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MSCs derived extracellular vesicles as a therapeutic paragon for neurodegenerative disorders: A viewpoint

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Abstract: Neurodegenerative disorders are a vicious woe to the public health and wellness. Uncertainty in their underlying causes, lack of effective biomarkers for their early detection, existence of only supportive therapy, and their ever rising incidence creates an unmatched need for targeted therapies. Mesenchymal Stem Cells (MSCs) have found to be promising candidates for regenerative and remedial therapy in neurodegenerative disorders, however several biological risks and practical issues impede in their translational utility. Deriving from MSCs are certain Extracellular Vesicles (EVs), which aid in the paracrine action of MSCs and have lately gained the scientific interest for their implacability in diverse set ups. Their cargo is of utmost importance and is being explored in various different diseases like heart diseases, neuronal diseases, respiratory diseases and hepatic diseases. They thereby hold the position of a likely prospective remedial candidate for therapy against neurodegenerative disorders.

Abbreviations

AD:	Alzheimer's diseases
ALS:	Amyotrophic lateral sclerosis
BBB:	Blood brain barrier
CDK5:	Cell division protein kinase
EV:	Extracellular vesicles
MS:	Multiple sclerosis
MSC:	Mesenchymal stem cells
NLRP3:	NAcht Leucine-rich repeat Protein 3
PD:	Parkinson's disease
UC:	Umbilical cord

Viewpoint

Neurodegenerative disorders cause a grave health menace and affect millions of people around the globe. The most common ailments in this spectrum of diseases include Alzheimer's diseases (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), Amyotrophic lateral sclerosis (ALS), Prion diseases, and Huntington's disease (Fayazi *et al.*, 2021). These diseases aggravate the day-to-day activities of the affected individuals, thereby deteriorating their standard of life and wellbeing. Cause of these diseases can be genetic or developmental. Some common causes include misfolding of proteins and their aggregates, neuroinflammation, generation of excessive reactive oxygen species, impaired mitochondrial function, exposure to toxic metals like lead, manganese, arsenic, and lifestyle factors (Shariati *et al.*, 2020). Alzheimer's and Parkinson's disease are the most commonly affecting maladies. As per the recent reports it is suggested that about 6.2 million people in America could be suffering from Alzheimer's disease and about 1.2 million people could develop Parkinson's disease by 2030 (https://www.parkinson.org/Understanding-Parkinsons/Statistics; https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf).

The morbific elements of these diseases are multifarious and the pathogenesis is unclear. Moreover, the absence of any reliable biomarkers poses a great challenge to the early detection of these diseases. As a result, there is unavailability of any definitive cure (Vilaça-Faria *et al.*, 2019). Furthermore, due to unsolicited side effects of pharmaceutical based medications, the remedial approaches against these disorders become limited for now. Therefore, the focus of therapeutics has recently shifted towards stem cell therapy (Vilaça-Faria *et al.*, 2019). The most popular stem cell types considered for cell therapy include Embryonic Stem Cells, induced Pluripotent Stem Cells, and Adult Multipotent Stem Cells, like Mesenchymal Stem Cells (MSCs). Due to the complex

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ethical concerns intervening in the use of the former, MSCs and their derivatives are now gaining the spotlight (Panda *et al.*, 2021). MSCs are adult multipotent stem cells that can be derived from various sources for instance Bone Marrow, Wharton's Jelly, Adipose Tissue and Dental pulp (Singh *et al.*, 2017). They possess strong differentiation capabilities and regenerative abilities, making them a compelling candidate for therapy against neurodegenerative disorders (Yao *et al.*, 2020; Singh *et al.*, 2020). Despite their immeasurable regenerative potential, they are still unable to be brought forward in the mainstream therapeutics due to several concerns with their transplantation. There have been several reports which suggest that MSCs, due to their large size and when administered in higher and repetitive doses for a substantial effect, are prone to causing emboli which can set off major bodily perils (Sharma *et al.*, 2021). Furthermore their viability is questionable which impedes in a sustained effect. Above that, the chief hindrance in using whole cells for therapy against neurodegenerative disorders is that these approaches require crossing of the blood-brain barrier (BBB), which is impervious to large molecules with size more than 400 Da (Fayazi *et al.*, 2021). In this context, the secretome of MSCs serve as an attractive contender for regenerative therapy against neurodegenerative disorders over their parent cells itself (Guy and Offen, 2020). MSCs, apart from differentiation, act through paracrine mechanisms i.e., by the release of soluble factors directly in their extracellular locale, and by the secretion of small membrane bound vesicles consisting bioactive molecules known as Extracellular Vesicles. These EVs have recently gathered the limelight and strong scientific interest of the researchers due to their small size aiding flexibility, and fascinatingly intricate cargo landscape (Gupta *et al.*, 2021). EVs can be classified into 3 broad categories including exosomes, microvesicles and apoptotic bodies, and could be characterized based upon their size, morphology and functionality (Willms *et al.*, 2018). Their functionality is aided by the cargo that they ferry.

The cargo of MSC derived EVs contain assorted molecules like mRNAs, miRNA, proteins, enzymes and many more which can potentially cause epigenetic manipulations. Of the EVs cargo, miRNAs have recently gained popularity as they have been found to cause epigenetic modulations via translational silencing and mRNA destabilization (Qing *et al.*, 2018). Their horizontal transfer of cargo via the means of EVs serves as a mechanism of genetic expression regulation which could be beneficial for neuronal regeneration and neuroprotection, mainly by suppression of neuroinflammation. This horizontal transfer could involve the transfer of miRNAs, siRNAs, mRNAs, proteins for respective epigenetic modulations as discussed above. MSCs and the EVs derived from them are widely known for their anti-inflammatory potential which can hold significance for reduction in neuroinflammation, which is one of the major underlying cause and phenomena in neurodegenerative disorders (Long *et al.*, 2017; Thomi *et al.*, 2019). For instance, miR-188-3p in MSCs EVs has been found to suppress autophagy, neuroinflammation and apoptosis by targeting CDK5 and NLRP3 and thereby exerting a neuroprotective and regenerative effect (Li *et al.*, 2021). Lee *et al.* (2014) showed that MSCs-EVs were found to transfer miR124 and miR145 which exerted regenerative and differentiation influence on astrocytes and human neuroprotective cells. Furthermore, Stem cells EV contains of miRs including miR-1000, miR-133b, miR-21, miR-34a, and miR-219 which are found to possess neuroprotective activities, like enhancing neural plasticity (Xin *et al.*, 2013), suppression of apoptosis (Ma *et al.*, 2013; Vallabhaneni *et al.*, 2015), and promotion of myelination (Pusic and Kraig, 2014). Gao *et al.* (2020) showed that MSC-EVs were able to rescue neurons and promote their survival *via* the transfer of miR-21. Also, upon hypoxic exposure to MSCs, it was found that the EVs derived from them were able to promote cerebral angiogenesis (Gregorius *et al.*, 2021). miR-106b carried by the MSC-EVs was suggested to enhance neuronal autophagy and it was also found to be a regulator and inhibitor of CDKN2B, thereby preventing neuronal apopotosis in Parkinson's disease (Bai *et al.*, 2021). Furthermore, the presence of membrane metallo-endopeptidases like neprilysin in MSCs-EVs help in cleavage of beta amyloid peptides, the accumulation of which is a pathological aspect in Alzheimer's Disease (Fayazi *et al.*, 2021; Vilaça-Faria *et al.*, 2019; Cone *et al.*, 2021). We would also like to highlight that these EVs also have a potent anti-oxidant property which may be exploited to combat the oxidative stress caused post seizures (Luo *et al.*, 2021). However it is necessary that the concentration of administration of EVs and the dosage repetitions be a point of consideration during therapy.

Certain studies have suggested that EVs are found to be involved in mitochondrial transfer as a rescue mechanism (Paliwal *et al.*, 2018). This could have a role in neurodegenerative diseases wherein mitochondrial function is impaired. Such studies evidence the biological potential and remedial action of MSCs-EVs as a therapeutic agent in neurodegenerative disorders wherein they could be recognized for both regenerative and diseases progression inhibiting actions (Silva *et al.*, 2020; Peruzzotti-Jametti *et al.*, 2021).

The strategy of using MSCs-EVs as a therapeutic agent is strongly promoted in our viewpoint due to the many advantages of EVs over their parent cells such as their nano-size which makes them safer to administer thereby negating the risk of embolism which persists upon whole cell transplantation (Sharma *et al.*, 2021; Upadhya and Shetty, 2019; Upadhya and Shetty, 2021). Also, this helps them in crossing physiological barriers, for instance, the Blood Brain barrier easily (Sharma *et al.*, 2021). Their viability and stability is unquestionable unlike their parent cells. Further, whereas MSCs have been found to get entrapped in the lung vasculature upon transplantation, they have a remote and far reaching effect (Sharma *et al.*, 2021).

EVs can also be modified to enhance their functionality. This can be done by the aid of biotechnological and bioengineering techniques which can, for example, be used to modify their surface markers for a targeted delivery. Additionally, their vesicular membrane bound structure can be utilized for encapsulation of drugs in order to employ them as a drug delivery vehicle (Panda *et al.*, 2021). However this field requires extensive research and an ADME database as suggested by Baek *et al.* (2019), should be established.

Despite their many advantages, MSC derived EVs are still in their nascent stages of therapeutic developments due to many hurdles, for instance, ambiguity in their cargo relative to the tissue specific differences of MSCs from various tissue sources (Shariati *et al.*, 2020). This serves as a major point of

consideration that due to the heterogeneity in their sources, MSC-EVs could possess differential molecular profile and functionality. The most popular MSCs sources to be used in clinical trials include Bone Marrow, Adipose Tissue and Umbilical Cord derived MSCs. In our viewpoint, we would like to suggest that Umbilical cord derived MSCs (UC-MSCs) could have an upper hand over the other tissue sources as they derive from an immunologically benefited site, and are naïve in terms of exposure to circumstantial stressors (Sharma *et al*., 2021). UC-MSCs are also found to be immunologically more potent and better in terms of immunomodulation, which promotes their use against neurodegenerative disorders, as brain inflammation and neuroinflammation are one of their characteristic pathophysiological features (Sharma *et al*., 2021; Rawat *et al*., 2018). In addition, the cargo profiling needs to be standardized upon different passage numbers as well. Furthermore the various types of EVs and their inherent differences need to be characterized as well. The large scale production and isolation of the EVs also pose a major challenge but is of utmost importance in order to ensure that it meets the need of the hour (Adlerz *et al*., 2020; Yuan *et al*., 2021).

In conclusion, we can suggest that even though the use of MSC-EVs is an attractive strategy for remedial approaches against neurodegenerative disorders, such in-depth standardization studies are the need of the hour to bring them forward as the key therapeutic envoy for treatment in neurodegenerative disorders.

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References

Adlerz K, Patel D, Rowley J, Ng K, Ahsan T (2020). Strategies for scalable manufacturing and translation of MSC-derived extracellular vesicles. *Stem Cell Research* **48**: 101978. DOI 10.1016/j.scr.2020.101978.

Baek G, Choi H, Kim Y, Lee HC, Choi C (2019). Mesenchymal stem cell-derived extracellular vesicles as therapeutics and as a drug delivery platform. *Stem Cells Translational Medicine* **8**: 880–886. DOI 10.1002/sctm.18-0226.

Bai X, Dong Q, Zhao L, Yao Y, Wang B (2021). microRNA-106b-containing extracellular vesicles affect autophagy of neurons by regulating CDKN2B in Parkinson's disease. *Neuroscience Letters* **760**: 136094. DOI 10.1016/j.neulet.2021.136094.

Cone AS, Yuan X, Sun L, Duke LC, Vreones MP et al. (2021). Mesenchymal stem cell-derived extracellular vesicles ameliorate Alzheimer's disease-like phenotypes in a preclinical mouse model. *Theranostics* **11**: 8129–8142. DOI 10.7150/thno.62069.

Fayazi N, Sheykhhasan M, Asl SS, Najafi R (2021). Stem cell-derived exosomes: A new strategy of neurodegenerative disease treatment. *Molecular Neurobiology* **21**: 1–21.

Gao X, Xiong Y, Li Q, Han M, Shan D et al. (2020). Extracellular vesicle-mediated transfer of miR-21-5p from mesenchymal stromal cells to neurons alleviates early brain injury to improve cognitive function via the PTEN/Akt pathway after subarachnoid hemorrhage. *Cell Death & Disease* **11**: 1–6.

Gregorius J, Wang C, Stambouli O, Hussner T, Qi Y et al. (2021). Small extracellular vesicles obtained from hypoxic mesenchymal stromal cells have unique characteristics that promote cerebral angiogenesis, brain remodeling and neurological recovery after focal cerebral ischemia in mice. *Basic Research in Cardiology* **116**: 1–9.

Gupta S, Krishnakumar V, Sharma Y, Dinda AK, Mohanty S (2021). Mesenchymal stem cell derived exosomes: A nano platform for therapeutics and drug delivery in combating COVID-19. *Stem Cell Reviews and Reports* **17**: 33–43. DOI 10.1007/s12015-020-10002-z.

Guy R, Offen D (2020). Promising opportunities for treating neurodegenerative diseases with mesenchymal stem cell-derived exosomes. *Biomolecules* **10**: 1320. DOI 10.3390/biom10091320.

Lee HK, Finniss S, Cazacu S, Xiang C, Brodie C (2014). Mesenchymal stem cells deliver exogenous miRNAs to neural cells and induce their differentiation and glutamate transporter expression. *Stem Cells and Development* **23**: 2851–2861. DOI 10.1089/scd.2014.0146.

Li Q, Wang Z, Xing H, Wang Y, Guo Y (2021). Exosomes derived from miR-188-3p-modified adipose-derived mesenchymal stem cells protect Parkinson's disease. *Molecular Therapy-Nucleic Acids* **23**: 1334–1344. DOI 10.1016/j.omtn.2021.01.022.

Long Q, Upadhya D, Hattiangady B, Kim DK, An SY, Shuai B, Prockop DJ, Shetty AK (2017). Intranasal MSC-derived A1-exosomes ease inflammation, and prevent abnormal neurogenesis and memory dysfunction after status epilepticus. *Proceedings of the National Academy of Sciences of the United States of America* **114**: E3536–E3545. DOI 10.1073/pnas.1703920114.

Luo Q, Xian P, Wang T, Wu S, Sun T et al. (2021). Antioxidant activity of mesenchymal stem cell-derived extracellular vesicles restores hippocampal neurons following seizure damage. *Theranostics* **11**: 5986–6005. DOI 10.7150/thno.58632.

Ma Y, Bao-Han W, Lv X, Su Y, Zhao X, Yin Y, Zhang X, Zhou Z, MacNaughton WK, Wang H (2013). MicroRNA-34a mediates the autocrine signaling of PAR2-activating proteinase and its role in colonic cancer cell proliferation. *PLoS One* **8**: e72383.

Paliwal S, Chaudhuri R, Agrawal A, Mohanty S (2018). Human tissue-specific MSCs demonstrate differential mitochondria transfer abilities that may determine their regenerative abilities. *Stem Cell Research & Therapy* **9**: 1–9. DOI 10.1186/s13287-018-1012-0.

Panda B, Sharma Y, Gupta S, Mohanty S (2021). Mesenchymal stem cell-derived exosomes as an emerging paradigm for regenerative therapy and nano-medicine: A comprehensive review. *Life* **11**: 784. DOI 10.3390/life11080784.

Peruzzotti-Jametti L, Bernstock JD, Willis CM, Manferrari G, Rogall R et al. (2021). Neural stem cells traffic functional mitochondria via extracellular vesicles. *PLoS Biology* **19**: e3001166. DOI 10.1371/journal.pbio.3001166.

Pusic AD, Kraig RP. (2014). Youth and environmental enrichment generate serum exosomes containing miR-219 that promote CNS myelination. *Glia* **62**: 284–299.

Qing L, Chen H, Tang J, Jia X (2018). Exosomes and their microRNA cargo: New players in peripheral nerve regeneration. *Neurorehabilitation and Neural Repair* **32**: 765–776. DOI 10.1177/1545968318798955.

Rawat S, Srivastava P, Prabha P, Gupta S, Kanga U, Mohanty S (2018). A comparative study on immunomodulatory potential of tissue specific hMSCs: Role of HLA-G. *IOSR Journal of Dental and Medical Sciences* **17**: 32–40.

Shariati A, Nemati R, Sadeghipour Y, Yaghoubi Y, Baghbani R, Javidi K, Zamani M, Hassanzadeh A (2020). Mesenchymal stromal cells (MSCs) for neurodegenerative disease: A promising frontier. *European Journal of Cell Biology* **99**: 151097. DOI 10.1016/j.ejcb.2020.151097.

Sharma Y, Gupta S, Mohanty S (2021). Mesenchymal stem cell-derived exosome as a nano weapon to target the COVID-19 pandemic. *BIOCELL* **45**: 517–520. DOI 10.32604/biocell.2021.014621.

Silva J, Murray LM, Su Y, Mc Auley DF, O'Kane CM, Krasnodembskaya A (2020). Transfer of mitochondria from mesenchymal stromal cells through extracellular vesicles improves alveolar epithelial-capillary barrier in ARDS. *ERJ Open Research* **6**: 98. DOI 10.1183/23120541.LSC-2020.98.

Singh M, Gupta S, Rawat S, Midha S, Jain KG et al. (2017). Mechanisms of action of human mesenchymal stem cells in tissue repair regeneration and their implications. *Annals of the National Academy of Medical Sciences* **53**: 104–120. DOI 10.1055/s-0040-1712752.

Singh M, Vaishnav PK, Dinda AK, Mohanty S (2020). Evaluation of priming efficiency of forskolin in tissue-specific human mesenchymal stem cells into dopaminergic neurons: An *in vitro* comparative study. *Cells* **9**: 2058.

Thomi G, Surbek D, Haesler V, Joerger-Messerli M, Schoeberlein A (2019). Exosomes derived from umbilical cord mesenchymal stem cells reduce microglia-mediated neuroinflammation in perinatal brain injury. *Stem Cell Research & Therapy* **10**: 1–6. DOI 10.1186/s13287-019-1207-z.

Upadhya D, Shetty AK (2019). Extracellular vesicles as therapeutics for brain injury and disease. *Current Pharmaceutical Design* **25**: 3500–3505. DOI 10.2174/1381612825666191014164950.

Upadhya D, Shetty AK (2019b). Promise of extracellular vesicles for diagnosis and treatment of epilepsy. *Epilepsy & Behavior* **12**: 106499. DOI 10.1016/j.yebeh.2019.106499.

Vallabhaneni KC, Penfornis P, Dhule S, Guillonneau F, Adams KV, Mo YY, Xu R, Liu Y, Watabe K, Vemuri MC, Pochampally R (2015). Extracellular vesicles from bone marrow mesenchymal stem/stromal cells transport tumor regulatory microRNA, proteins, and metabolites. *Oncotarget* **6**: 4953.

Vilaça-Faria H, Salgado AJ, Teixeira FG (2019). Mesenchymal stem cells-derived exosomes: A new possible therapeutic strategy for Parkinson's disease? *Cells* **8**: 118. DOI 10.3390/cells8020118.

Willms E, Cabañas C, Mäger I, Wood MJ, Vader P (2018). Extracellular vesicle heterogeneity: Subpopulations, isolation techniques, and diverse functions in cancer progression. *Frontiers in Immunology* **9**: 738. DOI 10.3389/fimmu.2018.00738.

Xin H, Li Y, Liu Z, Wang X, Shang X, Cui Y, Zhang ZG, Chopp M (2013). MiR-133b promotes neural plasticity and functional recovery after treatment of stroke with multipotent mesenchymal stromal cells in rats via transfer of exosome-enriched extracellular particles. *Stem Cells* **31**: 2737–2746.

Yao P, Zhou L, Zhu L, Zhou B, Yu Q (2020). Mesenchymal stem cells: A potential therapeutic strategy for neurodegenerative diseases. *European Neurology* **83**: 235–241. DOI 10.1159/000509268.

Yuan F, Li YM, Wang Z (2021). Preserving extracellular vesicles for biomedical applications: Consideration of storage stability before and after isolation. *Drug Delivery* **28**: 1501–1509. DOI 10.1080/10717544.2021.1951896.