Clinics in Oncology

Short Communication
Published: 12 Sep, 2017

Exosome and Its Applications as a Novel Drug Delivery System

Lichun Sun[1,2,3,], Quanyong He[1], Zuodong Qin[4], Jun Lei[1] and Bo Feng[5]*

[1]The Third Xiangya Hospital of Central South University, Changsha, China

[2]Department of Medicine, School of Medicine, Tulane University Health Sciences Center, New Orleans, USA

[3]Hunan Province Cooperative Innovation Center for Molecular Target New Drug Study, University of South China, China

[4]Key Laboratory of Comprehensive Utilization of Advantage Plants Resources in Hunan South, Hunan University of Science and Technology, China

[5]College of Environment and Resources, Xiangtan University, China

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For the therapeutics of certain human diseases such as cancers, immune diseases and arthritis, one of the major problems is that the common drugs used go throughout the whole body, rather than specifically targeting the pathologic tissues or organs, resulting in severe side effects and less drug efficacy. There is a pressing need to develop more efficient disease-targeted therapeutics, with the decrease of side effective toxicity and the increase of drug-targeted specificity. Currently, various drug delivery systems including antibodies, peptides, proteins, lipids, nanoparticles, polymers, exosomes, microvesicles have been used for the therapeutic improvement [1-5]. Among them, exosomes have been exploited, with their unique advantages of small sizes, natural cell-secreted sources and phospholipid bilayer membrane structures [6,7].

Exosomes were first discovered and reported by Dr. Pan three decades ago [8]. Exosomes are naturally membrane-derived nanovesicles with their range of 30 nm - 100 nm in diameter. Exosomes are released by many types of cells such as tumor cells, dendritic cells, endothelial cells, epithelial cells, T cells, B cells and cortical neurons [9-11], and secreted into the extracellular environments or physiological fluids. Exosomes can transfer biological messages from donor cells to surrounding cells or recipient cells in the cell-to-cell communication. Exosomes were observed to have a variety of different components including proteins, enzymes, antigens, lipids, nucleotides (RNAs and even DNAs), non-coding RNAs, microRNAs (miRNAs) [12,13]. Their contents are also different in a cell type-dependent manner. The component difference in exosomes from different cell sources determines their own critical and particular functions. Exosomes have been demonstrated with the involvement of various biological, physiological and pathological functions such as immune response, disease-spreading and tissue homeostasis. For instances, exosomes from tumor cells participated in tumor growth, tumor progression and tumor metastasis.

The characteristics exosomes have provided potential opportunities for exosome-based therapeutics. Tumor cell-derived exosomes contain tumor-specific antigens and tumor-associated biomarkers [12]. These molecules can be targeted for tumor treatments, or applied to recognize and diagnose these tumors. Also, exosomes might be applied to develop cancer vaccines. Dendritic cell-derived exosomes carrying various immune responsive factors can be potentially used for immunotherapy [14]. Exosomes released by virus-infected cells may spread infection over whole body system. Targeting these exosomes may stop the spreading of viral infection. Exosomes from neuron cells may be used to pass drugs through un-permeated neuron system and be potential therapeutics for neuron-associated diseases such as Alzheimer's disease. Due to their unique characteristics, exosomes have been exploited for human disease diagnosis, therapeutics and vaccine development. Meanwhile, exosomes have been applied for their broad drug-carrying ability to deliver different types of drugs or other payloads like proteins, siRNA, and small chemical molecules (hydrophobic and hydrophilic) (Figure 1) [6].

Serving as drug delivery vehicles, exosomes display their specific advantages. These exosomes are natural membrane vesicles with natural cell-released components. Therefore, they are well-tolerated, with lower toxicity and less immunogenicity [7]. Also, exosomes are small and flexible. They can pass

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Correspondence:
Lichun Sun, Department of Medicine, School of Medicine, Tulane University Health Sciences Center, New Orleans, USA,
E-mail: lsun@tulane.edu

Received Date: *12 Jul 2017*
Accepted Date: *14 Aug 2017*
Published Date: *12 Sep 2017*

Citation:
Sun L, He Q, Qin Z, Lei J, Feng B. Exosome and Its Applications as a Novel Drug Delivery System. Clin Oncol. 2017; 2: 1346.

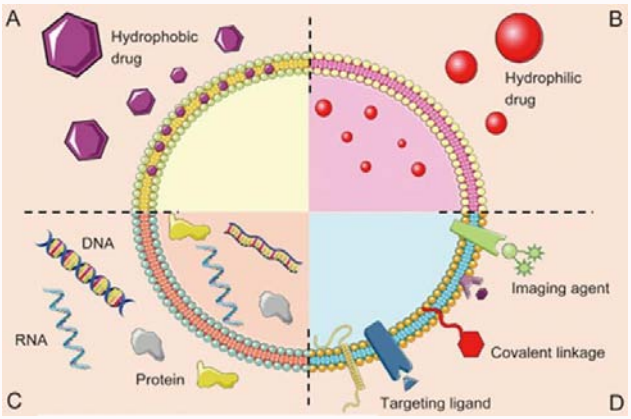

Figure 1: The different exosomal types of drug delivery systems. A, hydrophobic drug, B, hydrophilic drug, C, intracellular components (DNA, RNA and protein), D, membrane components (ligand and receptor) [6].

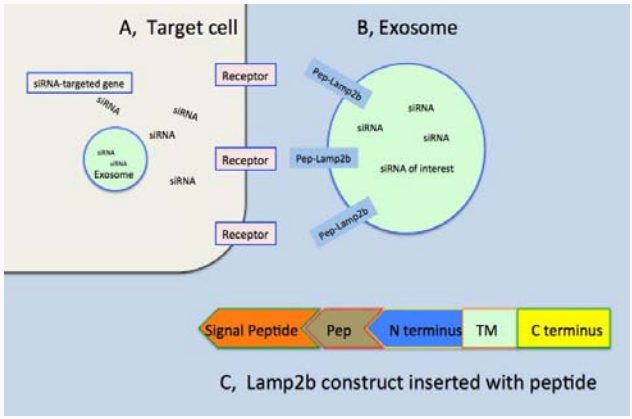

Figure 2: The ligand-receptor pairing drug delivery system.

through the major biological obstacles such as Blood-Brain Barrier (BBB) and deeply permeate inside tissues [15]. The bi-lipid structures of exosomes can keep the payloads more stable while avoiding quick degradation or clearance from body system. Another key advantage is that the therapeutic exosomes can also come from individual patient-derived tissue and be used for personalized drug delivery and therapeutics [7]. More importantly, exosomes from appropriate source cells are important for driving payloads to targeted tissues due to the lipid and cell surface components are unique to these exosomes and important to keep these unique characteristics. Exosomes from different cell sources have been investigated for the delivery of various payloads. Certain small molecules such as doxorubicin, paclitaxel, curcumin have been loaded into exosomes derived from different cell sources and display the enhanced anticancer efficacy [12]. Various siRNAs and miRNAs such as BACE1 siRNA, miRNA-21, miRNA-718 [16,17], and display their specific gene-targeting and potent efficacy, but one of the huge challenges is that these large size nucleotide molecules are hard to go through cell membranes. Serial studies have demonstrated that uploading them into exosomes may potentially be a promising approach to solve this problem. Exosomes also show their potentials to deliver macromolecular proteins. However, the exosomal technology has limited cell-targeting ability. Scientists are still searching for new strategies to improve the specificity of this technology and the enhanced anti-disease efficacy of the loaded drugs.

Lamp2b is an exosomal transmembrane protein. The peptide ligand gene of interest is inserted between the signal peptide and Lamp2b at its N terminus. The constructs of Lamp2b gene fused with peptide of interest are transfected into cells that in turn release exosomes with peptide-Lamp2b expressed on exosomal surfaces. The payloads such as siRNA or small molecule drugs are then uploaded into exosomes. The purified exosomes are eventually injected *in vivo* in animal models, delivered to the target sites, interact with the cell surface receptors via the peptide ligands, internalize and release drugs inside target cells. A, target cell, B, exosome, C, the lamp2b constructs inserted with peptides of interest. Engineered exosomes expressing the desired ligands on their surfaces can build ligand-receptor pairing drug delivery tools to carry drug of interest to targeted sites where the cell surface receptors are uniquely expressed (Figure 2). Dr. Wood first designed and established this system [18]. He constructed a Lamp2b-expressing plasmid and inserted neuron-specific peptide RVG between signal peptide and Lamp2b at its N-terminus. This new RVG-Lamp2b construct was transfected into dendritic cells. He harvested the exosomes released from dendritic cells and expressing RVG-Lam2b fusion protein and further engineered siRNAs of interest into these exosomes. This new exosomal system has been demonstrated to cross the blood-brain barrier and target neurons via RVG binding to its cognate acetylcholine receptor, implicating it might be a promising approach to treat neuron-associated diseases. This valuable exosomal ligand-receptor delivery system can be used to widely deliver various payloads like siRNAs, small molecules to targeted sites by inserting different peptide ligands that target different receptors preferentially expressing in unique tissues. For instances, some peptide genes like somatostatin, bombesin can be engineered into the Lamp2b plasmids and the exosomes expressing these peptides can carry drugs of interest to tissue sites highly expressing somatostatin receptors and bombesin receptors [19,20] and enhance the efficacy and specificity of the drugs via the interaction of peptides and receptors. Exosome may be an exciting next-generation payload delivery system. However, some questions like side effective toxicity of exosomes need to be answered. Simply, this exosomal technique provides us an alternative approach for disease-targeted therapeutics, diagnosis and precise molecular studies, especially for cancer-targeted therapy although it is a long way to go.

Acknowledgements

This work was supported by the Zhishan Plan Program Fund from the Third Xiangya HospitaI of Central South University ([2017]15), the Tulane Peptide Research Fund, and the National Natural Science Foundation of China (No. 21606079, No. 21777135).

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