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Exosome as a Paracrine Signal for Stem Cells

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Abstract

Exosomes are extracellular membranous vesicles of 30-100 nm in diameter secreted by different types of cells. It's essential for cell-cell communication and play important roles for stress response and cellular homeostasis during health and disease. In particular, exosomes released by stem cells was shown to facilitate stem cell maintenance, tissue regeneration, and delay neurodegeneration and tumorigenesis. This review will therefore briefly discuss the role of exosomes in stem cells and focus on the physiological role of exosome and cross talk between different tissues in organismal level.

Keywords: Exosomes; Cellular homeostasis; Cancer; Stem cells; Biomarkers

Introduction

In 1983, exosomes were firs discovered in sheep reticulocytes and named as “exosome” in 1987 [1,2]. Exosomes are secreted by differen types of cells and generally exists in many fluids It carries a variety of biologically active substances, including proteins, lipids, and nucleic acids, which function on the recipient cells [3]. Recent studies suggested that exosomes can also be used as biomarkers for various diseases, and hold therapeutic potentials for cardiovascular diseases, neurodegenerative diseases and cancer treatment.

Stem cells can proliferate and differentiat in response to stress and tissue injury and are crucial to maintain tissue homeostasis. Stem cell activity has to be tightly controlled, and excessive stem cell proliferation would cause tumor whereas stem cell pool exhaustion would lead to tissue functional decline and degeneration. It was wildly accepted that mechanical and chemical signals released from the niche govern stem cell proliferation and differentiat into functional cells to replenish the tissue. However, accumulating evidence also demonstrated that certain stem cells can produced exosomes, and biological active factors in these exosomes would affec the recipient cells through paracrine mechanism.

Studies have shown that stem cell-derived exosomes involve in tumorigenesis cancer immunity, cardiovascular disease, and tissue damage, etc [4-7]. In spite of these progress, further characterizing and analyze the biogenesis, identity, and physiological role of stem cell-derived exosomes would not only help understand the novel paracrine mechanism of cell-cell communication, also provides great opportunity for various diseases treatment.

The Biogenesis and Maturation of Exosomes

Exosomes are formed during earlier steps of endosomal pathway and released upon fusion of multiple vesicle bodies (MVBs) with the plasma membrane [8]. As part of cellular system for membrane traffi formation of exosomes shares a lot of key components with endocytic process. For instance, it was shown that the formation of exosomes requires Endosomal Sorting Complex Required for Transport (ESCRT), although ESCRT-independent mechanisms exist in certain circumstances [9,10]. ESCRT consists of four complexes, ESCRT-0, -I, -II and -III, plus several accessory components, such as VPS4, TSG101 [11]. ESCRT-0, together with fla clathrin coats, forms a protein network on endosomal membranes, capturing ubiquitinated cargo proteins and initiating their sorting into the MVB pathway [12]. ESCRT-I and -II complexes was shown to be responsible for membrane deformation into buds containing sequestered cargo, while ESCRT-III provides the core membrane-remodeling activity driving MVB formation [13,14].

ALG-2-interacting protein X (ALIX) is a protein that interacts with several ESCRT proteins and is thought to be involved in the germination and shedding process. *In vitro* binding assays shown that syndecans, syntenin and ALIX form tripartite complexes (syndecan–syntenin–ALIX), which plays a specifi role in the biogenesis of a major class of exosomes, the loading of exosomes with specifi cargo, or both [15]. In addition, as regulators of syntenin exosomes, the small GTPase ADP ribosylation factor 6 (ARF6) and its effecto phospholipase D2 (PLD2) were found to be able to affec exosomes by controlling the budding of intraluminal vesicles (ILVs) into multivesicular bodies (MVBs) [16]. Apart from this, autophagy-related gene 5(ATG5) has been shown to mediate acidificatio of the MVB lumen and allows MVB–PM (plasma membrane) fusion, knocking-out of ATG5 significantl reduces exosome release. Interestingly, the ATG12–ATG3 complex has also been found to regulate exosome biogenesis through their interaction with ALIX, indicating potential reciprocal regulation between autophagosome formation and exosome biogenesis [17].

The Secretion of Exosomes

Data Recent studies indicated that the secretion of exosomes mainly depends on Rab family proteins, which are associated with one intracellular compartment that broadly control budding, uncoating, motility and fusion of vesicles in most cell types [18]. Overexpression of the dominant-negative mutant of Rab11, Rab11S25N, inhibits exosomes release in K562 cells, indicating that Rab11 can modulate the exosomes pathway [19]. Studies also shown that two Rab27 isoforms have differen roles in the exosomal pathway, for instance, the size of MVBs was strongly increased by Rab27a silencing, whereas MVEs were redistributed towards the perinuclear region upon Rab27b silencing [20]. Th reduction of Rab27A by Rab27A-specifi shRNA significantl reduces the secretion of exosomes in A549 cells [21]. TBC1D10A–C regulates exosomes secretion in a catalytic activity–dependent manner by regulate their target, Rab35, and consistently, inhibiting the function of Rab35 leads to intracellular accumulation of endosomal vesicles and impairs exosomes secretion [22]. Similarly, depletion of Hrs, an ESCRT-0 protein, also lead to reduction of exosomes secretion in dendritic cells (DCs) [23].

SNAREs (soluble N-ethylmaleimide-sensitive fusion (NSF) attachment protein receptors, which forms a large protein superfamily with more than 60 members, mediate vesicular fusion events [24]. As expected, overexpressing VAMP7 (a member of the SNARE family) promotes exosomes release in K562 cells [25]. Mechanistically, studies have shown that Protein kinase D1/2 (PKD1/2) is a key regulator of MVB maturation and exosome secretion in T and B lymphocytes [26].

Together, despite substantial progress, much remains unknown regarding the source, biogenesis, secretion, targeting and destiny of these vesicles. For detailed review, please refer to [27].

Exosomes Derived from Stem Cells

Growing evidence indicates that many of the therapeutic potential of stem cells is attributed to their paracrine mechanisms by release of bioactive factors to the surrounding cells, and exosomes is one of the main sources for these paracrine factors [28]. Accumulating evidence have shown that stem cell-derived exosomes play pleiotropic roles for tissue regenerative and various diseases, such as neurodegeneration, and cancer [29].

Mesenchymal Stem Cells (MSCs) and exosomes. Mesenchymal stem cells are considered as major source for exosomes, since significantl more exosomes were produced by this type of stem cells. Due to their availability and multiple sources, MSCs exosomes was extensively studied and significan progress have been made about their roles in various diseases, such as cancer and neurodegenerative diseases. For instance, exosome derived from mesenchymal stem cells was shown to enhance the radiotherapy effec by inhibiting metastasis and tumor growth of melanoma cells [30]. Recent studies also shown that exosomes derived from MSCs stably overexpressing hypoxia inducible factor-1a (HIF-1α) have increased angiogenic capacity by increasing the packaging of Notch ligand Jagged1, which may shed new light on how exosomes could mediate the beneficia effect of MSCs [31]. Injection of exosomes from human umbilical cord MSC (hucMSC-ex) can alleviate type 2 diabetes by reducing insulin resistance and relieving Beta-cell destruction. However, the identity of paracrine factor(s) involved remains elusive [32].

MSC-derived exosomes have the ability to significantl down-regulated the expression of vascular endothelial growth factor (VEGF) in tumor cells, partially via miR-16, thereby inhibiting angiogenesis *in vitro* and *in vivo* [33]. Meanwhile, researchers found that mesenchymal stem cell-derived exosomes can promote muscle regeneration and angiogenesis in an *in vivo* muscle injury models, however, in this scenario, the effec are at least partially mediated by another microRNA, miR-94 [34]. Thes results suggested that exosomes in MSCs may secret differen paracrine factors, due to the source and stages of MSCs, which may explain the diverse effec of MSCs exosomes. Indeed, exosomes derived from human adipose mesenchymal stem cells improved ovarian function of premature ovarian insufficien disease via down-regulation of the SMAD signaling pathway [35]. In addition, treatment of adipose-derived stem cell exosome (ADSC-Exo) was shown to attenuate Alzheimer's disease associated phenotypes, indicating ADSC-Exo has therapeutic potential to ameliorate the progression of Aβ-induced neuronal death and AD [36].

Exosomes in other Stem Cell Types Recent studies demonstrated that embryonic stem cells (ESCs) also have the ability to produce exosomes, miRNA array revealed significan enrichment of miR290-295 cluster, especially miR-294 in ESC exosomes, which can promote cardiac regeneration and enhance cardiac function [37]. Recently, Cai and his colleagues showed that hypothalamic stem cells (HSCs) release exosomal miRNA into the cerebro-spinal flui in mice. When these microRNAs were injected into the brains of middle-aged mice, cognitive decline and muscle degeneration were reduced [38]. In addition to microRNA, cytokines released from exosomes are also important mediators. For instance, human menstrual blood-derived stem cell-derived exosomes released a series of cytokines including ICAM-1, angiopoietin-2, Axl, angiogenin, IGFBP-6, osteoprotegerin, IL-6, and IL-8, which help to reduce the number of liver mononuclear cells (MNCs) and the amount of the active apoptotic protein caspase-3 in injured livers, therefore improve liver function [39]. Induced pluripotent stem cells (IPSCs) can also secret exosomes. Recent studies also showed that exosomes derived from IPSCs stimulate the proliferation and migration of human dermal fibroblast (HDFs) under normal conditions and inhibit damages of HDFs caused by UVB irradiation [40].

Together, these results indicated that stem cells and the paracrine factors released from their exosomes are potential therapeutic targets for regenerative medicine.

Stem Cell Activity Regulated by Exosomes

Stem cells constantly sense and integrate local and systemic stimuli. Thes mechanic and chemical signals may be packed in exosomes to communicate with the stem cells. Surprisingly, whether paracrine exosomes can regulate stem cell activity remains largely unexplored.

Embryonic cerebrospinal flui nanovesicles, especially exosomes, contained proteins and microRNAs that target key determinants in the insulin-like growth factor pathway, which regulate neural stem cells proliferation [41]. Besides proliferative capacity, studies also shown that exosomes can switch differentiatio path. For instance, exosomes isolated from cell cultures can induce lineage specifi differentiatio of mesenchymal stem cells *in vitro* and *in vivo* [42]. Hematopoietic stem cell-derived exosomes also promote hematopoietic differentiatio of mouse embryonic stem cells *in vitro* by inhibiting the miR126/Notch1 pathway [43]. Interestingly, osteoblast and adipocyte exosomes augment extracellular matrix (ECM)-mediated differentiatio of human mesenchymal stem cells into the respective lineage, and it is mainly mediated by several miRNAs exist in the exosomes [44].

Together, these results indicated that exosomes control stem cell proliferation and govern differentiatio potential and lineage specificity However, most of the studies were carried out *in vitro* in cell culture system, the physiological and developmental role of exosomes on stem cell function remains largely unknown.

Conclusions and Future Perspectives

Exosomes as nanosized vesicles attract a lot of attention in recent years, largely due to existence of a lot of biological active factors, such as miRNAs, lncRNAs, proteins and lipid, etc. Especially, exosomes derived from stem cells was considered as a novel paracrine mechanism to regulate recipient tissue under physiological and pathological conditions (Figure 1).

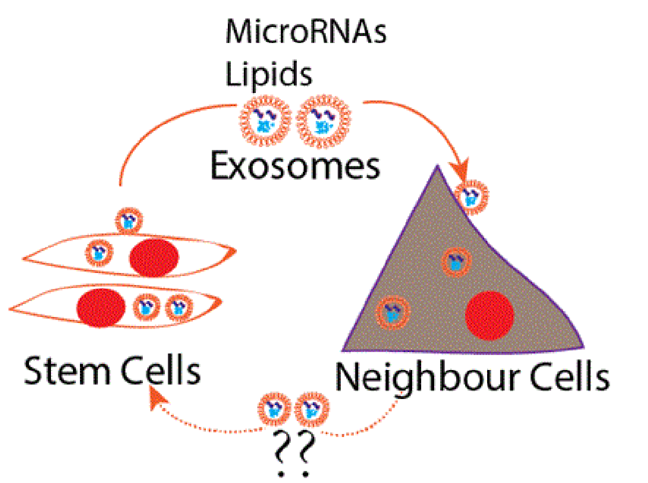

Figure 1: Cross talk between stem cells and neighboring cells via exosomes.

Although extensive progress has been made to describe their potential role as biomarkers and (or) therapeutic targets, a lot of fundamental questions need to be further addressed. For instance, little is known about targeting and fate of exosomes and how it interacts with other membrane traffic events, such as endocytosis, and autophagy. Meanwhile, exosomes are quite dynamics and heterogenous in terms of tissue source and culture condition. How it is dynamically regulated need to be further analyzed. Th last but not the least, how exosome and stem cells communicate under physiological conditions need to be examined *in vivo* models.

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