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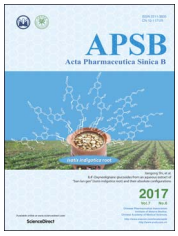

REVIEW

Cell membrane-based nanoparticles: a new biomimetic platform for tumor diagnosis and treatment

Ruixiang Li[a,b,†], Yuwei He[a,b,†], Shuya Zhang[a,b], Jing Qin[a,b], Jianxin Wang[a,b,c,*]

[a]*Department of Pharmaceutics, School of Pharmacy, Fudan University, Shanghai 201203, China*
[b]*Key Laboratory of Smart Drug Delivery, Ministry of Education, Shanghai 201203, China*
[c]*Institute of Materia Medica, Academy of Chinese and Western Integrative Medicine, Fudan University, Shanghai 201203, China*

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Abstract Taking inspiration from nature, the biomimetic concept has been integrated into drug delivery systems in cancer therapy. Disguised with cell membranes, the nanoparticles can acquire various functions of natural cells. The cell membrane-coating technology has pushed the limits of common nano-systems (fast elimination in circulation) to more effectively navigate within the body. Moreover, because of the various functional molecules on the surface, cell membrane-based nanoparticles (CMBNPs) are capable of interacting with the complex biological microenvironment of the tumor. Various sources of cell membranes have been explored to camouflage CMBNPs and different tumor-targeting strategies have been developed to enhance the anti-tumor drug delivery therapy. In this review article we highlight the most recent advances in CMBNP-based cancer targeting systems and address the challenges and opportunities in this field.

Abbreviations: CC, cancer cell; CMBNPS, cell membrane-based nanoparticles; CTC, circulating tumor cell; DOX, doxorubicin; DSPE, distearoyl phosphoethanolamine; EPR, enhanced permeability and retention; ICG, indocyanine green; NIR, near infrared; NPs, nanoparticles; PLGA, poly (lactic-*co*-glycolic acid); PM-NV, platelet membrane-coated nanovehicle; PTX, paclitaxel; RBC, red blood cell; TDDS, targeting drug delivery system; TRAIL, tumor necrosis factor-related apoptosis inducing ligand; VCAM1, vascular cell adhesion molecule-1

*Corresponding author at: Department of Pharmaceutics, School of Pharmacy, Fudan University, Shanghai 201203, China. Tel.: +86 21 51980088; fax: +86 21 51980002.

E-mail address: jxwang@fudan.edu.cn (Jianxin Wang).

†These authors made equal contributions to this work.

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1. Introduction

Cancer has long been a global threat and is the second leading cause of death[1]. As one of the most common strategies for the treatment of cancer, chemotherapy remains unsatisfactory due to the low targeting ability and severe adverse effects of anti-cancer drugs[2,3]. To address these problems, targeting drug delivery systems (TDDS), especially nanoparticle-based TDDS, have been intensively studied and developed[4]. The advantages of nanoparticles (NPs), such as high drug loading capacity, adjustable physiochemical properties and flexibility to be modified, make them appropriate to encapsulate anti-cancer drugs and thereby alter their solubility, stability and *in vivo* behavior[5]. Moreover, the surface modification of NPs can prolong their circulation in the blood and provide specific targeting so as to increase efficacy while decreasing adverse effects[6,7]. However, there are still many drawbacks limiting NPs to meet clinical expectations. Most NPs are recognized and eliminated as a foreign substance by immune system. PEGylation of NPs can decrease the fast elimination by reticuloendothelial system. Some studies discovered that the repetitive administration of PEGylated NPs can induce an immune response which can lead to faster elimination of NPs[8,9]. In addition, the desired targeting capacity of NPs was especially dependent on the surface modification, which was complicated to fabricate and difficult to achieve[10,11]. Consequently, nanoparticle-based TDDS have not yet reached their full therapeutic potential. Seeking a safer and more effective approach is urgently demanded.

In the early 1980s, cells were exploited as carriers to deliver drugs or nanoparticles[12,13], which significantly enhanced the retention and targeting efficiency of these drugs. Although the use of live cell-based carriers flourished, some deficiencies remain. One of major concern is the activity of passenger drugs, since drugs may be digested by the lysosomes of the cell carrier[14]. Moreover, it is difficult to control the release of drug, which may be leaked or exocytosed during transport[15]. Confronted with these problems, scientists have recently found a clue from nature to design biomimetic, cell membrane-based nanoparticles (CMBNPs). Initially, the original CMBNPs were fabricated from a red blood cell (RBC) membrane shell and a poly (lactic-*co*-glycolic acid) (PLGA) core, *via* a co-extrusion process, forming a core-shell structure. Subsequently, various CMBNPs have been explored with the flexibility of choosing different membrane materials and different nanoparticle cores. The translocation of a natural cell membrane to a synthesized NP can combine the advantages of a biomimetic cell membrane surface and the tailored flexibility of material chemistry[16,17]. One of the most important profits is that the CMBNPs can be disguised as autogenous cells, so as to escape immune system elimination and prolong the circulation time in the blood, which is extremely necessary for the enhanced permeability and retention (EPR) effect for tumor targeting[18].

In addition, the complex components of a natural cell membrane can be maintained in CMBNPs, which might endow the CMBNPs with some biological functions propitious to tumor targeting[19]. As reported, numerous cells are involved in or related to the development and progression of cancer, such as red blood cells, leukocytes, cancer cells and even sub-cellular platelets[20], and different cells play different parts in the process. The membrane-based functions of cancer-related cells, including extravasation, chemotaxis, and cancer cell adhesion, inspired researchers to explore the CMBNPs to be a carriers for tumor-targeting drug delivery[21,22]. We classify CMBNPs according to the type of source cells including red blood cells, leukocytes, cancer cells and platelets. Different types of cell membranes could endow CMBNPs with various functions, which will lead to diverse *in vivo* biological behavior. This classification covers most of currently reported CMBNPs and shows the basic mechanism of the biomimetic strategy.

Besides the versatile capacity of the coated membrane, the core of CMBNPs are also flexibly designed for various applications, such as anti-cancer drug delivery, tumor imaging, and photothermal therapy. All these advantages make CMBNPs promising for translation from bench to bedside. Therefore, in order to direct the rational design and further improvement of CMBNPs, it is necessary to understand their structural concepts and targeting mechanisms. Herein, we provide an up-to-date review of various membrane-derived CMBNPs for the treatment of cancer, as well as the challenges and opportunities related to the application of CMBNPs in cancer therapy.

2. Red blood cell membrane-coated nanoparticle

Red blood cells are the most abundant cellular constituent of the blood with the total number in human body approaching 30 trillion[23]. Human blood transfusion was first performed in France in 1667 and around 50 million blood units are transfused every year in clinics[24], which makes erythrocytes widely available. Furthermore, mature erythrocytes lack a cell nucleus and organelles, so the RBC membrane is convenient to extract and purify[25].

An optimal nano-sized drug delivery system requires relatively long blood circulation to achieve effective tumor targeting and efficacy[26,27]. The immune system, however, can recognize foreign bodies according to determinants absent on host cells or “markers of self” normally present[28]. Red blood cells, expressing a variety of immunomodulatory markers on their cell membrane, can be recognized as a self-component and circulate for about 40 days in mice, and 3 months in the human body[29]. One of the most typical markers is CD47, a transmembrane protein, which can bind to the inhibitory receptor signal regulatory protein alpha and emit a “don't eat me” signal that inhibits phagocytosis of RBCs by immune cells. It was reported that RBCs lacking CD47 were rapidly cleared from the bloodstream by macrophages[29]. Therefore, RBC membrane-coated NPs, a biomimetic strategy, are able to integrate the unique advantages of natural erythrocytes, such as long circulation, with artificial nanoparticles, which can protect the encapsulated drug. Red blood cell membrane-coated PLGA NPs were first reported and laid the foundation for subsequent studies[30]. After that, many studies from different research groups were carried out to demonstrate the utility of the RBC membrane for cancer treatment.

In order to preserve the membrane as long as possible, researchers usually prepare RBC membrane-coated nanoparticles with a well-established top-down method. For example, poly (lactic-*co*-glycolic acid) (PLGA), a biodegradable polymer approved by FDA, is used to fabricate the nanoparticulate cores. The purified RBC membrane is then fused around the NPs surface via an extrusion method[30]. It was shown that compared with the bare cores, biomimetic NPs exhibited greatly prolonged circulation time due to the preservation of “markers of self” on the RBC membrane in a right-side-out orientation[31]. Furthermore, results indicated that the functionalized NPs demonstrated significantly enhanced accumulation at tumor sites in a subcutaneous tumor model due to an increased ability to utilize the EPR effect[32]. Thus, the biomimetic strategy is promising to be an alternative to polyethylene glycol (PEG) stealth coating in a more biocompatible way. Many studies relevant to cancer drug delivery were carried

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