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Mini Review

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Regenerative Exosomes: A Theragnostic Repository

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Abstract

Exosomes are recently discovered biological nanoparticles (50-150 nm) that contain signaling cargo pertinent to paracrine cellular signalling within all tissue systems of the human body. Once thought of as cellular debris, exosomes have demonstrated a vast array of applications significant to both the medical and regenerative fields. These extracellular vesicles are secreted from cells as larger multivesicular bodies undergo exocytosis following endosomal processing. Exosome detection in bodily fluids during disease progression has demonstrated potential application as an early-detection disease biomarker. Furthermore, exosomes have been shown to upregulate regenerative effects, such as tissue repair and angiogenesis, in tissue microstructures. Due to the size and bioengineering versatility, exosomes have been the subject of extensive research into targeted drug and gene delivery system development. This minireview aims to characterize both the composition and reported functions of exosomes in addition to potential applications of this technology.

Keywords

Exosomes; Regeneration; Stem Cells;Therapy; Neovascularization; Bioengineering; Paracrine Signaling; Nanoparticle; Drug Delivery; Gene Delivery

Abbreviations

MVB: Multivesicular Bodies, EV: Extracellular Vehicles, MSC: Mesenchymal Stem Cells, BBB: Blood Brain Barrier, EXO: Exosomes, VEGF: Vascular Endothelial Growth Factor, EXPLOR: Exosomes for Protein Delivery via Optically Reversible Protein-Protein Interactions.

Introduction

Exosomes were originally observed 50 years ago when they were assumed to be the means by which cells disposed of waste products such as unneeded proteins and excess nucleic acids. The recognition of the true nature of what we now call exosomes came in the 1980's, from studies on the loss of transferrin during the maturation of reticulocytes into erythrocytes [1,2]. In the past decade, interest in exosomes has exploded. There was a tenfold increase in publications from 2006 to 2015 and the PubMed search term "exosome" returns nearly 10,000 articles for the year 2018 [3]. The pace and magnitude of exosome research continues to accelerate rapidly. Nonetheless, despite 20 years of research, the very basics of exosome biology are in their infancy and we know little of the part they play in normal cellular physiology, or their potential as therapeutic modalities. The objective of this mini review will be to elucidate on the characteristics and reported therapeutic applications of these extracellular vesicles.

Exosome Characteristics

Exosomes are roving packets of potent messenger molecules. Similar in mechanism to paracrine signaling utilizing growth factors and cytokines, exosomes are bioactive constituents of the secretome of the cell of origin [4]. Exosomes are lipid-bilayer-enclosed biological nanoparticles with sizes ranging from 30 to 150 nm, about 1/1000th the size of the average cell [5]. They are released into the extracellular space by most types of cells when intracellular multivesicular endosomes (MVE) fuse with the cell plasma membrane [5]. They are found in many body fluids including serum, plasma, urine, cerebrospinal fluid, saliva, semen, milk, bile, ascites, and amniotic fluid [6,7]. Also similar to other bio-signals, they can be taken up and affect the behavior of nearby recipient cells or travel through the bloodstream to influence biologic responses of cells in distant organs [6]. Exosomal cargo is mostly comprised of proteins and miRNAs, which represent a carefully selected fraction of those same molecules from their parent cells (Figure 1). In addition, the exosomal miRNAs, unlike cellular miRNAs, are highly enriched in pre-miRNAs, while the proteins are functionally clustered in several processes. Together, this selective composition of RNAs and proteins in exosomes demonstrates that exosome biogenesis is a highly regulated, and therefore an important, cellular process. Moreover, this exclusive RNA-protein composition continues to provide insights into various molecular targets for exosome-mediated functions.

Exosomes in Tissue Regeneration

Previous studies have demonstrated that the in vivo regenerative effects of stem cells are due to paracrine signaling via cytokines and growth factors that promotes tissue generation in the local environment [8-10]. Exosomes have been shown to play a similar role in this process through the intercellular transmission of protein and nucleic acid components which in turn initiate downstream

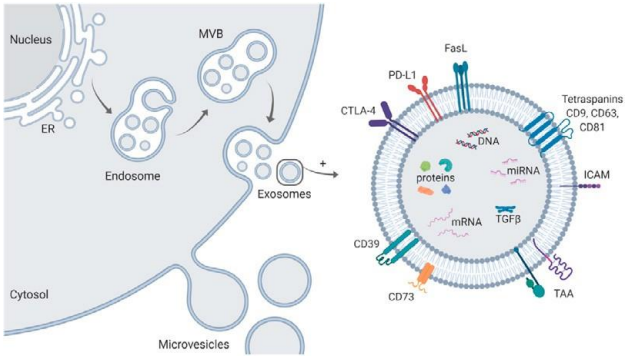

Figure 1: Schematic of exosome biogenesis and its associated cargo. Exosomes are formed by budding of the endosomal membrane, forming multivesicular bodies (MVB). MVB then fuses with the plasma membrane, and releases exosomes into extracellular space. Exosome has a lipid shell, and contains proteins, miRNA, mRNA, and DNA. Surface markers CD9, CD63, and CD81 are characteristics of exosome. Reproduced from [66] under Creative Commons license.

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effects in neighboring targeted cells [11,12]. In wound healing models, treatment with stem cell-derived exosomes have resulted in improvements in wound healing completion time, epithelial structure, and scarring reduction [13-15].These improvements are particularly important for wound healing in diabetic patients where these processes are strained by diabetes pathophysiology. Recent studies have described enhanced neovascularization in cardiac [16,17] and renal [18] tissue systems treated with exosomes isolated from umbilical cord derived mesenchymal stem cells (MSCs). Upregulation of functional proteins, such as Wnt4 and VEGF, have been shown to induce these downstream angiogenesis-promoting effects [19,20]. These regenerative capabilities have potential application to combat ischemia of transplanted tissue housed within bio-artificial devices.

Exosomes in Health & Disease

Containing cell-of-origin cytoplasmic contents including proteins, mRNAs, miRNAs, lipids and other macromolecules [6], the exosome cargo has the potential to affect targeted cellular functions in either healthy or pathological ways. Hence, exosomes are intrinsic to normal cellular communication and function [21], as well as being incriminated in the genesis and metastatic behavior of malignancies [22-25].

As essential messenger emissaries functioning throughout the body, they are attractive candidates as possible therapeutic envoys. For instance, because the blood brain barrier (BBB) prevents penetration of 98% of small molecule drugs, and exosomes have the ability to cross the BBB under inflammatory conditions, it may prove feasible to use exosomes in the treatment of neurological diseases and traumatic conditions [26,27]. This could have profound implications in treatments for Parkinson's and Alzheimer's diseases, and other neurologic maladies including stroke and traumatic injury. Indeed, recently published research, in which certain authors participated, demonstrates the value of mesenchymal stem cell-derived exosomes in treating a mouse model of multiple sclerosis [28,29].

Advances in Exosome Technology

The highly regulated cellular secretion of exosomes, including the specific composition of their cargo and cell-targeting specificity, are of immense biological interest. They have extremely high potential as non-invasive diagnostic biomarkers for many degenerative illnesses such as kidney disease [30,31], Alzheimer's disease [32,33], Parkinson's disease [34], and various types of cancer [35-37]. As biomarkers, they appear useful in evaluating normal and pathological biologic processes and monitoring the response to therapeutic intervention. Exosomes can thus provide insights on diagnosis, prognosis, regression or response to disease and disease treatments. Development of exosome-derived therapeutic nanocarriers for targeted drug and gene delivery have also been reported for numerous disease models [38-42]. The implications of these recent studies demonstrate the potential dual function to both diagnose and treat human diseases (Table1).

Conclusion

Once described as cellular debris, exosomes have been shown to have biologically intrinsic significance in cell communication and demonstrated versatility in functional application. Increased understanding of exosome physiology is poised to transform medical technology in myriad ways. In Table 1 we have provided examples of exosome uses for specific clinical indications. Exosome technology has potential to produce a new class of natural, functional, and cell-free drugs with both medical and regenerative relevance. Due to the infancy of the field, exosome research is projected to increase in popularity as more potential applications of this technology are discovered.

Table 1: Utility of exosomes. This table summarizes the various utility of exosomes both as diagnostic markers and delivery of active molecules in clinical setting.

Utility of exosome	References
Disease detection	[43, 44]
Cancer detection	
Breast cancer	[45]
Lung cancer	[46]
Prostate cancer	[47]
Colon cancer	[48]
Melanoma	[49]
Bladder cancer	[50]
Non-Hodgkin lymphoma	[51]
Renal cell cancer	[52]
Endometrial cancer	[53]
Leukemia	[54]
Pancreatic cancer	[55]
Thyroid cancer	[56]
Central nervous system diseases	
Parkinson's disease	[57]
Alzheimer's disease	[58]
Stroke and traumatic injury	[59]
Inflammation	[60]
Autoimmune disease	[61]
Regeneration markers	[62]
Wound healing	[63]
Drug delivery	[64]
Gene delivery	[65]

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