Wang W, et al., J Stem Cell Res Dev 2020, 6: 033
DOI: 10.24966/SRDT-2060/100033

HSOA Journal of
Stem Cells Research, Development and Therapy

Commentary

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"

Weiheng Wang[1#], Yuanyuan Qiu[2#], Jiangming Yu[1], Xin Gu[1], Yanhai Xi[1] and Xiaojian Ye[1*]

[1]Department of Orthopaedics, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China

[2]Trauma Center, Shanghai General Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 201620, China

[#]Equal Contribution

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 leaded 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

***Corresponding author:** Xiaojian Ye, Department of Orthopaedics, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China, Tel: +86 02181885624; Email: xjyespine@smmu.edu.cn

Citation: Wang W, Qiu Y, Yu J, Gu X, Xi Y, et al. (2020) 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". J Stem Cell Res Dev Ther 6: 033.

Received: April 03, 2020; **Accepted:** April 20, 2020; **Published:** April 27, 2020

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 NPCs apoptosis and reduce IDD [23]. Xia et al found that MSC-EXO ameliorated IDD via anti-oxidant 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 preconditioned mesenchymal stem cells repaired traumatic spinal cord injury by shifting microglial M1/M2 polarization [27]. Hypoxia-elicited mesenchymal stem cell-derived exosomes facilitates cardiac repaired 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.

Acknowledgement

This work was supported by the Shanghai Sailing Program (19YF1448400).

References

1. Steel N, Ford JA, Newton JN, Davis ACJ, Vos T, et al. (2018) Changes in health in the countries of the UK and 150 English Local Authority areas 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 392: 1647-1661.
2. Okuda S, Nagamoto Y, Matsumoto T, Sugiura T, Takahashi Y, et al. (2018) Adjacent Segment Disease After Single Segment Posterior Lumbar Interbody Fusion for Degenerative Spondylolisthesis: Minimum 10 Years Follow-up. Spine (Phila Pa 1976) 43: 1384-1388.
3. Tendulkar G, Chen T, Ehnert S, Kaps H-P, Nussler AK (2019) Intervertebral Disc Nucleus Repair: Hype or Hope? Int J Mol Sci 20: 3622.
4. Sakai D, Andersson GB (2015) Stem cell therapy for intervertebral disc regeneration: obstacles and solutions. Nat Rev Rheumatol 11: 243-256.
5. Silagi ES, Shapiro IM, Risbud MV (2018) Glycosaminoglycan synthesis in the nucleus pulposus: Dysregulation and the pathogenesis of disc degeneration. Matrix Biol 71-72: 368-379.
6. Urban JP (2002) The role of the physicochemical environment in determining disc cell behaviour. Biochem Soc Trans 30: 858-864.
7. Bartels EM, Fairbank JC, Winlove CP, Urban JP (1998) Oxygen and lactate concentrations measured in vivo in the intervertebral discs of patients with scoliosis and back pain. Spine (Phila Pa 1976) 23: 1-7.
8. Navone SE, Marfia G, Giannoni A, Beretta M, Guarnaccia L, et al. (2017) Inflammatory mediators and signalling pathways controlling intervertebral disc degeneration. Histol Histopathol 32: 523-542.
9. Skovrlj B, Cunn G, Guzman JZ, Qureshi SA (2015) Mesenchymal stem cell technology in the treatment of degenerative disc disease. J Neurosurg Sci 59: 25-35.
10. Wang W, Deng G, Qiu Y, Huang X, Xi Y, et al. (2018) Transplantation of allogenic nucleus pulposus cells attenuates intervertebral disc degeneration by inhibiting apoptosis and increasing migration. Int J Mol Med 41: 2553-2564.
11. Torras J, Herrero-Fresneda I, Lloberas N, Riera M, Ma Cruzado J, et al. (2002) Promising effects of ischemic preconditioning in renal transplantation. Kidney Int 61: 2218-2227.
12. Feng J, Yao W, Zhang Y, Xiang AP, Yuan D, et al. (2018) Intravenous Anesthetics Enhance the Ability of Human Bone Marrow-Derived Mesenchymal Stem Cells to Alleviate Hepatic Ischemia-Reperfusion Injury in a Receptor-Dependent Manner. Cell Physiol Biochem 47: 556-566.
13. Jang MJ, You D, Park JY, Kim K, Aum J, et al. (2018) Hypoxic Preconditioned Mesenchymal Stromal Cell Therapy in a Rat Model of Renal Ischemia-reperfusion Injury: Development of Optimal Protocol to Potentiate Therapeutic Efficacy. Int J Stem Cells 11:157-167.
14. Wang W, Huang X, Lin W, Qiu Y, He Y, et al. (2018) Hypoxic preconditioned bone mesenchymal stem cells ameliorate spinal cord injury in rats via improved survival and migration. Int J Mol Med 42: 2538-2550.
15. Wang W, Wang Y, Deng G, Ma J, Huang X, et al. (2018) Transplantation of Hypoxic-Preconditioned Bone Mesenchymal Stem Cells Retards Intervertebral Disc Degeneration via Enhancing Implanted Cell Survival and Migration in Rats. Stem Cells Int 2018:7564159.
16. Vadala G, Sowa G, Hubert M, Gilbertson LG, Denaro V, et al. (2012) Mesenchymal stem cells injection in degenerated intervertebral disc: cell leakage may induce osteophyte formation. J Tissue Eng Regen Med 6: 348-355.

17. Pobiel RS, Schellhas KP, Pollei SR, Johnson BA, Golden MJ, et al. (2006) Diskography: infectious complications from a series of 12,634 cases. AJNR Am J Neuroradiol 27: 1930-1932.

18. Han I, Ropper AE, Konya D, Kabatas S, Toktas Z, et al. (2015) Biological approaches to treating intervertebral disk degeneration: devising stem cell therapies. Cell transplantation 24: 2197-2208.

19. Phinney DG, Prockop DJ (2007) Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair--current views. Stem Cells 25: 2896-2902.

20. Humphreys BD, Valerius MT, Kobayashi A, Mugford JW, Soeung S, et al. (2008) Intrinsic epithelial cells repair the kidney after injury. Cell Stem Cell 2: 284-291.

21. Thomou T, Mori MA, Dreyfuss JM, Konishi M, Sakaguchi M, et al. (2017) Adipose-derived circulating miRNAs regulate gene expression in other tissues. Nature 542: 450-455.

22. Zhang Y, Kim MS, Jia B, Yan J, Zuniga-Hertz JP, et al (2017) Hypothalamic stem cells control ageing speed partly through exosomal miRNAs. Nature 548: 52-57.

23. Cheng X, Zhang G, Zhang L, Hu Y, Zhang K, et al. (2018) Mesenchymal stem cells deliver exogenous miR-21 via exosomes to inhibit nucleus pulposus cell apoptosis and reduce intervertebral disc degeneration. J Cell Mol Med 22: 261-276.

24. Xia C, Zeng Z, Fang B, Tao M, Gu C, et al. (2019) Mesenchymal stem cell-derived exosomes ameliorate intervertebral disc degeneration via anti-oxidant and anti-inflammatory effects. Free Radic Biol Med 143: 1-15.

25. Yao X, Wei W, Wang X, Chenglin L, Bjorklund M, et al. (2019) Stem cell derived exosomes: microRNA therapy for age-related musculoskeletal disorders. Biomaterials 224: 119492.

26. Zhang X, Sai B, Wang F, Wang L, Wang Y, et al. (2019) Hypoxic BMSC-derived exosomal miRNAs promote metastasis of lung cancer cells via STAT3-induced EMT. Mol Cancer 18: 40.

27. Liu W, Rong Y, Wang J, Zhou Z, Ge X, et al. (2020) Exosome-shuttled miR-216a-5p from hypoxic preconditioned mesenchymal stem cells repair traumatic spinal cord injury by shifting microglial M1/M2 polarization. J Neuroinflammation 17: 47.

28. Zhu LP, Tian T, Wang JY, He JN, Chen T, et al. (2018) Hypoxia-elicited mesenchymal stem cell-derived exosomes facilitates cardiac repair through miR-125b-mediated prevention of cell death in myocardial infarction. Theranostics 8: 6163-6177.

HERALD

Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752