

Bone marrow mesenchymal stem cell treatment improves post-stroke cerebral function recovery by regulating gut microbiota in rats

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Abstract

Early intervention with bone marrow mesenchymal stem cells to change the form and function of the gut microbiota may help rats regain neurological function after a stroke.

Key Words: Ischemic stroke; Bone marrow mesenchymal stem cells; Neurological function; Gut microbiota

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Core Tip: Using bone marrow mesenchymal stem cells (BMSCs) as a therapy method may be a successful technique to combat neurological conditions like ischemic stroke. The dysbiosis of the gut microbiota can impact stroke prognosis, according to the gut-brain axis. Zhao *et al*'s study examined the interaction between BMSCs and the gut flora. Zhao *et al*'s research showed that the ischemic stroke treatment provided by BMSCs may have an impact on the structure and function of the microbiome.

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TO THE EDITOR

We recently read the work by Zhao *et al*[1] in the *World Journal of Stem Cells* with interest. They presented three groups, including a sham surgical control group, a group with temporary middle cerebral artery occlusion (MCAO), and a group with MCAO treated with bone marrow mesenchymal stem cells (BMSCs).

In this study using rats, Zhao *et al*[1] investigated the therapeutic effects of BMSC transplantation in the treatment of ischemic stroke as well as the relationship between BMSC transplantation and gut microbiota outcomes in terms of enhancing the recovery of neurological function after stroke. Overall, the authors' excellent unique contribution to the current investigation of bone marrow mesenchymal stem cell therapy in ischemic stroke, together with a concise explanation of its therapeutic potential, were both greatly appreciated.

A more thorough explanation of Zhao *et al*[1] research is required, in order for the readers to understand clearly what is happening in the background. In addition, more proof is required to support the writers' claims. Possible changes in infarction volume following BMSC treatment is one area that has to be looked into in order to verify the authors' assertions in this article. Immunomodulation, the release of trophic factors to promote therapeutic effects, inducing angiogenesis, promoting neurogenesis, reducing infarct volume, replacing damaged cells, and secreting extracellular vehicles are just a few of the therapeutic mechanisms used by MSCs and the primary proteins in the treatment of stroke[2-4].

In animal models, MSC transplantation resulted in the production of inflammatory mediators and altered cytokine expression. The anti-inflammatory cytokines interleukin (IL)-4, IL-10 and tumor necrosis factor can be produced in greater quantities by MSCs. On the other hand, it has been demonstrated that pro-inflammatory cytokines including IL-1, interferon, and membrane cofactor protein-1 are inhibited from being expressed by MSCs. By altering these cytokines, MSCs reduced inflammation by affecting a variety of immune cell and immunological response pathways. The production of trophic factors used in the treatment of stroke was helped or created by MSCs. The trophic factors that were investigated included neurotrophic factors like brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), as well as trophic factors like nerve growth factor, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). MSC-secreted trophic factors decrease infarct size, limit neuron death, enhance neuron proliferation, and activate angiogenesis. Following transplantation, MSCs moved from the vascular network outside of the lesion to the infarct site and secreted BDNF to decrease the infarct volume. Both MSCs and MSCs carrying the *BDNF* gene decreased infarct volume and boosted neurogenesis; however, the latter effect was more pronounced because MSCs carrying the *BDNF* gene maintained high BDNF levels during the crucial post-stroke period. Additionally, transplanted *GDNF*-gene-positive MSCs decreased infarct volume similarly to *BDNF*-gene-positive MSCs. Furthermore, if the *BDNF* gene is overexpressed, MSCs might enter the brain development route. Moreover, MSCs can be guided toward brain growth by the overexpression of the *BDNF* gene. VEGF aids in angiogenesis as well. PDGF promoted angiogenesis, axon growth, cell migration, primary cortical neuron growth, and inhibited neuroinflammation. In addition to preventing neuroinflammation, PDGF promoted cell migration, primary cortical neuron proliferation, angiogenesis, and axon growth[4,5].

Is there a connection between BMSC therapy and better infarction volume and gut microbiota regulation? A magnetic resonance imaging (MRI) assessment of the ischemic lesion volume is necessary to provide an answer to this query[6]. Some researchers have used MRI measures for ischemic lesion volume in their research after BMSC injection in MCAO model rats, according to the literature[7,8]. Immunohistochemistry, enzyme-linked immunosorbent test, and numerous other behavioral function tests, in addition to MRI measures[6,9-12], are strongly advised in study of Zhao *et al*[1]. However, to determine whether there is a connection between stroke recovery and gut microbiota regulation following treatment with bone marrow-derived mesenchymal stem cells, the results of previous studies (such as assessment of neuronal nuclei (NeuN) and VEGF expression and measurement of rat endothelial cell antigen 1 and platelet-derived growth factor receptors (PDGF-R), treadmill stress test and MRI studies, and measurement of infarct volume) could be compared to the results of Zhao *et al*[1].

Cho *et al*[11], for instance, measured the proportion of NeuN- and VEGF-positive cells in the ischemia boundary zone using immunohistochemistry[6,9-12].

Furthermore, the treadmill stress test was utilized for behavioral function analysis in two research investigations conducted after BMSC injections to a rat MCAO model[6,10]. Other tests, such as 2,3,5-triphenyl tetrazolium chloride staining, contribute to the study's results[13]. Previous study evaluations could help provide evidence for Zhao *et al*[1] investigation and reveal a possible link between stroke recovery and gut microbiota regulation after BMSC treatment.

A recent work by Xia *et al*[14] used fecal transplantation from stroke patients with high-stroke dysbiosis index (SDI-H) to mice to examine the possible microbiota dysbiotic influence on stroke injury in a mouse model. The spleen and small intestine of SDI-H recipient mice displayed an increased abundance of pro-inflammatory (IL-17+) $\gamma\beta$ T cells, although CD4+CD25+ helper T (T helper) cells and regulatory T cells (Treg) (CD4+ Foxp3+) cells were lacking in both the spleen and small intestine. The findings showed that following stroke, SDI-H recipient mice had an increased infarct volume and had worse neurological functional outcomes[14].

Another study used germ-free animals to colonize the gut microbiota in order to show the neuroprotective impact of this microbiome on ischemia injury[15]. Thus, in the ischemic brain of the post-stroke mice, there were more microglia/macrophages and a noticeably higher expression of proinflammatory cytokines[15]. After stroke, the number of T helper, Treg, and Th17 cells rose in Peyer's patches and was even boosted in the spleens. A similar pattern was also seen in the ischemic brain, which resulted in a decreased lesion volume in mice's brains[15].

Through the use of three groups (the Sham, MCAO, and BMSCs groups) of 30 samples, Zhao *et al*[1] were able to extract 1494295 quality-filtered 16s rRNA gene sequences, with an average of 498101281 reads per sample. When the microbial diversity of the Sham, MCAO, and BMSCs groups were evaluated, there was no statistically significant difference between the three groups according to the Shannon and Chao index values.

Consequently, it appears that beta gut microbiota diversity may provide more information regarding the gut microbiota-stroke link in addition to alpha gut microbiota[16].

FOOTNOTES

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REFERENCES

- 1 **Zhao LN**, Ma SW, Xiao J, Yang LJ, Xu SX, Zhao L. Bone marrow mesenchymal stem cell therapy regulates gut microbiota to improve post-stroke neurological function recovery in rats. *World J Stem Cells* 2021; **13**: 1905-1917 [PMID: 35069989 DOI: 10.4252/wjsc.v13.i12.1905]
- 2 **Li W**, Shi L, Hu B, Hong Y, Zhang H, Li X, Zhang Y. Mesenchymal Stem Cell-Based Therapy for Stroke: Current Understanding and Challenges. *Front Cell Neurosci* 2021; **15**: 628940 [PMID: 33633544 DOI: 10.3389/fncel.2021.628940]
- 3 **Zhang Y**, Dong N, Hong H, Qi J, Zhang S, Wang J. Mesenchymal Stem Cells: Therapeutic Mechanisms for Stroke. *Int J Mol Sci* 2022; **23** [PMID: 35269692 DOI: 10.3390/ijms23052550]
- 4 **Fayazi N**, Sheykhhasan M, Soleimani Asl S, Najafi R. Stem Cell-Derived Exosomes: a New Strategy of Neurodegenerative Disease Treatment. *Mol Neurobiol* 2021; **58**: 3494-3514 [PMID: 33745116 DOI: 10.1007/s12035-021-02324-x]
- 5 **Jingli Y**, Jing W, Saeed Y. Ischemic Brain Stroke and Mesenchymal Stem Cells: An Overview of Molecular Mechanisms and Therapeutic Potential. *Stem Cells Int* 2022; **2022**: 5930244 [PMID: 35663353 DOI: 10.1155/2022/5930244]
- 6 **Kiyose R**, Sasaki M, Kataoka-Sasaki Y, Nakazaki M, Nagahama H, Magota H, Oka S, Ukai R, Takemura M, Yokoyama T, Kocsis JD, Honmou O. Intravenous Infusion of Mesenchymal Stem Cells Enhances Therapeutic Efficacy of Reperfusion Therapy in Cerebral Ischemia. *World Neurosurg* 2021; **149**: e160-e169 [PMID: 33618048 DOI: 10.1016/j.wneu.2021.02.056]
- 7 **Ukai R**, Honmou O, Harada K, Houkin K, Hamada H, Kocsis JD. Mesenchymal stem cells derived from peripheral blood protects against ischemia. *J Neurotrauma* 2007; **24**: 508-520 [PMID: 17402856 DOI: 10.1089/neu.2006.0161]
- 8 **Ding G**, Chen J, Chopp M, Li L, Yan T, Li Q, Cui C, Davarani SP, Jiang Q. Cell Treatment for Stroke in Type Two Diabetic Rats Improves Vascular Permeability Measured by MRI. *PLoS One* 2016; **11**: e0149147 [PMID: 26900843 DOI: 10.1371/journal.pone.0149147]
- 9 **Nagahama H**, Nakazaki M, Sasaki M, Kataoka-Sasaki Y, Namioka T, Namioka A, Oka S, Onodera R, Suzuki J, Sasaki Y, Kocsis JD, Honmou O. Preservation of interhemispheric cortical connections through corpus callosum following intravenous infusion of mesenchymal stem cells in a rat model of cerebral infarction. *Brain Res* 2018; **1695**: 37-44 [PMID: 29802840 DOI: 10.1016/j.brainres.2018.05.033]
- 10 **Nakazaki M**, Sasaki M, Kataoka-Sasaki Y, Oka S, Namioka T, Namioka A, Onodera R, Suzuki J, Sasaki Y, Nagahama H, Mikami T, Wanibuchi M, Kocsis JD, Honmou O. Intravenous infusion of mesenchymal stem cells inhibits intracranial hemorrhage after recombinant tissue plasminogen activator therapy for transient middle cerebral artery occlusion in rats. *J*

- Neurosurg* 2017; **127**: 917-926 [PMID: 28059661 DOI: 10.3171/2016.8.JNS16240]
- 11 **Cho DY**, Jeun SS. Combination therapy of human bone marrow-derived mesenchymal stem cells and minocycline improves neuronal function in a rat middle cerebral artery occlusion model. *Stem Cell Res Ther* 2018; **9**: 309 [PMID: 30413178 DOI: 10.1186/s13287-018-1011-1]
 - 12 **Lambertsen KL**, Biber K, Finsen B. Inflammatory cytokines in experimental and human stroke. *J Cereb Blood Flow Metab* 2012; **32**: 1677-1698 [PMID: 22739623 DOI: 10.1038/jcbfm.2012.88]
 - 13 **Sanchez-Bezanilla S**, Nilsson M, Walker FR, Ong LK. Can We Use 2,3,5-Triphenyltetrazolium Chloride-Stained Brain Slices for Other Purposes? *Front Mol Neurosci* 2019; **12**: 181 [PMID: 31417355 DOI: 10.3389/fnmol.2019.00181]
 - 14 **Xia GH**, You C, Gao XX, Zeng XL, Zhu JJ, Xu KY, Tan CH, Xu RT, Wu QH, Zhou HW, He Y, Yin J. Stroke Dysbiosis Index (SDI) in Gut Microbiome Are Associated With Brain Injury and Prognosis of Stroke. *Front Neurol* 2019; **10**: 397 [PMID: 31068891 DOI: 10.3389/fneur.2019.00397]
 - 15 **Singh V**, Sadler R, Heindl S, Llovera G, Roth S, Benakis C, Liesz A. The gut microbiome primes a cerebroprotective immune response after stroke. *J Cereb Blood Flow Metab* 2018; **38**: 1293-1298 [PMID: 29846130 DOI: 10.1177/0271678X18780130]
 - 16 **Sun H**, Gu M, Li Z, Chen X, Zhou J. Gut Microbiota Dysbiosis in Acute Ischemic Stroke Associated With 3-Month Unfavorable Outcome. *Front Neurol* 2021; **12**: 799222 [PMID: 35153980 DOI: 10.3389/fneur.2021.799222]



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