ACS Chemical Neuroscience

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Cell-Derived Exosome Therapy: A Novel Approach to Treat Post-traumatic Brain Injury Mediated Neural Injury

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Cite This: https://dx.doi.org/10.1021/acschemneuro.0c00368 Read Online

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ABSTRACT: Traumatic brain injury (TBI) causes serious neuronal injury that often leads to death. To date there is no clinically successful treatment strategy that has been reported which offers repair of the brain injury or neural injury. Significant attempts have been made to develop effective therapies for TBI, and one of the most promising approaches is a stem cell based therapeutic approach with mesenchymal stem cells (MSCs). This approach is regarded as having the most potential in regenerative medicine. Toward this venture, the generation and release of exosomes can be attributed to the therapeutic effects of MSCs. Exosomes are nanosized vesicles, carry proteins, lipids, mRNA, and miRNA, and assist in cell−cell communication. Exosomes can interact with brain parenchyma cells and with the neurogenic niche, which can help in neurogenesis and brain remodeling. Exosomes derived from MSCs and human-induced pluripotent stem cells (hiPSCs) can be a promising approach in neuronal injury healing. In this Viewpoint, we discussed the most recent knowledge for exosome therapies for neural injuries and highlighted the major advantages of this therapy.

KEYWORDS: *Traumatic brain injuries, MSCs, hiPSCs, regenerative medicine, exosome therapy, neurogenic niche, neurogenesis, brain remodeling*

Traumatic brain injuries (TBIs) are caused by a jolt to the head that interferes with the normal function of the brain. Approximately, 30 million of people suffer from TBIs globally and TBI causes the death of millions of injured persons. Immediately after TBI, "reactive gliosis" takes place, which will activate microglia and astrocytes by increasing inflammatory mediators. The primary damage phase of neuroinflammation includes injury of axons, hemorrhage, and brain swelling, and the secondary damage phase results in neurodegeneration and cell death. Studies showed that cell therapy using mesenchymal stem cells (MSCs) can be a promising treatment strategy for TBI. MSCs interact with parenchymal cells in the brain, resulting in a decrease in the expression of axon inhibitory molecules and an increase in the production of neuroprotective factors, which influences neurite outgrowth and promotes recovery of normal neurological function after neural injury. The concept that recovery from TBI after MSC therapy is due to the replacement of injured tissue by differentiated MSCs is more unlikely because a relatively small number of MSCs survive after transplantation, and among the surviving MSCs only a small portion can differentiate into neural cells, which is not sufficient for recovery. The likely cause can be secretion and expression of factors by MSCs or induction of neighboring cells to express regulatory molecules, which increase the survival and division of brain parenchymal cells and assist in brain remodeling. MSC therapy suffers from some disadvantages: a relatively small amount of MSCs can be injected intracranially and can cause brain ischemia, distribution of MSCs in the whole body due to intravenous injection, and uncontrolled growth of the transplanted cells.[1] Studies showed that the therapeutic effect of MSCs is due to the vigorous generation and release of exosomes. Exosomes are endosome derived nanosized vesicles that help in cell−cell communication, which can carry proteins, peptides, lipids, mRNA, noncoding RNAs, and regulate cellular functions. Cell-free exosomes derived from MSCs can be used in TBI cases. Zang et al. showed that, with intravenous treatment with cell-free exosomes derived from MSCs after 24 h of injury, the cortical lesion volume remained the same and significant improvement was reported in cognitive and functional recovery, neuroblasts, mature neurons, with an enhanced number of endothelial cells in the dentate gyrus (DG) and decrease in neuroinflammation. They have also reported a decrease in GFAP+ astrocytes and CD68+ microglia/macrophage activation after treatment, which is associated with increased angiogenesis, neurogenesis, and decreased neuroinflammation in the brain.[2] Another study by Zang et al. suggests that human MSCs (hMSCs) seeded in 3D scaffolds generate a greater number of exosomes compared to hMSCs seeded in 2D conditions and that exosomes derived from 3D culture provide a better result in learning compared to the 2D condition in spite of administration of equal amounts of exosome from both cultures. So we can interpret from the above data as the content of the exosome is associated with treatment outcome and exosome content differs with culture

Received: June 13, 2020
Accepted: June 16, 2020

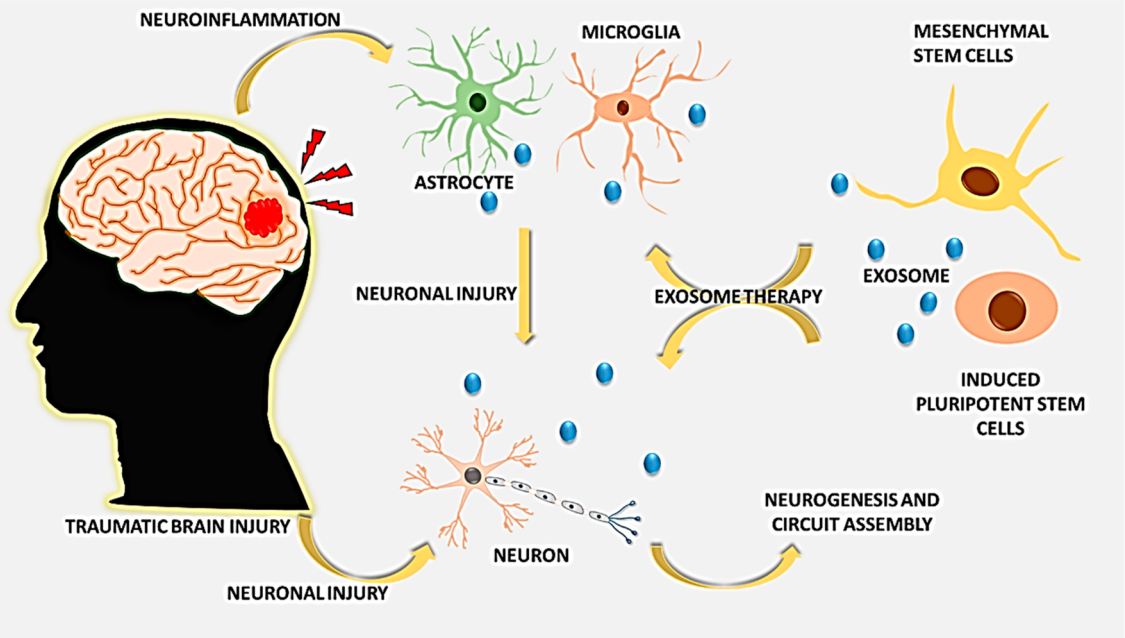

Figure 1. Schematic representation of exosome therapy following traumatic brain injury.

conditions. Noncoding RNA like miRNA contained in exosomes can play a major role in modulating cellular processes of recipient cells in the neurogenic niche present in the DG in the hippocampus and lateral ventricles and influence the neurogenesis process. A group of scientists discovered that MSCs and related exosomes had increased levels of miR-133b after MSCs were cultured in ischemic tissue extracts from rats with middle cerebral artery occlusion (MCAo). They have shown an increase in miR-133b concentration is observed in neurons and glial cell primary culture supplemented with exosomes derived from MSCs. By miR-133b knockdown in MSCs, they confirmed that an increase of miRNA levels in astrocytes is a result of exosome-mediated transfer of miRNA from MSCs. Further, they experimentally proved that transfer of miRNA to neurons and glial cells significantly increased the number of neurite branches and neurite total length and helped in brain remodeling.[3] Apart from hMSCs, a current study by Sharma et al. showed that exosomes derived from induced pluripotent stem cell (iPSC)-generated neurons can help in neurogenesis and can regulate neural circuit development. This study demonstrated the increase of proliferation in neural culture and in the DG of the P4 mouse upon exosome treatment. By comparing the proteome of exosomes released by iPSC-generated neural cultures lacking Methyl-CpG-binding protein 2 (MECP2), a model representing Rett syndrome, with genetically identical rescue control neural culture-derived exosomes, they interpreted that control exosomes contain multiple functional signaling networks that help in neuronal circuit development. They further demonstrated that treatment of exosomes from control neural to MECP2 knockdown neuron culture could rescue the shortfalls in neuronal division, differentiation, synapse generation, and neuronal firing.[4] In addition to systemic administration, Li et al. has developed an innovative strategy for exosome administration using a peptide hydrogel with exosomes immobilized in it (Exo-pGel). Their study suggests that transplantation of Exo-pGel helps in retention and controlled release of exosomes in host injured tissue and can evoke remarkable nerve recovery by successfully alleviating inflammation.[5] From the above-mentioned studies, we can interpret that cell-derived exosome therapy can be a promising strategy for neuronal injury treatment. Figure 1 shows a schematic representation of different outcomes of TBI and the role of exosome therapy in rescue from neuronal injuries.

In conclusion, exosomes derived from MSCs or hiPSCs can interact with brain parenchyma and induce the neurogenic niche, which can help in efficient rescue from neuronal injuries. The advantages that make exosomes superior over other therapy include the following: (1) exosomes can cross the blood-brain barrier, are less invasive, are less or not tumorigenic, and are less or not immunogenic, (ii) their shelf life and half-life are longer in patients, which is good for long-term storage without any loss of function, and (iii) they do not replicate or induce microvascular embolism. Finally, we envision that this approach has much potential for therapy of TBI patients in near future.

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Complete contact information is available at: https://pubs.acs.org/10.1021/acschemneuro.0c00368

https://dx.doi.org/10.1021/acschemneuro.0c00368
ACS Chem. Neurosci. XXXX, XXX, XXX−XXX

Author Contributions

Satyajit Ghosh, Shubham Garg, and Surajit Ghosh discussed this area for exploration of therapeutic approaches for TBI and jointly wrote the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Satyajit Ghosh and Shubham Garg thank MHRD, IIT Jodhpur, for their fellowship. Surajit Ghosh kindly acknowledges SERB India (CRG/2019/000670) for financial support and IIT Jodhpur for initiation grant and infrastructure.

■ REFERENCES

(1) Xiong, Y., Mahmood, A., and Chopp, M. (2017) Emerging potential of exosomes for treatment of traumatic brain injury. *Neural Regener. Res. 12* (1), 19.

(2) Zhang, Y., Chopp, M., Meng, Y., Katakowski, M., Xin, H., Mahmood, A., and Xiong, Y. (2015) Effect of exosomes derived from multipluripotent mesenchymal stromal cells on functional recovery and neurovascular plasticity in rats after traumatic brain injury. *J. Neurosurg. 122* (4), 856−867.

(3) Xin, H., Li, Y., Buller, B., Katakowski, M., Zhang, Y., Wang, X., Shang, X., Zhang, Z. G., and Chopp, M. (2012) Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. *Stem Cells 30* (7), 1556−1564.

(4) Sharma, P., Mesci, P., Carromeu, C., McClatchy, D. R., Schiapparelli, L., Yates, J. R., Muotri, A. R., and Cline, H. T. (2019) Exosomes regulate neurogenesis and circuit assembly. *Proc. Natl. Acad. Sci. U. S. A. 116* (32), 16086−16094.

(5) Li, L., Zhang, Y., Mu, J., Chen, J., Zhang, C., Cao, H., and Gao, J. (2020) Transplantation of Human Mesenchymal Stem Cell-Derived Exosomes Immobilized in An Adhesive Hydrogel for Effective Treatment of Spinal Cord Injury. *Nano Lett. 20* (6), 4298−4305.

https://dx.doi.org/10.1021/acschemneuro.0c00368
ACS Chem. Neurosci. XXXX, XXX, XXX−XXX