International Journal of Pharmaceutics 521 (2017) 167–175

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Exosomes as novel bio-carriers for gene and drug delivery

Xin-Chi Jiang, Jian-Qing Gao*

Institute of Pharmaceutics, College of Pharmaceutical Sciences, Zhejiang University, PR China

ARTICLE INFO

Article history:
Received 23 November 2016
Received in revised form 13 February 2017
Accepted 14 February 2017
Available online 17 February 2017

Keywords:
Exosomes
Cell-free therapies
Drug delivery system
Nucleic acids

ABSTRACT

Clinical treatments have stalled in certain diseases due to a lack of proper therapeutic delivery systems. Recent studies have identified exosomes for their potential use as cell-free therapies, which may provide a novel mechanism for solving this problem. Exosomes are nanoscale extracellular vesicles that can transport rich cargos of proteins, lipids, DNA, and RNA. It is increasingly recognized that exosomes play a complex role in not only the physiological conditions but also pathological ones. Accumulating evidence suggests that exosomes are of paramount importance in distant cell-cell communication because they can enter the circulation when secreted and pass through additional biological barriers. As a result, interest has exploded surrounding the functional parameters of exosomes and their potential applications as delivery vehicles for small molecule therapies. In this review, we discuss the potential of exosomes to be utilized as "natural nanoparticles" to deliver drugs and genes, and their advantages and disadvantages are compared to other delivery mechanisms.

Contents

1. Introduction

Development or identification of a delivery system for effectively conveying therapy is integral to combatting disease. The ideal vehicles should be safe, efficient and have optimal bioavailability. In addition, stability, mitigating toxicity and immunogenicity, and the ability to successfully target the vehicle to a specific tissue/cell population is also very important (Smith et al., 2015). Nanocarriers such as viruses, liposomes, ligand-conjugated nanoparticles, magnetic nanoparticles and ultrasound microbubbles have been extensively studied due to their several advantages as drug delivery vehicles (Li et al., 2009; Moritake et al., 2007; Ruan et al., 2014). For example, they are capable of carrying a high payload of drugs, loading of multiple drugs is possible, their contents are protected from degradation, and their structures allow enhanced endocytosis (Davis et al., 2008; Gong et al., 2015; Kowalczuk et al., 2011). However, their non-uniform particle size distribution, the tendency to form agglomerates, non-specific uptake, and rapid recognition and clearance by the reticuloendothelial system (RES) limits the usefulness of these nanocarriers (Hu et al., 2010; Prete et al., 2006; Shubayev et al., 2009). Moreover,

* Corresponding author at: Institute of Pharmaceutics, College of Pharmaceutica Sciences, Zhejiang University, Hangzhou, 310058, PR China.
E-mail addresses: shincy_j@163.com (X.-C. Jiang), gaojianqing@zju.edu.cn (J.-Q. Gao).

http://dx.doi.org/10.1016/j.ijpharm.2017.02.038
0378-5173/

issues related to their artificial nature can cause toxicology issues (Ferrari, 2008). Synthetic drug delivery vehicles may cause severe side effects, including organ toxicity and/or immune responses (Kim et al., 2016; Kim and Kim, 2009). It has been reported that the use of liposomes leads to adverse immunogenic reactions (de Boer and Gaillard, 2007).

In recent years, several pioneers have explored the possibility of using cells as drug delivery vehicles. In particular, stem cells have been exploited to selectively deliver therapeutic genes or drugs to tumors (Hu et al., 2012; Hu et al., 2013; Pascucci et al., 2014; Zhang et al., 2014). Mesenchymal stem cells (MSCs) have been utilized as potential carriers to deliver drugs because of the ease with which they can be isolated and expanded *in vitro*. In addition, MSCs are able to home in on inflammatory microenvironments or tumor masses (Pascucci et al., 2014). In a previous study, we modified MSCs to express suicide genes and then co-administered them with prodrug-encapsulated liposomes to achieve synergistic anti-tumor effects. This strategy resulted in a significant decrease in tumor colonization and a subsequent increase in the survival of a murine melanoma lung metastasis model (Zhang et al., 2015a). The limitation of cell based carriers is the unknown fate of MSCs *in vivo* and whether MSCs may be able to enhance or initiate tumor growth (Hu et al., 2010). In contrast, exosomes, which are nanovesicles secreted by cells, could provide an untapped source of effective delivery strategies.

Exosomes are phospholipid bilayer vesicles, and they were first identified as a part of reticulocyte maturation (Johnstone et al., 1987; Pan and Johnstone, 1983). Exosomes can be produced by most cell types, including B cells, T cells, dendritic cells(DC), macrophages, neurons, glial cells, most tumor cell lines, and stem cells (Simpson et al., 2008; van Niel et al., 2006). The particle size of exosomes is between 40 and 120 nm, and their sucrose density ranges between 1.13–1.19 g/ml (Denzer et al., 2000; Liu et al., 2013). As the smallest type of extracellular vesicles, when the multivesicular bodies fuse with the plasma membrane, exosomes are secreted out of the cell (Fig. 1). Recently, accumulating evidence suggests that exosomes can deliver rich cargo between cells in a natural pathway for genetic material transfer within organisms (Liu et al., 2013). Exosome delivery to recipient cells is a key step in mediating changes in cellular behavior (Lakhal and Wood, 2011; Vallhov et al., 2011). In addition, they also play essential roles in intercellular communication (Zhang and Chopp, 2016). For these natural characteristics, exosomes are being explored as drug and gene delivery vehicles.

Here we review the current state of knowledge surrounding exosomes, describe their therapeutic potential and provide examples of their function as natural carriers for delivery of drugs and/or genes in different types of disease. While the field of exosome study is still largely in its infancy, the therapeutic potential of exosomes (and their analogues) as vehicles for drug delivery is self-evident.

2. Exosomes: naturally occurring cell-to-cell transporters

Different from the initial discovery of exosomes in the 1980s, they are regarded as postmen that deliver both genetic and proteomic information between cells and target tissues rather than cellular garbage bags capable of packing unwanted metabolic contents for disposal. As naturally occurring cell-to-cell transporters, the content of exosomes varies widely, ranging from proteins and lipids to DNAs and RNAs that have a regulatory effects on recipient cells (Hong et al., 2009; Kim et al., 2013; Valadi et al., 2007). Research has previously suggested that the sorting of lipids and proteins into exosomes is a selective process (Johnstone et al., 1987). Over 4000 different proteins and over 2400 different RNAs have been identified and described in exosomes (van Dommelen et al., 2012). In addition to containing a common set of exosomal proteins, additional protein and miRNA cargo varies depending

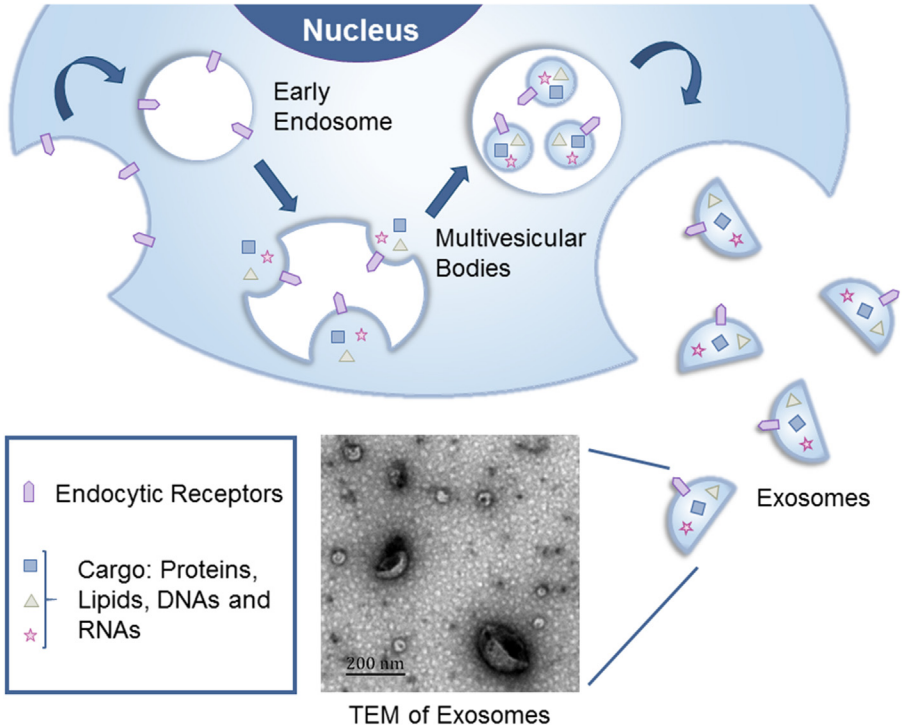

Fig. 1. Exosomes arise from the endocytic pathway that begins with the invagination of the plasma membrane to form an endosome. They are cup-shaped and can contain numerous proteins, lipids, DNAs and RNAs.