Possible Research Directions of Stem Cell Transplantation for Intervertebral Disc Degeneration: Commentary on “Transplantation of Hypoxic-Preconditioned Bone Mesenchymal Stem Cells Retards Intervertebral Disc Degeneration via Enhancing Implanted Cell Survival and Migration in Rats”

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The incidence of lower back pain caused by Intervertebral Disc Degeneration (IDD) is increasing due to changes in modern living and working, which places severe family and social burdens [1]. The clinical treatments for IDD are mainly symptomatic conservative and surgical operations. None of the current methods can reverse IDD, and surgery may even accelerate the process of IDD in adjacent segments [2].

Tissue engineering brings hope and challenge to the treatment of IDD [3,4]. The pathological feature of IDD is that Nucleus Pulposus Cells (NPCs) are replaced by fibroblasts. This results in a reduction in the number of cells and extracellular matrix (ECM) components [5]. There is a special hypoxic microenvironment in the intervertebral disc under physiological conditions. The partial pressure of oxygen in the intervertebral disc decreases sharply from the outer fiber ring (7.5kPa) to the nucleus pulposus (0.5kPa) [6]. Due to blood vessel invasion and fibrous ring rupture, etc., the oxygen partial pressure in the nucleus pulposus increased (1.04-12.67kPa) during IDD [7], and the levels of inflammation and oxidative stress in the disc increased [8]. These factors led to low survival rate and poor differentiation of stem cells transplanted into the intervertebral disc, which greatly restricted the effect of stem cell treatment to IDD [9]. These are consistent with our previous research: most of the stem cells transplanted into the intervertebral disc disappeared within a few days [10].

Hypoxia can significantly increase the ability of stem cells to resist damage, which is a powerful endogenous protective mechanism [11]. Hypoxic-preconditioned stem cells had been used in the treatment of liver and kidney ischemia-reperfusion injury [12,13], spinal cord injury [14] and other diseases, which had achieved good results. Based on the beneficial effects of hypoxia on stem cells and the special hypoxic microenvironment in the intervertebral disc, our research team found that hypoxia can greatly improve the early survival rate and the migration of transplanted Bone Mesenchymal Stem Cells (BMSCs) in the intervertebral disc, which greatly improves the early results of stem cell transplantation for IDD (within 4 weeks) [15]. Our follow-up study showed that the number of transplanted BMSCs in the disc was significantly reduced after 8 weeks, and the transplanted BMSCs were undetectable after 12 weeks. These results indicated that hypoxic-preconditioned BMSCs still cannot survive in the intervertebral disc for more than 12 weeks. Therefore, we proposed that although hypoxic-preconditioned BMSCs can greatly improve the early effect for IDD, it still cannot finally solve the problem of long-term survival of transplanted BMSCs in the intervertebral disc. How to improve the long-term survival rate of transplanted stem cells in the intervertebral disc is still a difficult and important point of current research. In addition, there is such the following problem stem cell transplantation: cells leakage [16], intervertebral disc infection [17], and potential tumorigenesis, which also greatly limit the research progress.

It was believed that the main role of stem cell transplantation for IDD is to differentiate into nucleus pulposus cells and secrete ECM through stem cell homing [18]. However, more and more studies indicated that the repair effect of stem cell transplantation may not mainly depend on its homing and differentiation effects, but on paracrine function [19,20]. Studies had found that most of the transplanted stem cells were inactivated in the liver, spleen and lungs. The number of stem cells migrated to the site of injury is less than 1%, and the stem cells cannot survive for a long time, which seriously affected the treatment effect [19]. Humphreys et al found that the regenerated cells in animal models came from their own cells, not transplanted cells by using gene fate mapping technology [20]. In addition, the special hypoxic hyperosmotic closed microenvironment in the intervertebral disc...
disc makes transplanted stem cells more difficult to survive. One of the most promising breakthroughs in the future of stem cell transplantation for IDD may be the paracrine function of stem cells.

Exosomes are important performers of the paracrine effects of stem cells. Exosomes play a role in transmitting information between stem cells and endogenous cells through endocytosis. Exosomes are lower immunogenicity, stronger tissue barrier penetration ability, better stability and controllability compared with stem cells, which play an important role in the treatment of various diseases [21,22]. Exosomes have unique advantages in the field of IDD repair due to their stability and controllability, because of the low-oxygen closed microenvironment in the intervertebral disc. The theoretical and applied research on stem cell-derived exosomes for IDD is still in its infancy, with only research articles. Cheng et al found that mesenchymal stem cells deliver exogenous (MSC-EXO) miR-21 via exosomes to inhibit NPC apoptosis and reduce IDD [23]. Xia et al found that MSC-EXO alleviated IDD via antioxidant and anti-inflammatory effects [24]. Although the current research has achieved some results, the treatment effect is not so good due to the heterogeneity of the materials in MSC-EXO. The exert therapeutic effects of proteins, miRNAs and lncRNAs in MSC-EXO may only occupy a small proportion, and even different types of EXO may have opposite effects on the regulation of recipient cells [25]. Therefore, how to accurately select and enhance the efficacy of repairing MSC-EXO is a hot and difficult point in the current research of EXO repairing IDD.

Hypoxia is a powerful endogenous cell protection mechanism, which can not only regulate the function of BMSCs, but also regulate the types and functions of BMSC-EXO [26,27]. BMSC-EXO contains a total of 857 proteins and 166 miRNAs. It fully represents 32 biological processes, including EXO formation and immune regulation. These 857 proteins and 166 miRNAs are regulated by various factors and will not be expressed at the same time. Hypoxia may be an effective way for precise selection and amplification of potency of MSC-EXO. Studies have shown that exosome-shuttled miR-216a-5p from hypoxic pre-conditioned mesenchymal stem cells repaired traumatic spinal cord injury by shifting microglial M1/M2 polarization [27]. Hypoxia-elicited mesenchymal stem cell-derived exosomes facilitates cardiac repair through miR-125b-mediated prevention of cell death in myocardial infarction [28]. These findings indicate that hypoxia is an effective method to optimize the therapeutic effect of BMSC-EXO, and the combination of EXO and miRNA can provide an effective treatment strategy. The effects of hypoxia on MSC-EXO and whether hypoxia is an effective method for IDD treatment need to be further studied.

In conclusion, stem cell transplantation remains one of the most promising breakthroughs in the treatment to IDD. Although hypoxic-preconditioned stem cells can greatly improve the early effect for IDD, it still cannot finally solve the problem of long-term survival of transplanted stem cells in the intervertebral disc. How to improve the long-term survival rate of transplanted stem cells in the intervertebral disc is still a difficult and important point of current research. One of the hotspots in future stem cells transplantation therapy for IDD research is to perform MSC-EXO transplantation. How to accurately select and enhance the efficacy of repairing stem cell EXO is a hot and difficult point in the current research of EXO repairing IDD. Perhaps hypoxic-preconditioned of MSC-EXO is one of the breakthroughs in the treatment to IDD.

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References


