swell and burst the outer membrane and release the inner cell contents. To enhance the efficiency of the rupture, freeze-thaw cycles can be introduced to form intracellular ice crystal which disrupt the outer membrane more thoroughly. As for nucleate cells like white blood cells

and cancer cells and Gram-negative bacteria, the rupture methods are much more complicated. Mechanical grinding, ultrasonication or freeze-thaw cycle-erosion may be introduced and the outcome homogenate will be further processed with gradient centrifugation to isolate pure outer membranes from organelle or nuclear membranes. One of the drawbacks of the membrane extraction method is that large-scale manufacture cannot be realised at present. To preserve the functional proteins expressed on the surface of MCNPs, the entire extraction and purification process should be carried out in ice bath environment. In addition, ethylenediaminetetraacetic acid solution should be used instead of trypsin when digesting and collecting cells for trypsin may do harm to the structure of membrane proteins. Besides, protease inhibitors such as phenylmethylsulfonyl fluorid and cocktail should be added to prevent protein degradation or destruction. Then the obtained cell membrane solution is washed several times with pre-cooled phosphate buffer solution to remove mixed organelles and cytoplasm.[7, 16, 17, 19, 20]

Design and fabrication of nanocores

To fit in the nanocore structures, the NPs should meet some basic demands. For example, the surface of NPs should be negatively charged, so that NPs can exist stably in membrane leaflet with negatively charged surface, ensuring the cell membrane wraps the nanocore right side out.[16, 21] NPs can be artificially divided into three categories, namely organic NPs, inorganic NPs, and hybrid NPs. Organic nanocores include polymers (such as PLGA, polydopamine), hydrogels, biological macromolecules (such as albumin, peptides, RNA), and small molecule inhibitors. Inorganic NPs consist of two major categories, namely metal NPs (such as gold NPs, ferric oxide NPs) and non-metal NPs (such as silicon NPs). In recent years, there have been some new types of hybrid NPs that cannot be simply classified into these two categories, such as metal-organic frameworks, which have been widely concerned and applied due to their superior physicochemical properties.[22-25] According to the usage of NPs, the nanocores can be roughly divided into two categories, namely nanocarriers and nanodrugs. When used as drug carriers, nanocores should possess specific characteristics which are conducive to drug loading, such as high porosity, large surface area. In addition, some nanocarriers have also shown microenvironmental responsiveness (i.e., pH responsiveness, photosensitiveness). For example, alkaline polymers can reactively decompose in inflammatory tissues (pH = 6.5) and tumour tissues (pH = 6.5–7.2), thereby releasing the drugs loaded inside them to achieve controlled release at the time of localisation.[26] Besides, photothermal materials like melanin granules or polydopamine NPs can convert light energy into thermal energy under infrared irradiation.[27] When the nanocores are used as anti-tumour drugs, they can exert direct or indirect effects according to the mechanism of action. Antineoplastic drugs, such as doxorubicin, platinum-based chemotherapeutic agents, can be directly coated in the membrane vehicles and delivered to the tumour tissues before exerting anti-tumour effect. Indirect therapeutic nanocores like photothermal and photodynamic agents (such as indocyanine green), and starvation therapy drugs (such as glucose oxidase), which can inhibit proliferation or migration of tumours by changing the physical and chemical conditions of the tumour microenvironment, are also widely concerned, and shed lights on future advanced anti-tumour strategies. The composition of the nanocore can be a single agent or a combination of multiple drugs. Specific combination of components can exert synergistic tumour-killing effect as well as reduce the dosage of each component which lower the side effects.[19, 20, 26, 28]

Coating the nanocores with membranes

Coating the prepared biological membranes on the surface of nanocores is one of the most critical steps in the preparation of MCNPs, and it is also a research frontier in recent years. At present, co-extrusion is the most used method in MCNPs' fabrication. The homogenised mixture of cell membrane and nanocore is pressurised through porous polycarbonate membrane with mini-pores in the extruder back and forth for many times. The mechanical force generated by the extrusion forces the cell membrane to wrap the nanocore without damaging the structure and function of the cell membranes. The diameter of the core-envelope configuration obtained by extrusion can be artificially controlled by the pore size on the polycarbonate films, for example, extrusion with a 400 nm pore size polycarbonate film can obtain MCNPs with a particle size ranging around 400 nm, and the remaining membrane residues that is not encapsulated on the nanocore will be removed by differential centrifugation.[29] Other coating methods include ultrasonic method, microfluidic method, electroporation method and co-incubation method.[7, 16, 30] Sonication method refers to coating the membranes onto the NPs under ultrasonic conditions. The membranes are destabilised which make them spontaneously polymerized on the surface of NPs via the interactions of surface charges. Due to its passive and random nature, this method has lower yield than co-extrusion, and the sizes of MCNPs cannot be accurately controlled. The integrity of membrane proteins may be damaged during the sonication, which made this method rarely used. Recently, microfluidic electroporation method is emerging as an advanced technology which can create core-envelope configuration by microfluidic pulse shock tube. Through the delicate control of the voltage, current duration and flow rate of the homogenised mixture, the stable generated electrical pulses can break the dielectric layer of the membrane structures, and push the negatively charged nanocore into the hole punched by the current. Due to the fluidity of the phospholipid bilayer membrane, the pores are slowly closed after the creation of core-envelope structures, so that the NPs are completely wrapped. This method has higher yields than sonication method and is more protective of membrane proteins. Although it is expensive, it may obtain large number of MCNPs that meet the requirements in large quantities in the future.[30] MCNPs can also be fabricated by directly co-incubating nanocores with living cells, inducing living cells to engulf NPs. MCNPs will be secreted in the form of exosome-like vesicles, however, the low yield, completely uncontrollable particle size range, and complex vesicle contents making this method unsatisfied to use directly.[31-33] In summary, co-extrusion is the most mature method for the synthesis of

MCNPs at present, and microfluidic electroporation method may take its place in the future.

Characterisation of membrane-coated nanoparticles

The function of biomaterials *in vivo* depends on their excellent physical and chemical properties. Therefore, the characterisation of MCNPs, such as particle size, shape, surface potential, and ligand density, will have crucial impacts on the absorption, distribution, metabolism, and excretion of NPs (**Figure 3**).[34]

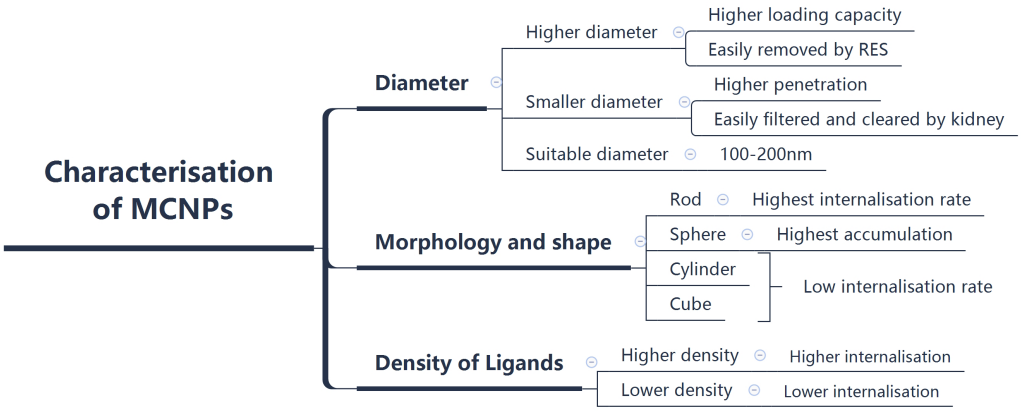

Figure 3. Characterisation of MCNPs. Characteristics such as diameter, morphology and shape of MCNPs, and the density of ligands on the surface of MCNPs have crucial impacts on the behaviour of MCNPs. Created with Xmind software. MCNP: membrane-coated nanoparticle.

Diameters of membrane-coated nanoparticles

The diameters of nanomaterials can directly affect drug loading, circulating half-life *in vivo*, and the ability to target and penetrate tumour tissues. On the one hand, taking the most common spherical NPs as an example, particles with smaller particle size are more likely to penetrate and accumulate deeply in tumours due to enhanced penetration and retention effect. It has been found that spherical NPs with diameters around 50 nm have the fastest uptake rate and highest cumulative concentration in mammalian cells.[34, 35] However, small particles are also tended to accumulate in the normal tissues and organs, resulting in organ toxicity, such as liver and kidney damage. In addition, NPs with a diameter of less than 10 nm are easily filtered and cleared by kidneys before exerting therapeutic effects. Therefore, the diameters of MCNPs should not be less than 10 nm. On the other hand, although NPs with larger particle size have higher drug loads, NPs with a diameter greater than 200 nm are easily removed by the reticuloendothelial system. In addition, they can also activate the complement system and accumulate in the liver and spleen.[36]

Particle size is crucial to the function of ligand-receptor interaction. A single receptor has little ligand-binding force to the surface of tumour cells, making it difficult to adhere or exert signal transduction. MCNPs with a larger radius of curvature can concentrate more receptor-ligand interactions locally, which significantly reduce the local free Gibbs energy, inducing the endocytosis of the MCNPs by tumour cells. Above all, MCNPs with a diameter ranging from 100 to 200 nm are the most suitable.[36, 37]

Morphology and shape of membrane-coated nanoparticles

The shape of NPs is associated with cellular uptake ability. It is reported that rod NPs have the highest internalisation rate, followed by spheres, cylinders, and cubes. Although the absorption rate of nanorods is higher than that of spherical NPs, the increase of the aspect ratio of nanorods will reduce the total accumulation in cells. In other words, the uptake rate of spherical NPs is lower than that of rod particles, but the total uptake is larger. So far, there have been few studies focusing on non-spherical NPs. Limited studies have indicated that the interaction between non-spherical NPs and cells is more complex than that of spherical particles. When the membrane-coated nanorods interact with cells, the number and density of receptors that can be invoked on the long-axis and short-axis are different, resulting in different modes of internalisation. The potential mechanism needs to be further investigated and revealed.[36-39]

Density of ligands on the membrane-coated nanoparticles

MCNPs can actively target tumour cells through ligands on the membrane surface, such as antibodies (α-Herceptin, Rituxan), peptides (Arg-Gly-Asp (RGD) sequence, Asn-Gly-Arg sequence), aptamers, folic acid molecules, β-mannose. These ligands can achieve a high degree of targeting by binding to receptors highly expressed on tumour cells or in tumour microenvironment. Higher ligand density can greatly reduce the local Gibbs free energy by forming cross-linked ligand-receptor clusters on the surface of the tumour cell membrane, thereby promoting the phagocytosis of MCNPs.[39, 40]

Different Types of Membrane-Coated Nanoparticles with Different Functions

In the former part we have discussed the classifications of nanocores, in which we focus on the unique functional characteristics of MCNPs given by nanocores. According to

the source of coating membranes, MCNPs can be divided into several groups. In this section we discussed the application of several groups of widely used classifications in the treatment of tumours (**Figures 4** and **5**).

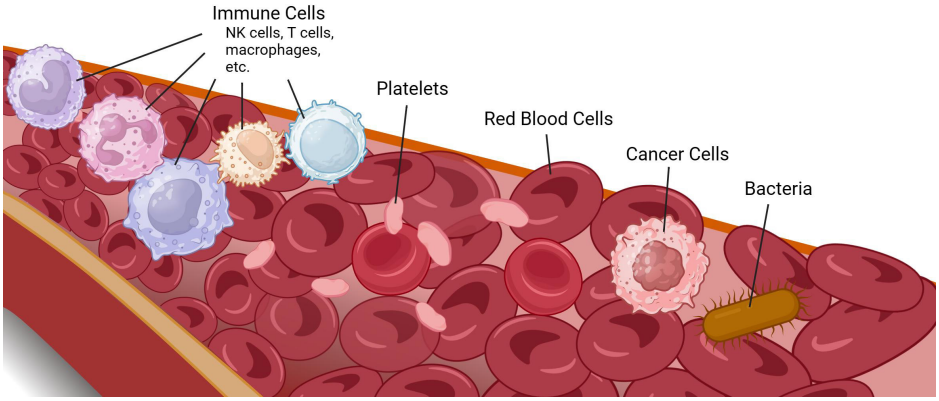

Figure 4. Common sources of membrane materials in MCNPs. The most common natural membrane sources of MCNPs are RBCs, platelets, cancer cells (and stem cells), immune cells and bacteria. Different sources of cell membrane have different physical or chemical properties. Created with BioRender.com. MCNP: membrane-coated nanoparticle; NK: natural killer; RBC: red blood cell.

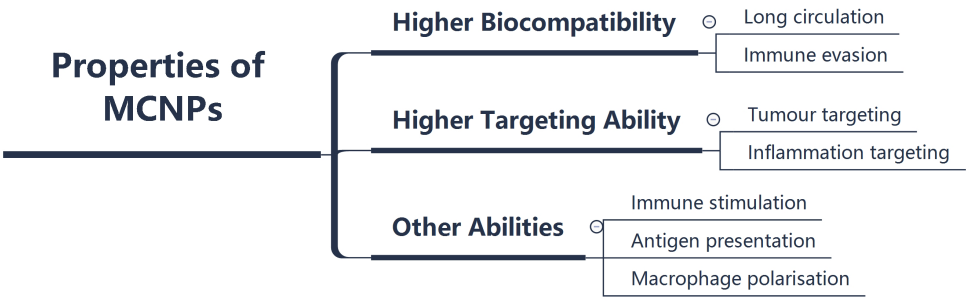

Figure 5. Properties of MCNPs. The membranes can endow the MCNPs with properties such as higher biocompatibility, higher targeting ability and some specific capabilities. Created with Xmind software. MCNP: membrane-coated nanoparticle.

Red blood cell membrane-coated nanoparticles

A variety of biomembranes can prolong the cycle time of drugs by camouflaging foreign antigenic epitopes. The most representative of which are erythrocytes. RBCs are the most abundant cellular component in the human body, with a cycle life of up to 120 days. RBCs are the simplest cells with almost no organelles, which makes it easy to rupture and purify to collect cell membranes.[14, 41, 42] On the surface of RBCs' membranes, self-identification markers (i.e., CD47, complement regulatory molecules) are highly expressed.[43-46] The presence of these markers can interact with the signal regulatory protein-α receptors on the macrophages, and preserve the inner nanocores from immune identification and rejection, prolonging the circulation time of MCNPs. Longer retention time and immune evasion will promote the accumulation of MCNPs in disease sites via enhanced penetration and retention effect.[42, 47, 48]

In 2011, Hu et al.[13, 15] extended the half-life of the NPs *in vivo* from 15.8 hours to 39.6 hours after coating the RBC membrane on the surface of PLGA nanospheres. Ren et al.[49] used erythrocyte membrane-coated magnetic nanoclusters for image-guided photothermal therapy. Rao et al.[50] designed erythrocyte membrane-coated ferric tetroxide NPs, which significantly increased the antiphagocytic ability of the MCNPs compared with the ferric tetroxide NPs alone or NPs modified by PEG surface. The distribution of nanodrugs in the liver and spleen was also significantly reduced. These results indicate that erythrocyte membrane coating is a promising strategy for long circulation drug delivery.

Platelet membrane-coated nanoparticles

PLTs are a group of acaryotic cells that also abundant in circulation, playing important roles in coagulation regulations.[51] PLTs are widely used as membrane sources in

MCNPs fabrication, endowing MCNPs with longer retention time and immune evasion ability. Besides, PLT-derived membrane envelopes also have their unique functions such as anti-inflammation or tumour targeting ability. Their targeting ability comes from tendency towards adhesive proteins expressed on formed thrombosis, subendothelium, activated endothelial cells and even circulating cancer cells.[51-56] The special characteristic can accumulate the MCNPs and the payloads within the tumour and realise targeted therapy effect.[57] Zhuang et al.[58] reported a PLT membrane-coated metal-organic framework NPs to delivery high concentration of small interfering RNA *in vivo*, and realised pH-reliable release before silencing targeted genes and exerting significant anti-tumour efficacy. Bahmani et al.[59] transported resiquimod (R848), a Toll-like receptor agonists, via PLT membrane-camouflaged nanocarriers. They tested the anti-tumour effect of obtained nanoplatform in solid tumours such as colon and breast cancer model, augmented immune activation were observed which leaded to complete tumour regression and inhibited lung metastases.[59]

Immune cell membrane-coated nanoparticles

Immune cells consist of dendritic cells (DCs), natural killer (NK) cells, macrophages, T cells, neutrophils. The existence of chronic inflammation is one of the characteristics of tumours. A variety of immune cells, including lymphocytes, granulocytes, macrophages, NK cells, often infiltrate in the tumour tissue, regulating the tumour microenvironment.[60] Researchers used to regard immune cells as defenders of the body, however, advanced sequencing methods reveal that immune cells can be divided into multiple sub-groups which act totally different roles in inflammation and tumour microenvironments. For example, macrophages can be artificially classified into two subsets, namely M1 and M2. M1 macrophages are regarded killers against bacteria, viruses, and tumours via producing proinflammatory cytokines and eliminating pathogens through phagocytosis. M1 macrophages can also present antigens to T cells and activate powerful cell-mediated immune effects. Nevertheless, M2 macrophages act as anti-inflammation cells, exerting profound effect in wound healing and immune regulation.[61, 62] In the early stage of tumourigenesis, the immune cells infiltrated in the tumour tissue mainly act as anti-tumour defenders, while in the middle or late stages of tumour development, immune cells recruited by tumour cells often promote tumour growth and metastasis. In that case, membrane materials derived from different subtypes of immune cells may confer different properties, or even completely opposite effects.[63, 64]

Macrophage membrane can promote the adhesion between NPs and cells, and exert certain tumour targeting ability. Neutrophil membrane coating can improve the permeability of NPs to tissues and venous walls, thereby promoting their targeting ability to tumour cells. NK cell membrane coating can bind to receptors on tumour cell membranes and exert a tumour-killing effect directly.[65] Parodi et al.[21] coated macrophage membranes on the surface of silicon-mesoporous NPs, protecting nanodrugs from recognition and clearance by other immune cells in the body. The obtained MCNPs can recognise inflammatory receptors that highly expressed on the tumour vascular endothelium through membrane proteins such as CD11a, accumulating the nanodrugs in the tumour tissues.[21] To figure out the potential recognition mechanism of macrophages, Zhang et al.[66] found that C-X-C motif chemokine receptor 1 and C-X-C motif chemokine receptor 2 receptors expressed in tumour tissues may play a role in guiding the enrichment of macrophage MCNPs in tumours. When the researchers knocked down the expression of these two inflammatory receptors in tumours, the accumulation ability of MCNPs in tumour tissues significantly decreased.66 Bhattacharyya and Ghosh[67] coated tumour necrosis factor-α modified macrophage membranes onto chitosan-based NPs, in which tumour necrosis factor-α-modified cell membranes were collected from macrophages co-incubated with bacterial lipopolysaccharide for 4 to 5 hours. The functionalised macrophage membranes can exert concentration-dependent anti-proliferation effect, as well as promote tumour apoptosis, which may be potential strategy for a variety of other disease models, such as rheumatoid arthritis.[66, 67] Meng et al.[68] designed a kind of MCNP via coating macrophage membranes on the surface of ferric oxide NPs, which improved the circulating half-life and tumour targeting ability of NPs. These studies suggest that immune cell membranes, especially macrophage membranes, are a potentially effective source of tumour cell targeting vehicle.[68]

Tumour metastasis often relies on the migration and colonisation of circulating tumour cells (CTCs) in the blood. Locating and eliminating CTCs is a vital measure to solve tumour metastasis from the beginning. Activated neutrophils can recognise and kill CTCs through adhesion molecules on the membrane surface.[69] Based on this, Kang et al.[70] designed a neutrophil membrane-coated biomimetic system with PLGA as nanocore, which can effectively target and kill CTCs, and recruit many immune cells into the tumour lesions, which ultimately reduced the tumour burden and the number of metastases significantly. Cao et al.[71] coated neutrophil membranes on the surface of PEG/PLGA for the treatment of pancreatic cancer. They found that MCNPs can effectively penetrate the blood-pancreas barrier and enter pancreatic cancer tissues to exert anti-tumour effects. The tumour growth and liver metastasis were significantly reduced, resulting in prolonged overall survival time in patients with pancreatic cancer.[71]

In addition to neutrophils and macrophages, DC membranes and NK cell membranes are also widely used in the development of novel anti-tumour strategies,[72, 73] and the U.S. Food and Drug Administration has approved an immunotherapy vaccine for prostate cancer based on DCs, indicating a promising prospect.[74, 75] Cheng et al.[76] designed and synthesised a DC membrane-coated (using cell membrane extracted from activated DCs co-incubated with tumour cells) and an interleukin-2 molecule-loaded PLGA NP for immunotherapy of ovarian cancer. The obtained MCNPs can act as "small DCs" to present tumour antigens and activate T cells to eliminate tumour cells. These artificial "small DCs" have a longer half-

life than normal DCs, and are insensitive to the effects of immunosuppressants and regulators that suppress immunity in the tumour microenvironment. Therefore, the MCNPs avoid the limitations of existing DC vaccines, and effectively overcome the immune escape effect of tumours, thereby inhibit ovarian cancer growth and metastasis.[76]

Stem cell and tumour cell membrane-coated nanoparticles

Homing effect is a very special phenomenon existing among stem cells and tumour cells.[77, 78] Take cancer cells for an example, tumour cells gradually evolved homologous adhesion ability and immune escape ability, thereby evading the clearance of the immune system, and forming stable tumour foci in the body. The homologous adhesion ability of tumours is derived from a variety of adhesion glycoproteins expressed on the surface of tumour cell membranes, such as integrin protein, N-cadherin, epithelial cell adhesion molecule. MCNPs coated with stem cell/cancer cell-derived membranes can be endowed with tumour cell-mimicking properties including tumour targeting capability.[25, 77-81] In addition, the coated tumour cell membrane also expressed various tumour associated antigens, which can be used as vaccines to activate cell-mediated immune effect and rescue the exhausted tumour-associated microenvironments.[80, 82] Nowadays, human sourced tumour tissues resected in surgery can be dispersed into cells to extracted autologous cancer cell-membranes. When these membranes are combined with immunologic adjuvant, such design can significantly augment the immune effect against tumours.[83]

Different from cells like erythrocytes and leukocytes, stem cells and tumour cells can be continuously expanded in the in vitro environment after extraction, and their source is more stable.84 Rao et al.[85] developed a tumour probe imaging system that can accurately identify tumour sites by encapsulating indocyanine green in tumour cell membrane-coated PLGA NPs, achieving non-destructive *in vivo* tumour fluorescence imaging. In addition to imaging, this homologous targeted membrane coating technology can also be used for drug delivery, thereby improving the accumulation of nanodrugs in tumours, as well as maintaining drug stability and prolonging drug circulation time during *in vivo* circulation. Our group achieved highly targeted delivery of photodynamic-starvation combination therapy agent to tumour sites through tumour membrane-coated nanocarriers, which could exert highly effective and synergistic anti-tumour effects in osteosarcoma.[19, 20]

As mentioned above, DC membranes coating can be used as a potential delivery system for tumour immunotherapy. In fact, tumour cell membranes can also activate the immune system through tumour antigens on the surface, playing a direct and effective role as a tumour vaccine. In addition, tumour cell membrane-coated tumour vaccines can overcome the limitations of the traditional peptide vaccines, such as short circulation time, difficulty in directly contact with immune cells, lack of immune adjuvants, and low potency.[69] Fang et al.[80] and Yang et al.[86] designed a tumour cell membrane-coated nanocarrier loaded with immune adjuvant, respectively, which can both be used as a highly effective tumour vaccine that aggregates around the tumour and interacts with immune cells around the tumour. MCNPs retain most of tumour epitopes on the surface of tumour cell membranes, which stimulate the activation of antigen-presenting cells along with the contained immune adjuvant and induce anti-tumour immunity.[80, 86]

Bacteria membrane-coated nanoparticles

Apart from the MCNPs coated with cells derived from human body, membranes come from other species are also potential materials. Using bacteria to activate immune system and fight tumour have been a popular concept for hundred years. Thus, coating NPs with bacteria derived membranes may stimulate innate immunity via the pathogen-associated molecular patterns and reshape the suppressive tumour microenvironment to ameliorate the efficacy of multiple therapeutic strategies such as immunetherapy.[87] Recent years, the close relationship between microbe and human disease is gradually depicted via cutting-edge microbiota analysis and metagenome technology. Researchers indicated that bacteria exist in almost everywhere and play important role in pathogenesis of many diseases. Therefore, bacteria-derived membranes may have potential effects in all kinds of therapeutic modalities towards multiple disease models.

Engineered membrane-coated nanoparticles

In the previous sections, we discussed the properties of the natural cell membrane and their contribution to the drug delivery system. However, in tumour therapy, researchers require multifunctional delivery systems with maximised performances. Therefore, artificially modifying functional molecules on the surface of native cell membranes can not only preserve the original functions of cell membrane, but also endow nanocarriers with more valuable properties such as stronger specificity and higher adhesion capability.

Folate receptors and integrin receptors are highly expressed on the surface of tumour cells, and folic acid can specifically bind to folate receptors with a high affinity. Fang et al.[88] modified nucleolin-targeting aptamer (AS1411) and folic acid molecules on the surface of erythrocyte membrane to achieve higher accumulation of coated nanodrugs in tumour tissue. However, due to the immunogenicity of folic acid, the modified MCNPs are easy to be cleared by immune system. RGD sequences, composed of arginine-glycine-aspartic acid, are a class of functional peptides. RGD sequence can specifically bind to integrin receptors that are highly expressed on the surface of tumour cell membranes. Consequently, RGD can exert a highly targeted effect on tumours, and improve the uptake of RGD-containing NPs by tumour cells.[89, 90] Sun et al.[91] modified the RBC membranes with the tumour-penetrating peptide (RGD) to prepare nanocarriers with both long circulation and high targeting ability for the transport of paclitaxel, a broad-spectrum anticancer drug. They observed satisfied anti-cancer effects of the obtained MCNPs towards both primary tumour and lung metastases in animal models of metastatic breast cancer. Nevertheless, the structural instability of linear RGD leads to its short half-life and easy degradation by proteases,

which is insufficient to meet the therapeutic needs. Cycle-shaped RGD sequences (cRGDs) containing two disulfide bonds have higher affinity for integrin receptors than RGD, they can bind multiple integrin receptors simultaneously to generate cross-linked clusters, which improve adhesion and recognition specificity to tumour cells.[91] Our team developed a cRGD-labelled erythrocyte membrane-encapsulated phosphorylated peptides to neutralize endogenous programmed death ligand-1 in tumour cells, significantly amplified the accumulation of artificially synthesised peptides in tumour cells, leading to reduced tumour proliferation.[92] This targeting strategy was further confirmed using cRGD-labelled tumour cell membranes coated polydopamine particles. The obtained novel photothermal controlled-release nanoreactor can be loaded with photodynamic agents, hypoxia-activated chemotherapeutic drugs or starvation treatment drugs, so that the drugs can be efficiently engulfed by tumour cells, therefore exerting synergistic anti-tumour activity in osteosarcoma therapy.[19, 20] Similarly, in another approach, tumour targeting molecules azide (N3) and boron carbon nitride were tagged on the surface of T cell membranes before coated onto NPs loaded with photothermal agent indocyanine green. The resulting nanoformulations (N3-labeled T cell membrane-coated indocyanine green-PLGA nanoparticles) can be highly enriched in tumour tissues and enabling efficient photothermal effect.[93] In terms of other applications, engineered cell membranes are widely used in the development of tumour vaccines, novel imaging agents, and other disease models (e.g., infections, autoimmune diseases).[66, 94-96]

Due to the fluidity of cell membranes, it is possible to fuse two or several kinds of cell membranes together to fabricate hybrid cell membranes, combining the functions of different cell membranes to obtain the optimal membrane carrier for drug delivery.[97, 98] Dehaini et al.[99] fused erythrocyte membranes and PLT membranes together, and the results showed that the resulting hybrid membrane nanodrug delivery platform bestowed the NPs with long circulation associated with RBCs and tumour targeting properties of PLTs. Hybrid membranes composed of RBC and tumour cells have been used to coat melanin particles or gold nanocages loaded with doxorubicin to achieve photothermal therapy or triple synergistic treatment of tumours with photothermal, radiological, and chemotherapy, conferring both homologous targeting capability of tumour cells and the long circulation provided by erythrocyte membranes to inner nanoformulations.[97, 100-102] Li et al.[103] designed a hybrid membrane from tumour cells and bacterial cell membranes and obtained a potent tumour vaccine. The epitopes on the surface of the bacterial membrane can be used as immune adjuvants to augment the validity of the immune response to tumour cell membrane antigens. The hybrid membrane also aggregates the phagocytosis of immune-presenting cells such as DCs.[103] To achieve integrated tumour antigen presentation and co-stimulation to activate the immune system, Ma et al.[104] and Liu et al.[105] designed a fusion membrane from DCs and tumour cells, which combined tumour epitopes with co-stimulatory molecules on DCs.

In summary, the engineered cell membrane obtained by ligand modification or membrane fusion combines the advantages of different natural cell membranes and artificial modification, providing a thriving trend of nanomedicine research. The membrane sources mentioned above along with their advantages in anti-tumour therapy are summarised in **Table 1**.

Table 1. Common membrane sources and their properties

Membrane source	Immune evasion	Special property
Red blood cell	√	Easy fabrication
		Simple structure
Platelet	√	Tumour targeting
		Inflammation targeting
Immune cell	√	Tumour targeting
		Inflammation targeting
		Immune stimulation
		Antigen presentation
		Macrophage polarisation
Tumour cell	√	Homotypic tumour targeting
		Immune stimulation
		Tumour antigen presentation
		Macrophage polarisation
Stem cell	√	Tumour targeting
		Inflammation targeting
Bacteria	×	Immune stimulation
		Antigen presentation
		Macrophage polarisation
Engineered/hybrid	–	Editable and combinable functions

Note: The most used membrane sources are listed in the table along with their advantages in anti-tumour therapy. √: The specific membrane source possesses such characteristic; ×: the specific membrane source does not possess such characteristic; –: omitted.

Future Opportunities and Challenges Associated with Membrane-Coated Nanoparticles

At present, traditional therapies for tumours (such as chemotherapy) are developing rapidly, however, chemotherapeutic drugs are lack of targeting ability and prone to causing adverse effects on normal tissues. Thus, it is extremely critical to develop a highly targeted and safe delivery system for anti-tumour therapy.[101] Over the past years, biomimetic-inspired cell membrane-coated nanodrug delivery systems have provided a new perspective to solve this problem. Compared to conventional nanomaterial drug delivery systems, MCNPs retain the functional properties of the NPs themselves, and bestow the nanocores with characteristics of the sourced cell membrane, which achieve effective, targeted, and low-toxic transportation. Different from natural nanocarriers like exosomes, the diameters, and functions of MCNPs are editable to meet the demands of different applications. Compared with the traditional method of directly modifying functionalised groups on the surface of the carrier, the membrane coating technology provides a better modification strategy that is closer to the native state. MCNPs will also avoid the side effects of direct application of cell therapy, such as stem cell tumourigenesis.[7] In this review, we reviewed the development, technical details, and advantages of membrane coating technologies. We also discussed the effects of different physicochemical properties of NPs and their anti-tumour applications, overviewed our experience for the design and application of MCNPs. Finally, we summarised the functional characteristics and application status of cell membranes from different sources. However, some limitation of the review should be noted. First, the applications we discussed are all from published papers, which result in publication bias. Besides, we only searched in PubMed and Web of Science database, which may lead to insufficient sample size. Nowadays, researchers are exploring the border of translating experimental MCNPs into clinical application. Even though various MCNP platforms are designed and tested, additional works are still needed in large scale fabrication for clinical use. Engineered MCNPs are the current direction of development of membrane coating technology, which is gradually applied in many research fields such as anti-tumour drug delivery, phototherapy, immunotherapy, tumour vaccines and imaging. Attempts towards the diagnosis and treatment of other disease models such as infections and autoimmune diseases are also emerging.[9, 96, 106] At present and in the foreseeable future, microfluid technology might facilitate the development of MCNPs, transforming membrane coating technology into a therapeutic method that can be applied in clinical practice. Many efforts and considerations need to be addressed, such as improving the current detection methods for the process display of MCNPs *in vivo* to test its long-term accumulation toxicity and impact *in vivo* before realising the leap from animal experimental research to clinical application. In the future, the membrane-coating technology is bound to become one of the most potential drug delivery strategies, leveraging unique properties to augment the performance of traditional therapeutics depending on different requests. We believe MCNPs will have bright outlooks and bring hope to more researchers and cancer patients.

Author contributions

HG and MG: Conceptualization, investigation, methodology, writing-original draft; ZX: writing-review&editing; ZS: funding acquisition, writing-review & editing; HG: software,supervision, writing-review & editing. All authors have given final approval for this version of the manuscript.

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