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EXPERT OPINION

Emerging potential of exosomes and noncoding microRNAs for the treatment of neurological injury/ diseases

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Recent discoveries of cellular generation of exosomes, small (~ 30 – 100 nm) complex lipid membrane structures which encapsulate and transport proteins, RNAs, including microRNAs (miRNAs) have provided new insight in how cells within organisms communicate. These discoveries will likely have a major impact on the treatment of disease, with cancers and neurological diseases as evident targets. Exosomes provide a major medium of intercellular communications and thereby, there being a potential by altering communications and instructions for protein production, we can employ exosomes to treat diseases. We now have an opportunity to treat neurological disease by modifying intercellular communication networks. Recent work demonstrating that the therapeutic benefit provided by stem cells for the treatments of stroke and traumatic brain injury depend on their generation and release of exosomes provides a foundation for exosome-based therapy. Cell-free exosomes have also been recently employed to effectively treat stroke and brain trauma. The content of exosomes, particularly their miRNA cargo which can concurrently impact the post-transcriptional regulation of many genes, can be regulated. We are at the cusp of capitalizing on this important means of intercellular communications for the treatment of diseases, such as cancers and neurological diseases, among many others.

Keywords: exosomes, microRNA, neurorestorative therapy, stroke, traumatic brain injury

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We have emerged into an era of information technology which has revolutionized all forms of communication. We also stand on the threshold of another revolution in communication, in the biological and medical realms. Recently, a body of literature has revealed that microvesicles released by cells in all living systems from microorganisms to plants to humans encapsulate important biological cargo which is transported to adjacent cells and tissues and over long distances and essentially provide a medium of information transfer in living systems. Here, we focus on a particular set of biologically potent microvesicles, exosomes.

Exosomes play vital roles in physiology and pathophysiology [1-3]. They are small lipid microvesicles (~ 30 – 100 nm) and active biological containers, which mediate intercellular communication by transferring proteins and genetic information and instructions between cells [1-3]. The membrane structure and cargo of these lipid containers reflect their birth cells and the physiological and environmental conditions of these cells. The discovery of exosomes with their varied and rich content will likely alter our understanding of the generation and progression of disease, particularly that of autoimmune disease, cancers and neurodegenerative diseases and, as we will discuss, may provide novel ways to treat disease.

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In this editorial, we will focus on how exosomes transmitting their nucleotide and protein cargo may be used for the treatment of neurological diseases. Our attention will primarily be on stroke, neural injury and neurodegenerative diseases, such as multiple sclerosis (MS). For treatment of ischemic stroke, conventional neuroprotective therapy dictates that we race against the clock and rapidly attempt to lyse the offending vascular obstruction inhibiting cerebral perfusion by using FDA-approved tissue plasminogen activator as a thrombolytic agent. For treatment of traumatic brain injury (TBI), there are no FDA-approved therapeutic agents, but the therapeutic logic is to reduce secondary damage caused by progressive neurotoxic processes such free radicals and excitotoxicity, and attempt to maintain physiological function and homeostasis. Treatment of neurodegenerative disease, such as MS, has traditionally targeted means to reduce inflammation and to modulate the immune system, ostensibly to treat an autoimmune process. With new insight into the nature of intercellular communication mediated by exosomes, we may identify novel and varied options to treat diseases, particularly neurological diseases. We also propose that the goals of the treatment of neurological injury, stroke and neurodegenerative disease should be refocused from the traditional neuroprotection, that is, reducing tissue damage and death, to neurorestoration, where the primary outcome is improvement of neurological function, mediated by neurovascular remodeling and enhancement of CNS plasticity. The means to promote neurorestoration may reside in our ability to regulate via exosomes, intercellular communication of proteins and genetic and epigenetic instructions.

Although the exosomal membrane is a complex structure that may identify the signature of the cell of origin and the cellular address of where the exosome is to be delivered, here, we narrow our interest to the exosome cargo. Exosome cargo consists of a vast array of molecules, including proteins; using proteomics, we have found > 600 proteins within exosomes generated by multipotent mesenchymal cells (MSCs). In addition, as noted, exosomes contain nucleotides, including mRNA and microRNA (miRNA), among others [1-3]. Our discussion targets miRNAs, short (22 – 25 nucleotides) noncoding RNAs, which regulate gene translation and play primary roles in mediating a vast range of biological functions. It is because miRNAs have such a broad effect on post-transcriptional protein expression that we focus our attention on the miRNA content of exosomes as mediating intercellular communication.

Each miRNA may impact protein translational suppression as well as activation of many, if not hundreds, of gene targets [4]. The miRNAs also affect other miRNAs and transcription factors that create a network, a biological web of events that evoke a multitude of biological responses [4]. We and others have shown that neural injury and stroke concurrently affect many diverse molecular pathways throughout the body [5-7]. As an example, stroke causes changes in gene expression within neural progenitor cells residing within the subventricular zone on the brain as well as in cellular sites remote from the stroke, such as in the MSCs in the bone marrow [5]. How this is done is unclear, but increasing evidence demonstrates systemic multiorgan responses to stroke. A way to obtain insight into this multi-targeting is that the organs of the body are in communication via the release of microvesicles. Thus, an injury to the brain such as a stroke stimulates the release of exosomes from parenchymal and vascular cells, whose contents including miRNAs are modified by the injury and molecular microenvironment. These exosomes are then transmitted via the vascular system to various parts of the body. The presence of miRNAs, acting as master molecular switches, contained within the protective shield of exosomes provides a conceptual framework and insight into the variety of bio-responses to disease and injury. Exosomes are essential for the transmission of information, particularly, post-transcriptional protein translation instructions transmitted by miRNAs. Naked miRNAs without the protection of their exosomal lipid encasement would be rapidly (hours) degraded in the bloodstream by voracious RNases. The miRNAs contained within exosomes are remarkably stable (days) even at room temperature and are not degraded within biological fluids [8]. Exosomes are abundant with ~ 3×10^6 exosomes/μl in biological fluids. Thus, the body bathes in fluids facilitating an active communication network.

There is robust evidence for the use of miRNAs to treat disease. An early example is in the treatment of cancer [9]. The miRNAs and their exosome containers emitted from tumor cells modify their microenvironment and create conditions, angiogenic and immunosuppressive, for enhancing tumor growth, migration and infiltration [9]. The miRNAs have been employed to target tumors, and exosomes carrying specific miRNAs are presently in clinical trials for treatment of type 1 diabetes and several cancers. The use of exosomes as carriers has also made inroads in the treatment of neurological diseases. Exosomes robustly contribute to the therapeutic effects of the treatment of stroke with MSCs. MSCs release exosomes which are absorbed by the parenchymal cells and alter their protein translational programs and thereby promote neurovascular remodeling and neural plasticity which in concert enhance neurological recovery [10-12]. Modulation of specific miRNA content of the MSCs by means of transfection generates exosomes with parallel miRNA alteration and concomitant modulation of functional outcome. Essentially, MSCs as well as other cells including stem and tumor cells act as factories for the production of exosomes, and the content of the exosomes may be altered by changing the content of the MSC miRNAs [13]. How miRNAs and other contents are specifically loaded into the exosomes released by the generating cells is basically unknown. However, the generation of robust numbers of exosomes by stem, progenitor, vascular and many other cells, whose miRNA content may be tailored, provides therapeutic opportunities. Therefore, a logical extension of the stem cell studies for the treatment of

stroke is the direct employment of solely exosomes as a treatment modality. Instead of using cells as a source of exosomes, intravascular administration of the product of the cell source, the exosomes themselves, were demonstrated to have significant beneficial effects in the treatment of stroke, TBI and cardiac disease, among others [7,10-12,14]. The direct use of exosomes from specific cell sources has prominent therapeutic potential. There are multiple ways to enrich the therapeutic potential of exosomes. Again, here we focus primarily on the treatment of stroke and neural injury, but the principles of exosome treatment are applicable to a wide array of diseases.

There are many opportunities as well as challenges to move forward in exosome development for therapeutics [3]. One can consider the use of exogenously administered exosomes and possibly the modification of endogenously generated exosomes as a means to enhance neurological recovery. Regarding endogenously produced exosomes, there is robust evidence that biological systems respond to disease and injury as treatment by modification of their exosomal content particularly their miRNAs, and these modifications are being sought as biomarkers for disease [1]. Whether endogenously generated exosomes can be modified and regulated and the possible effects of their alterations on outcome are unknown at this time, and it is premature to consider discussion of this approach. Given the present state of knowledge and evidence from preliminary data, the engineering and utilization of exogenously administered exosomes provides the most viable therapeutic options for the treatment of neurological disease and injury. However, technical and quality control obstacles must be overcome prior to clinical application. Quality control, efficient and reproducible means for the production and purification of exosomes must be provided. The biology of exosomes and how to selectively load their cargo require major investigation. Engineering challenges for which headway is being made include the targeting of exosomes to particular cell populations. This may be accomplished by inserting surface membrane and select anchoring proteins. Production quality control issues, as with all sources of therapy whether pharmaceutical or cell-based, are required. Safety concerns clearly must be addressed. Exosomes appear to have little or no adverse immunological effects [15]. Exosomes may also be safely delivered from autologous or possibly from allogeneic sources.

In summary, exosomes are major means by which cells communicate with and interact with their environment. They are distinct bio-carriers of proteins and nucleotides, which appear to protect their cargo and efficiently deposit, by many pathways, this cargo into recipient cells. We have an opportunity to employ exosomes for the treatment of neurological diseases, such as stroke and TBI. Preliminary work demonstrates that exosomes derived from stem/progenitor cells provide therapeutic benefit and that we can, by manipulating the parent cell, impact the cargo of their exosomes. Thus, select and designer exosomes may be employed to treat neurological diseases. Exosomes are far more than passive bio-carriers, as they may target specific cell populations and respond to environmental cues and thereby alter their cargo, including master translational mediators of miRNAs. Here, we have only touched on the implications of using exosomes from MSCs as a means to treat diseases. Far more therapeutic opportunities are evident. Major questions which will help in bringing exosome-based therapies to clinical fruition include enhanced bioinformatics of how miRNA, protein cargoes transmitted by exosomes between cells, impact the entire web of protein generation and provide feedback under physiological and pathophysiological conditions.

Declaration of interest

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