

*Letter to Editor*

Meeting Prometheus: The Mechanism of MSC-Based Therapies; Cell Replacement or “Pretended Bystander Effects”?

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To the Editor;

We read with great interest the article by Chen et al. entitled “Protective Effect of adenovirus (Ad)-VEGF-Bone Mesenchymal Stem Cells on Cerebral Infarction” in Turkish Neurosurgery (1). In this article, Chen et al. reported that “intracerebroventricular transplantation of vascular endothelial growth factor (VEGF) gene-modified bone mesenchymal stem cells (BMSCs) in rats after cerebral infarction could reduce reactive gliosis, ameliorate neurological deficit, diminish the percentage of cerebral infarction volume in rats, and facilitate angiogenesis”. We agree with the conclusions drawn from Chen et al. (1). But there are many thorny issues about the genetically modified MSCs and the potential dangers of adenoviruses. These issues are still in debate and further studies are needed to clarify these issues. We will share our ideas and provide the potential solutions on this topic.

Over the years, our understanding of the nature and function of MSCs has undergone a number of paradigm shifts. Initially MSC-based therapies were anticipated to augment the structure and function of damaged or diseased tissues via direct cell replacement (2,3,5). However, it soon became apparent that relatively few MSCs engrafted at these sites of injury and studies in rodents and dogs confirmed that intravenously administered MSCs are caught in the capillaries of the lung,

spleen and lymph nodes, and most MSCs are largely cleared (7). It had been long-known that MSCs produced abundant growth factors and bio-active cytokines, many of which modulate the immune system, limiting inflammation, and aiding healing (6); the field adopted the revisionist viewpoint that MSCs affect tissue repair largely via their paracrine factors and stimulation of host cells, which suggest that MSCs repair damaged tissue due to the “Pretended Bystander Effects”, meaning that the therapeutic participation of MSCs is non-cell, and it may be via cell-to-cell communication or exosomes and/or some metabolites and cytokines (4,7,8).

In our study, we found that allogeneic umbilical cord derived mesenchymal stem cells (UCMSCs) transplantation can play a therapeutic role, but the transplanted cells can only live in the body for about 2 months. We hold the opinion that both “Pretended Bystander Effects” and Cell Replacement play a therapeutic role together. In the process of cell therapy, the former is the main one at the early stage (about a month after cell therapy) and the latter at the later stage (usually a month after cell therapy).

We will provide two solutions to ensure stem cell therapy is more efficient, more practical and more feasible. The first approach is to more effectively target MSCs to tissues and organs, that including the coating of MSCs with antibodies or peptides, modifying the surface molecules into endothelium

binding molecules, biotinylating cell surface molecules and then coating the cells with streptavidin and biotinylated antibodies, which makes the MSCs therapy more targeted, more accurate and more efficient. The second solution is “cell-free” treatment. There are several advantages of using MSC-derived exosomes/microvesicles, extracted from the MSCs culture medium. First, their use avoids the transfer of cells which may have mutated or damaged DNA. Second, the vesicles are small and circulate readily whereas MSCs are too large to circulate easily through capillaries and many MSCs do not get beyond the first pass capillary bed. Third, the dose of infused MSCs quickly diminishes post-transplant, and it may be that the delivery of MSC derived vesicles can achieve a higher “dose” that circulates to a greater extent than the larger cells (7). Therefore, careful attention to detail in “targeted MSCs” and “cell-free” treatment may provide a new therapeutic paradigm for MSC-based therapies. Another solution is efficient induction of targeted differentiation of stem cells to play a substitution role.

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■ REFERENCES

1. Chen B, Zhang F, Li QY, Gong A, Lan Q: Protective effect of Ad-VEGF-Bone mesenchymal stem cells on cerebral infarction. *Turk Neurosurg* 26:8-15, 2016
2. Chopp M, Li Y: Treatment of neural injury with marrow stromal cells. *Lancet Neurol* 1:92-100, 2002
3. Dong HJ, Shang CZ, Li G, Niu Q, Luo YC, Yang Y, Meng HP, Yin HJ, Zhang HX, Zhao ML, Lin L: The Distribution of transplanted umbilical cord mesenchymal stem cells in large blood vessel of rats with traumatic brain injury. *J Craniofac Surg* 28:1615–1619,2017
4. Kurozumi K, Nakamura K, Tamiya T, Kawano Y, Ishii K, Kobune M, Hirai S, Uchida H, Sasaki K, Ito Y, Kato K, Honmou O, Houkin K, Date I, Hamada H: Mesenchymal stem cells that produce neurotrophic factors reduce ischemic damage in the rat middle cerebral artery occlusion model. *Mol Ther* 11:96-104, 2005
5. Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, Lanino E, Sundberg B, Bernardo ME, Remberger M, Dini G, Egeler RM, Bacigalupo A, Fibbe W, Ringden O, Developmental Committee of the European Group for B, Marrow T: Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: A phase II study. *Lancet* 371:1579-1586, 2008
6. Li G, Yang Y, Dong HJ, Lin L: The research progress of mesenchymal stem cells in the treatment of traumatic brain injury. *Turk Neurosurg* 2017 Jul 16 (Epub ahead of print)
7. Phinney DG, Pittenger MF: Concise review: MSC-derived exosomes for cell-free therapy. *Stem Cells* 35:851–858, 2017
8. Zhang B, Wu X, Zhang X, Sun Y, Yan Y, Shi H, Zhu Y, Wu L, Pan Z, Zhu W, Qian H, Xu W: Human umbilical cord mesenchymal stem cell exosomes enhance angiogenesis through the Wnt4/beta-catenin pathway. *Stem Cells Transl Med* 4:513-522, 2015