

Exosomes and their applications in cell-based therapies



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Introduction

Expanding knowledge about nanometer-sized fluid filled vesicles budding from cells, packaged with molecular cargo has placed exosomes to the stage where innovative engineering techniques translate them for clinical use. Exosomes are exploited for diagnostics and drug delivery systems. These extracellular vesicles (EVs) generated by double invagination of plasma membrane from cells and formation of intracellular multivesicular bodies harboring intraluminal vesicles which are secreted as exosomes of 40-160nm diameter (1). The heterogeneity of exosome is the reflection of its various sizes, content, functional impact and origin. The inherent cell physiology determines the content of exosomes. They may possess membrane proteins, cytosolic and nuclear proteins, nucleic acids, non-coding RNAs, and metabolites (2). At present, 9,769 proteins, 3,408 mRNAs, 2,838 miRNAs and 1,116 lipids have been reported as their composition(3). Exosomes serves as a non-canonical intercellular communication mode with the nexus of composition capable of multicellular and multi-centric targeting simultaneously. The potentiality to deliver molecular cargo to target cells and modify their intracellular mechanisms makes them ideal therapeutic agents and delivery systems for multiple diseases (4). The advantages of exosomal cargos over classical cell-based therapies that includes stem cells are lack of inherent risk, lack of replicating potential, lack of immunogenic response and site specificity(5).

Ischemia and metabolic diseases

Patients with ischemia often have diabetes. Exosomes derived from plasma of non-diabetic rats demonstrated cardioprotective signaling in cardiomyocytes from diabetic rats (6). Effective drug delivery targeting ischemic brain by engineered exosomes have been explored for the treatment of ischemic stroke(7). Another report suggests that anti-inflammatory potential of exosomes derived from human neural progenitor cells as therapeutic effectors against cerebral ischemia (8).

Cancer

Multifunctional nanoparticles as polymeric micelles have emerged as have been employed as smart drug carriers that can specifically target specific cancer sites by using both endogenous or exogenous stimuli (9). The contribution of exosomes for development of cancer vaccines can be attributed by studies such as exosomes bearing fibrosarcoma antigen induces anti-tumor immune reaction conducted in the murine models of fibrosarcoma; exosomes derived from macrophages with enrichment of HSP70 HSP70, naloxone, propranolol and/or staphylococcal

enterotoxin B exhibited anti-tumoral properties (10,11). Further, tumor cell derived exosomes serve as a drug carrier for cancer therapeutics (12). In another report, therapeutic recombinant P53 protein loaded extracellular vesicles targeted towards mitochondria drives breast cancer cells towards cell death mechanisms (13). siRNA to HER2 loaded engineered exosomes have shown anti-tumorigenic efficacy in breast cancer cells (14,15). Again, engineered exosomes loaded with triptolide suppressed the tumor progression in malignant melanoma in mice (16,17). Various studies have also identified the peptide functionalization of exosomes in glioma therapy (Table 1; 18,19).

Neurodegenerative diseases

The capacity of carrying genetic material and transfer at specific target sites by exosomes has been explored in neurodegenerative diseases (20). siRNAs loaded exosomes targeting alpha-synuclein in Huntington's disease model have demonstrated effective brain distribution following systemic injection (21). Reportedly, a study was conducted under in vivo and in vitro conditions that explored the delivery mechanisms of exosomes with a saturated solution of dopamine reported to cross the blood brain barrier and deliver into the brain for a better therapy for Parkinson's disease (22). In another study, curcumin loaded liposomes mitigated oxidative stress in neuronal cells and provided neuroprotective effect (23). In some in vitro studies, exosomes derived from bone marrow stromal cells and adipose-derived stem cells contains enzyme that can degrade Ab and attenuate neurotoxic effects (24,25).

Conclusion

Exploring new aspects of exosome biology demands both cell culture systems and animal models that can give insight into its biogenesis, trafficking, and intracellular entry. The site-specific targeting of cellular derived molecular cargo by exosomes is explored for designing therapeutics. The low immunogenicity and extreme biocompatibility emerged exosomes as an efficient drug delivery system. Although there is a long challenging way to go in commercial exploration of exosome-based drug delivery system, an understanding of the detailed biological mechanisms and clinical studies will herald them as next-generation nanoplatform for different diseases. Exploration of exosomes has opened up new possibilities for management of diseases like cancer within the purview of personalized medicine. The application potential of exosomes is anticipated while providing research support towards clinical use of exosomes for treatment of different diseases. The global burden of aging gives thrust towards the development of new therapeutics for neurodegenerative diseases in order to improve the quality of life of elderly population and thereby reducing the necessity of public management and heavy burden on caregivers. The development of cell specific therapy by employing exosomes opens new avenues for treatment of neurodegeneration considering less risk of autoimmune rejection and improved safety and biocompatibility. To our opinion, stem cell derived exosomes can form the foundation for a possible cure in various neurodegenerative conditions. Stem cell derived exosomes being superior in ability to surpass physiological barriers and effective migration to the sites of brain lesions thereby avoiding post transplant adverse events. Further, genetically or chemically engineered exosomes for directing them towards targeted cargo delivery can be employed in an advanced version of gene therapy for various genetic disorders.

Table: 1 Summary of investigating studies that reflects the therapeutic and drug delivery utilities of exosomes

Disease	Exosomal source	Exosomal product	Therapeutic potential	Ref.
Ischemia and diabetes type II	Serum	-	Cardioprotective efficacy	6
Cerebral ischemia	Engineered exosomes	Curcumin	Anti-inflammatory, anti-apoptotic potential	7
Cerebral ischemia	Human neural progenitor cell line	Recombinant protein	Anti-inflammation bioactivity	8
Sarcoma	Macrophage	WEHI-164 cell lysate, HSP70, naloxone, propranolol and/or staphylococcal enterotoxin B	Anti-tumoral properties	11
Breast Cancer	Breast cancer cell	Recombinant P53 protein	Cell death	13
Breast Cancer	Engineered exosomes	siRNA to HER2	Gene downregulation	14
Malignant melanoma	Engineered exosomes	Triptolide	Anti-tumorigenic, reduced toxicity of triptolide	16
Glioblastoma	Engineered exosomes	superparamagnetic iron oxide nanoparticles and curcumin	Anti-tumorigenic effect	18
Glioblastoma	Engineered exosomes	miR-21	Reduction in tumor size	19
Huntington's disease	Engineered exosomes	Asymmetric targeting siRNA Huntingtin mRNA	Bilateral oligonucleotide distribution and silencing upto 35%	21
Parkinson's disease	Blood exosomes	Dopamine	Increased distribution of drug in brain	22
Alzheimer's disease	Exo-liposomes	Curcumin	Reduction in oxidative stress and neuroprotective effect	23

Exosomes can be engineered to bind nucleic acids that facilitate encapsulation of plasmids carrying the desired gene sequence leading to efficient loading. Manipulation of exosomes for encapsulation of large vectors or mRNA transcripts while retaining their avoidance of immunological rejection and targeting ability will provide impetus for development in the field of gene therapy. Breakthroughs in exosome-based vector systems and optimized gene editing tools will provide the momentum necessary for establishment of exosomes as a practicable treatment for genetic diseases.

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