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The emerging role of cell-derived microvesicles in stem cell research and therapy

Abstract

Recently, there has been growing interest in cell-derived microvesicles (MVs) or extracellular vesicles (EV) due to their vital roles in inter-cellular communications and great potential of therapeutic applications. The mechanism behind these roles involves encapsulation of bioactive molecules from MV-producing cells and delivery to receipt cells nearby or at long distance through blood circulation. Proteins, mRNA, miRNA or even certain phospholipids can be bioactive molecules in different MVs that transfer signals from producing cells to receipt cells and change their fate. Stem cells can produce MVs which are able to enhance proliferation of target cells. Among them, MVs derived from mesenchymal stem cells are well studied and have been shown to have multiple therapeutic applications. As an emerging area, there are still more work needed to be done, including but not limited to MV body distribution and pharmacokinetics, before these existing biofunctions found *in vitro* can be translated to patients.

Keywords: microvesicle, exosome, extracellular vesicle, pharmacokinetics

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Jinlin Jiang,[1] Xuyang Song[2]
[1]Department of Chemical and Biomolecular Engineering, University of Delaware, USA
[2]Department of Pharmaceutics, University of Florida, USA

Correspondence: Jinlin Jiang, Department of Chemical and Biomolecular Engineering, University of Delaware, 15 Innovation Way, RM 243, Newark, DE 19711, USA, Tel 3013982987, Email jiangjl@udel.edu

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Abbreviations: MV, microvesicle; EV, extracellular vesicle; MSC, mesenchymal stem cell; ESC, embryonic stem cell; PK, pharmacokinetics

Introduction

Microvesicles (MVs) or microparticles are one type of extracellular vesicles (EVs) which can be produced by all types of cells under physiological or pathological conditions. The diameter of MVs ranges from 100nm to 1000nm. MVs are different from exosomes which are smaller (20nm-100nm) and originate from multivescular bodies.[1] MV biogenesis is always associated with cell growth, activation or apoptosis. The process involves direct budding of plasma membrane and a wide range of external signals can stimulate cells to produce MVs. The stimulator can be physical stress (such as, shear, hypoxia and oxidative stress), physiological agonists (such as, thrombin and TNFα) or non-physiological activators (such as, phorbol myristate acetate and calcium ionophore). MV generation process is complex and multiples mechanisms have been employed by cells, including caspase activation, lipid rafts, cytoskeletal reorganization and so on.[2] MVs are heterogeneous with respect to their surface marker expression, membrane phospholipid composition, and internal protein and RNA repertoires even when they are produced by the same parent cells but with different stimulations.[2]

For a long time, these membrane-bounded MVs were considered as cell debris in the cell culture and had no biological functions. However, numerous studies have demonstrated MVs produced from different types of cells are used as a tool for communication between different types of cells since milestone work presented by Ratajczak et al.[3] Compared to other endocrine signaling pathways, MVs have advantages of being enriched and protective for signaling molecules. The biological function of MVs is dependent on the bioactive molecules carried by MVs which can be proteins, mRNA, miRNA or even DNA in MV lumen or phospholipids or surface proteins on MV membrane. Several studies show these bioactive molecules are specifically enriched in the MVs compared to MV parental cells, suggesting that a sorting process takes place during MV biogenesis.[3] For the signal to be transduced successfully, MVs need to bind to target cells through surface receptor-ligand interaction which may determine target-specific of MVs.[4] In most cases, subsequent uptake of MVs is required through two main mechanisms: MV-cell fusion and cell endocytosis.[5,6] After uptakes, the internal signaling molecules within MVs are released and phospholipids on MV membrane are incorporated into target cells to exert their functions.

Intrinsic function of stem cell derived mvs

Among all stem cells, MVs produced by mesenchymal stem cells (MSCs) are widely studied and have been shown to facilitate recovery of multiple injuries both *in vitro* and *in vivo*, including acute kidney injury, myocardial infarction, endotoxin-induced lung injury, and ischemic stroke.[7] Thus, MSCs are considered as injury "drugstore".[7] For example, MVs derived from MSCs under serum starvation condition are able to promote survival and proliferation of tubular epithelial cells through RNA transfer and improve functional recovery from acute kidney injury.[8] In another example, MVs with size around 100nm produced by MSCs under hypoxia condition are beneficial for angiogenesis process via enhancement of cell proliferation, migration and tube formation of endothelial cells and intramyocardial injection of these MVs in an acute myocardial infarction rat model significantly enhances blood flow recovery. In addition to[9] aforementioned one-way communication between MSCs and injured tissue, cross talk between these two cell populations exists. MVs from MSCs treated with normal rat brain extract or stroke-injured rat brain extract have significantly greater efficacy for ameliorating ischemic brain injury with improved functional recovery.[10] Under normoxia condition, MSCs experience oxidative stress in mitochondria and, as a result, MSC growth and survival are impaired.[11] To manage this intracellular oxidative stress, MSCs export impaired and depolarized mitochondria to extracellular space through MVs which can be engulfed by surrounding macrophages.[12]

In addition to MVs from MSCs, MVs released from adipose-derived stem cells have the same potential application in angiogenic therapy for ischemic diseases, as these MVs were able to increase the migration and tube formation of human umbilical vein endothelial cells.[13] During embryo development, embryonic stem cells (ESCs) employ MVs to communicate with trophoblasts and induce phenotypic change of trophoblasts.[14] The extracellular matrix proteins, fibronectin and laminin, carried by ESC-derived MVs can stimulate trophoblast migration to uterus and increase the embryo implantation efficiency,[14] suggesting a potential therapeutic use of ESC-derived MVs in fertilization and embryo implantation. In another milestone study, Ratajczak et al. showed that MVs from ESCs can reprogram hematopoietic stem cells and increase their pluripotency through horizontal transfer of mRNAs.[3] In addition to ESCs, human neural stem cells can generate MVs that have neurocognitive benefits and ameliorate radiation-induced cognitive deficits brought on during radio- and chemo-therapeutic treatment of brain cancers.[15]

Pharmacokinetics of EVs

Despite the exciting findings with regarding to stem cell-derived MVs, there are still a few hurdles standing before translation of these findings to clinical use. One of them is the bio-distribution and pharmacokinetics (PK) of MVs in human bodies. How are these MVs distributed *in vivo*? How to deliver MVs to target tissue for them to exert their biological function? What is the effective dose? These and other questions need to be addressed first before we can see promising therapies. However, up to now, the pharmacokinetics information of MVs that are injected into blood circulation is limited and only very few studies are dedicated to answer above questions. Like MVs, exosomes are membrane vesicles generated by cells with smaller size and participate intercellular communications. Thus, the pharmacokinetics of exosomes can shed lights on MVs. To this end, the recent pharmacokinetics and bio-distribution of exosomes are discussed here. Masaki et al.,[16] summarized the up-to-date PK and bio-distribution information of exosomes and EVs.[16]

The pharmacokinetic properties of injected exosomes or EVs secreted from different cell types, including mouse dendritic cells and human MSCs, have been characterized in recent studies.[16–21] Charoenviriyakul et al.,[18] compared the PK and bio-distribution of 5 different types of exosomes (B16BL6 murine melanoma cells, C2C12 murine myoblast cells, NIH3T3 murine fibroblasts cells, MAEC murine aortic endothelial cells, and RAW264.7 murine macrophage-like cells) labelled with a fusion protein of Gaussia luciferase and lactadherin. These exosomes with mean diameter around 100nm were injected into mice via the tail vein with at a dose of 5μg/200μl/shot.[18] They found that these exosomes have comparable PK properties. Systemic exposure of exosomes were detected after intravenously injected into mice with the mean the area under the concentration-time curve (AUC0-4h) in serum of 0.945-1.87 (% of dose·h/ml). The short $t_{1/2\alpha}$ ranged from 2.77 to 4.08minutes with a two-phase exponential decline and the clearance ranged from 53.7-114mL/h. Similar findings were reported by other research groups.[21–26] The same research group also found that the fast clearance of exosome *in vivo* is macrophage-dependent within liver and spleen.[18,19] In another study, Lai et al.,[20] reported the similar bio-distribution of EVs derived from HEK293T cells with size ranging from 50nm to 400nm using bioluminescence to track in mice after intravenous injection. They demonstrated that exosomes were mainly taken up in the liver and spleen within 30minutes after injection and then in lungs and kidneys and that brain, heart and muscle showed limited amount of exosomes.

Conclusion

MVs present to us the exciting potential therapeutic applications in many types of disease. In addition to the current strategy to harness the intrinsic biological functions of MVs, another way to employ MVs is to use them as delivery vesicles within gene therapy areas with great advantage of target specificity compared to current delivery system. To achieve the clinical success, many open questions within basic and translational research need to be addressed first.[27]

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Conflict of interest

The author declares no conflict of interest.

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