Proceedings of the 5th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/99/2025.22555

Effect of Hypoxia on the Biological Characteristics of MSCs

Jiaye Fan

School of Life and Health Sciences, Hainan University, Haikou, China
20223001816@hainanu.edu.cn

Abstract: Mesenchymal stem cells(MSCs) possess biological characteristics such as self-replication and multipotential differentiation,playing a significant role in the treatment of various diseases. In traditional in vitro cell culture, the oxygen concentration is maintained at 20%, whereas in vivo and under many pathological conditions, cells reside in a hypoxia enviroment. By reviewing relevant literature on MSCs, this article addresses current challenges in stem cell transplantation technology. It explores the effects and mechanisms of hypoxia conditions on various biological characteristics of MSCs, including proliferation ability,migration ability,apoptosis and differentiation potential. The aim is to investigate whether hypoxia conditions can optimize the efficacy of MSCs, thereby identifying more suitable in vitro culture conditions to improve cell quality and enhance their application in clinical therapies.

Keywords: Hypoxia, Mesenchymal stem cells, Biological characteristics, in vitro culture

1. Introduction

Mesenchymal stem cells (MSCs) are a type of adult stem cells characterized by self-renewal and multidirectional differentiation potential. They primarily reside in connective tissues and organ mesenchyme. Current research focuses on MSCs derived from bone marrow, umbilical cord blood, peripheral blood, and adipose tissue. Studies have shown that MSCs exhibit characteristics such as cytokine secretion and microvesicle production, which are associated with their immunomodulatory effects [1,2]. Due to advantages including diverse sources, ease of isolation and culture, absence of ethical restrictions, and retention of stem cell properties through multiple passages, MSCs have emerged as ideal seed cells. Combined with scaffold materials and cytokines, they are now employed in cell and gene therapies for tissue repair and organ regeneration [3,4].

Under appropriate in vitro culture conditions, MSCs can be directionally induced to differentiate into adipocytes, osteoblasts, chondrocytes, and other cell types. While traditional in vitro culture typically occurs under normoxic conditions (20% oxygen concentration), the physiological and pathological environments often present hypoxic conditions. For instance, oxygen levels range from 10%-13% in human blood, 3%-9% in normal tissues/interstitial spaces, and 1%-7% in bone marrow cavities [5-7]. Oxygen significantly influences cellular proliferation and differentiation, as insufficient oxygen supply during in vitro culture may lead to cell death. However, studies modifying oxygen concentrations revealed that while MSCs are sensitive to ischemic/hypoxic conditions, hypoxia alone minimally induces apoptosis. When injected into ventricles of myocardial infarction mice, most MSCs died within 4 days under ischemic/hypoxic conditions [8]. Ferreira et al. reported that MSCs cultured under hypoxia alone for 48 h remained viable, but combined hypoxic

DOI: 10.54254/2753-8818/99/2025.22555

and prolonged serum-free conditions caused significant cell death [9]. Thus, hypoxic conditions may not inherently disadvantage cell culture [9-10]. Consequently, modifying in vitro culture microenvironments to better mimic physiological or pathological hypoxic conditions has become an important research focus.

Current clinical applications of MSC-based transplantation face critical challenges. After migrating to lesion sites, MSCs exhibit low survival rates under hypoxic conditions, limiting their therapeutic efficacy while potentially promoting tumor growth or metastasis [11-12]. These limitations hinder MSC therapeutic applications. In response, researchers are optimizing in vitro culture conditions to enhance MSC biological properties. For example, Li et al. enhanced MSC migration by modifying substrate surface roughness [13], while Liu demonstrated that low pH conditions suppress nucleus pulposus MSC proliferation and promote apoptosis [14]. Recent studies have increasingly focused on identifying optimal in vitro culture conditions to improve MSC quality and functionality, thereby addressing current therapeutic limitations.

This review systematically examines the effects and mechanisms of hypoxic conditions on MSC characteristics from four perspectives: proliferation capacity, migration ability, apoptosis, and differentiation potential. The findings may guide the development of improved in vitro culture environments for MSCs and offer potential strategies to overcome current clinical challenges in MSC-based therapies.

2. Effects of hypoxia on MSC biological characteristics

2.1. Proliferative capacity

Continuous hypoxic culture in vitro has been shown to enhance the proliferative capacity of MSCs, as evidenced by multiple studies. For instance, human umbilical cord Wharton's jelly-derived MSCs exhibited increased proliferation under 5% oxygen concentration [15]. Guo et al. found that nucleus pulposus-derived MSCs cultured under 2% oxygen entered the doubling phase earlier, with accelerated proliferation rates compared to normoxic conditions. Additionally, hypoxia significantly upregulated the expression of proliferation-related genes CCND1 and MYC in these cells [14]. Since cell proliferation involves a cell cycle that produces two daughter cells, the distribution of cells across cell cycle phases can reflect MSC proliferative activity. Analysis of G0/G1 and S phase cell populations revealed that human umbilical cord MSCs cultured under 3% oxygen (passage 7) exhibited fewer cells in the G0/G1 phase and an increased proportion in the S phase compared to normoxic controls, further confirming hypoxia-induced proliferation enhancement [16].

Although the precise mechanisms underlying hypoxia-mediated proliferation remain unclear, several hypotheses have been proposed. Proliferating Cell Nuclear Antigen (PCNA), a nuclear protein that facilitates DNA polymerase δ activity during DNA synthesis, serves as a marker of proliferative capacity. Xiong et al. compared PCNA expression in rat bone marrow MSCs cultured under 1% O2, 5% O2, and 18% O2, revealing significantly higher PCNA levels in the 1% hypoxia group. This suggests a potential association between hypoxia-induced proliferation and PCNA upregulation, though its mechanistic role requires further exploration [17]. Other studies propose that hypoxia-enhanced proliferation may depend on extracellular signal-regulated kinase (ERK). Hypoxic conditions promote ERK phosphorylation, activating downstream signaling pathways that regulate cell cycle progression and proliferation. Several reports have confirmed elevated phosphorylated ERK levels in hypoxically cultured MSCs [18-20].

However, divergent responses have been observed across MSC tissue sources. For example, Li et al. reported that hypoxia slightly suppressed the proliferation of rat intervertebral disc-derived MSCs, albeit to a limited extent [21]. These findings highlight the tissue-specific variability in MSC responses to hypoxic conditions.

DOI: 10.54254/2753-8818/99/2025.22555

2.2. Migratory ability

The efficacy of MSCs in cell and gene therapy hinges on their homing ability—the capacity to spontaneously migrate to injured or diseased sites for tissue repair. Therefore, identifying optimal in vitro culture conditions to enhance migratory capacity is critical for maximizing MSC therapeutic potential.

Numerous studies have demonstrated that hypoxic culture enhances MSC migration. For instance, Lee et al. reported a significant increase in MSC migratory capacity after 6–18 hours of culture under 2.2% oxygen [22]. Similarly, Transwell migration assays revealed enhanced migratory efficiency in bone marrow-derived MSCs from Sprague-Dawley (SD) rats under hypoxia compared to normoxia [23].

The modulation of migratory capacity is closely linked to the stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4 [24-27]. MSCs express CXCR4 on their surface, and its expression is regulated by various factors [28-29]. He et al. demonstrated that 24-hour culture under 2% oxygen significantly upregulated CXCR4 expression in adipose-derived MSCs, with a positive rate of 56.5%, and enhanced SDF-1-directed migration[10]. Hypoxia-induced CXCR4 overexpression correlates with improved migratory ability. Furthermore, supplementing hypoxic cultures with 120 g/mL SDF-1 markedly amplified MSC chemotactic responses under low oxygen, further validating the mechanistic role of hypoxia in modulating migration [23].

2.3. Apoptosis

After setting MSCs48h in the hypoxic group with 1%, 3%, 5% and 10% oxygen, by comparing the number of human amniotic MSCs in the normoxic group, Tang et al found that the percentage of apoptosis in all hypoxic groups was lower than that in the normoxic group, confirming that continuous culture under hypoxic conditions reduced apoptotic [30].

In addition, due to the acute cell damage caused by early hypoxia stress, cells will regain their activity after continuous culture under low oxygen for a period of time, which is also supported by Li et al. Apoptosis was increased at 1% oxygen for 6h and 12h, but at up to 24h and 72h [16]. At the same time, Song also showed that the apoptosis rate of 3% hypoxic group was significantly lower than that of 20% normoxic group, and again confirmed that hypoxic continuous culture could reduce apoptosis [16].

Currently, the mechanism by which hypoxia suppresses apoptosis in MSCs is still being gradually explored. Adams shows that the inhibition of apoptosis in MSCs by hypoxia involves two important oncogenes, Bax and Bcl-2, and apoptosis is regulated by the ratio of the two. Bax is to promote apoptosis, while Bal-2 can inhibit apoptosis [31]. By real-time PCR, proapoptotic Bax mRNA expression in each hypoxic pretreated group was lower than the normoxic control group, while Bal-2 mRNA expression was higher in the hypoxic group than [30] in the normoxic group. Zhu et al also concluded that Bal-2 expression and diminished Bax expression were enhanced in MSCs under persistent hypoxia, which also confirmed the anti-apoptotic effect of persistent hypoxia on MSCs [32]. In addition, the reason for short-term hypoxia and apoptosis is that hypoxia causes the decrease of MMP in MSCs, which then leads to the release of cytochrome C and the activation of cysteine protease-3 (Caspase-3). At the same time, the mitochondrial electron transport chain in cells will also produce a large amount of reactive oxygen species (ROS). The excessive accumulation of ROS will destroy the DNA and protein of cells, which will lead to the apoptosis of cells. However, the duration and intensity of hypoxia treatment can also enhance mitochondrial function and reduce apoptosis [33].

DOI: 10.54254/2753-8818/99/2025.22555

2.4. Multiplication capacity

Mesenchymal stem cells (MSCs), a type of adult stem cell with multilineage differentiation potential, can differentiate into various tissue types and have been actively applied in clinical therapies. Hypoxic culture conditions enhance the differentiation capacity of MSCs. For example, Guo et al. evaluated the osteogenic potential of bone marrow-derived MSCs under physiological hypoxia by measuring osteogenesis-related gene expression (Opn, Alp), protein levels (RUNX2, OPN), and key transcription factors (Runx2). These results demonstrated that all assessed markers were elevated under hypoxia compared to normoxic controls [34]. Additionally, in vivo transplantation of hypoxia-preconditioned human bone marrow-derived MSCs promoted chondrocyte proliferation and cartilage-like tissue formation in germ-free mice [35].

During hypoxic culture, MSCs exhibit distinct differentiation characteristics and mechanisms depending on the target cell lineage [36]. For instance, studies on chondrogenic differentiation revealed that hypoxia promotes cartilage formation by modulating the KDM6A/SOX9 signaling pathway. Hypoxia activates the expression of lysine-specific demethylase 6A (KDM6A), which demethylates the promoter of the chondrogenic transcription factor SOX9, thereby enhancing SOX9 transcription and driving MSC chondrogenesis [37-38]. In contrast, Li et al. inhibited HIF-1α nuclear accumulation and transcriptional activity using the blocker 2-MeOE2, finding no difference in the expression of tenogenic differentiation marker genes (SCX mRNA, TNMD mRNA) between hypoxic and normoxic groups. This indicates hypoxia-specific mechanisms in tenogenic differentiation [39].

However, the effects of hypoxia on MSC differentiation are not universally consistent. Cicioned et al. reported reduced adipogenic and osteogenic differentiation capacities in human bone marrow-derived MSCs after 21 days of induction under 1% oxygen [40]. Conversely, Martin-Rendon et al. observed no significant differences in differentiation outcomes between hypoxic (1.5% oxygen) and normoxic cultures after the same duration [41]. These discrepancies suggest that hypoxia-mediated effects on MSC differentiation may depend on oxygen tension levels, tissue sources, exposure duration, and other variables, leaving the debate over its pro-differentiative or inhibitory roles unresolved.

3. Discussion

Hypoxic environments can enhance the proliferation capacity, migration potential, differentiation capability, and inhibit apoptosis of mesenchymal stem cells (MSCs). However, due to variations in tissue sources and other culture conditions, conflicting experimental results persist. The precise mechanisms underlying hypoxia's effects on these characteristics remain unclear, necessitating further investigation into this topic.

Other studies have explored additional properties of MSCs under hypoxia. Guo et al. demonstrated improved stemness maintenance in hypoxic conditions by detecting elevated expression levels of pluripotency-related genes OCT4, NANOG and SOX2[16]. Another study revealed enhanced adhesion capacity in bone marrow-derived MSCs after 24 hours of culture under 2% oxygen [42]. Hypoxia also affects mitochondrial dynamics in MSCs, inducing denser and thicker tubular mitochondrial morphology. Compared to normoxic conditions, hypoxia regulates mitochondrial quality and quantity to sustain normal metabolic activities in MSCs [43-44]. Collectively, hypoxia has been found to enhance multiple biological properties of MSCs to varying degrees.

Investigating hypoxia's influence on MSC performance is essential for determining the optimal oxygen concentration for in vitro culture, thereby optimizing their efficacy and improving their survival and functionality within recipients. Despite significant advancements in recent years,

challenges remain. First, heterogeneity in MSC quality derived from diverse individuals and tissues, coupled with a lack of standardized criteria, may lead to divergent or contradictory results. Second, as the optimal culture conditions remain under investigation and techniques are not yet fully matured, challenges such as difficult isolation or limited accessibility of certain MSCs may hinder experimental efficiency.

As a promising therapeutic approach for various clinical diseases, MSCs cultured under hypoxia-based on this review of hypoxia-induced changes in their properties-may exhibit enhanced therapeutic potential. Establishing optimal culture protocols could enable MSCs to better exert their biological functions in vivo, thereby improving treatment outcomes and expanding their prospects in cell-based therapies.

4. Conclusion

Despite significant advancements in current research on mesenchymal stem cells (MSCs), numerous challenges persist. This paper focuses on the effects of hypoxic conditions on MSC characteristics-specifically proliferation, migration, apoptosis, and differentiation-and explores related mechanisms. By comparing hypoxic-treated MSCs with normoxic groups, based on reviewed literature, the findings of this paper demonstrate that hypoxia enhances MSC proliferation, migration, and differentiation capacities while suppressing apoptosis. Further analysis of existing experimental methodologies and conclusions reveals potential mechanisms underlying these effects. For instance, improved proliferation under hypoxia correlates with elevated PCNA expression and ERK phosphorylation, while enhanced migration is primarily mediated by the SDF-1/CXCR4 axis.

However, certain limitations exist in this review. Due to incomplete literature coverage, the analysis of hypoxia-induced changes in MSC properties remains insufficiently comprehensive. Current evidence suggests that hypoxia's impact on MSCs involves multifactorial constraints, leaving precise outcomes and detailed mechanisms unresolved. Future research should focus on advancing mechanistic understanding and keeping pace with emerging developments in the field to facilitate the clinical translation of MSCs and maximize their therapeutic potential.

References

[1] *Li, H., Miao, B., Han, Z.H. & Zhang, B.R. (2024). The mechanism of the difference of osteogenesis capacity between dental pulp and periodontal ligament stem cells[J]. Chinese Journal of Osteoporosis. 30(8), 1102-1107+1115. DOI:10.3969/j.issn.1006-7108.2024.08.002.*

[2] *Yang, J., Liu, F., Li, Y., Wu, D.B., Deng, M.D., Yang, C.Y., Yin C. & Hu, X. (2024). Mechanism Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Mice with Gestational Diabetes[J]. Acta Laser Biology Sinica. 33(3), 236-242. DOI:10.3969/j.issn.1007-7146.2024.03.006.*

[3] *Li, S. H., Guo, P. D., & Wang, W. J. (2010). Research progress of bone marrow mesenchymal stem cells differentiation into nerve-like cells induced by traditional Chinese medicine. Zhongguo gu Shang= China Journal of Orthopaedics and Traumatology, 23(3), 233-235. PMID: 20415091*

[4] *Jiao, Y. (2021). The role of PTBP-1 in the plasticity of umbilical cord mesenchymal stem cells to repair brain damage in young MIA-HIE rats [D]. Doctor thesis, Dalian Medical University.*

[5] *Wang, Y.M. (2021). Investigating Early Human Trophoblast Cell Development and Function Using Embryos and Embryo-like Models[D]. Doctor thesis, University of Chinese Academy of Science.*

[6] *Wang, Y.Q. (2021). Effects of Hypoxia on Culture and Osteogenic Differentiation of Mouse Bone Marrow Mesenchymal Stem Cells in Vitro[D]. Master thesis, Gansu: Lanzhou University.*

[7] *Lee, J. H., & Kemp, D. M. (2006). Human adipose-derived stem cells display myogenic potential and perturbed function in hypoxic conditions. Biochemical and biophysical research communications, 341(3), 882-888. DOI: 10.1016/j.bbrc.2006.01.038.*

[8] *Gou, T. T., Hu, M. H., Xu, M., Chen, Y. C., Chen, R., Zhou, T., .Liu, J. J., Guo, L., Ao, H. & Ye, Q. (2023). Novel wine in an old bottle: Preventive and therapeutic potentials of andrographolide in atherosclerotic cardiovascular diseases. Journal of pharmaceutical analysis, 13(6), 563-589. DOI:10.1016/j.jpha.2023.05.010.*

[9] Wu, M.J. & Kang, R. (2023). Advances in Micro-environmental Regulation of Intervertebral Disc Tissue Engineering[J]. Jiangsu Medical Journal. 49(3),316-320. DOI:10.19460/j.cnki.0253-3685.2023.03.024.

[10] Hou,Y.L., Li, T., Zhang, C., Yan, X.Y., Zhu, Z.Y., Gao, Y.T. & Wu, P. (2011). Effect of hypoxia treatment by CoCl2 on the expression of vascular growth factor in UC-MSCs[J]. Chinese Heart Journal. 23(1), 59-64. DOI: 10.13191/j.chj.2011.01.65.houyl.004.

[11] Liang, S. Y., Zhou, J., Yu, X. L., Lu S. & Liu, R. T. (2024). Neuronal conversion from glia to replenish the lost neurons[J]. Neural Regeneration Research. 19(7), 1446-1453. DOI:10.4103/1673-5374.386400.

[12] Wei, Q.X., Shi, Y.Z., Sun,R., Zhang, F. & Cao, L.R. (2023). Effect of local lactate microenvironment on proliferation and inflammatory regulation ability of human umbilical cord derived mesenchymal stem cells[J]. Drug Evaluation Research. 46(7), 1519-1526. DOI:10.7501/j.issn.1674-6376.2023.07.016.

[13] Chen, M.J., Wang, X.Y., Chen, K.H. & Lu, H.X. (2021). Research progress of mesenchymal stem cells in the treatment of pulmonary fibrosis[J]. Basic & Clinical Medicine, 41(7), 1056-1059. DOI:10.3969/j.issn.1001-6 325.2021.07.024.

[14] Guo, C.Z. (2018). Effect on biological characteristics of human nucleus pulposus mesenchymal stem cell under different oxygen concentrations[D]. Master thesis, Hubei: Anhui Medical University.

[15] Li, P.D. (2022). Therapeutic effects and mechanisms of human umbilical cord mesenchymal stem cells-derived exosomes in osteoarthritis of rat[D]. Doctor thesis, Jilin: Jinlin University.

[16] Song. X.N. (2014). The Impact of Hypoxia on the Biological Characteristics and Proliferation of Human Umbilical Cord Mesenchymal Stem Cel[D]. Master thesis, Beijing: Peking Union Medical College.

[17] Xiong ,L. (2016). Effects of low oxygen concentration on proliferation of rat bone marrow-derived mesenchymal stem cells in vitro[D]. Master thesis, Hunan: Hunan Normal University.

[18] Jing, H.S. (2022). Protectivetive effect and mechanism of melatonin on oxidative stress of pilose antler mesenchymal stem cells[D]. Master thesis, Hubei: Huazhong Agriculture University.

[19] Crisostomo, P. R., Wang, Y., Markel, T. A., Wang, M., Lahm, T., & Meldrum, D. R. (2008). Human mesenc hymal stem cells stimulated by TNF-α, LPS, or hypoxia produce growth factors by an NFκB-but not JNK-de pendent mechanism. American Journal of Physiology-Cell Physiology, 294(3), C675-C682. DOI: 10.1152/ajp cell.00437.2007.

[20] Wu, J., Niu, J., Li, X., Li, Y., Wang, X., Lin, J., & Zhang, F. (2014). Hypoxia induces autophagy of bone marrow-derived mesenchymal stem cells via activation of ERK1/2. Cellular Physiology and Biochemistry, 33(5), 1467-1474. DOI: 10.1159/000358711.

[21] Zhang, J., Zhang, W., Sun, T., Wang, J., Li, Y., Liu, J., & Li, Z. (2022). The influence of intervertebral disc microenvironment on the biological behavior of engrafted mesenchymal stem cells. Stem Cells International, 2022(1), 8671482. DOI: 10.1155/2022/8671482.

[22] Zhang, Y.W. (2023). Effects of hypoxic preconditioning of umbilical cord mesenchymal stem cell derived secretions on proliferation of pulmonary artery smooth muscle cells[D]. Master thesis, Qinghai: Qinghai University.

[23] Jiang, Y., Li, Y.T, Xu, G.Q., Guo, L.N., Zhang, H.T., Sheng, L., Yao, L.J. & Wang, Y. (2018). Preliminary Study on the Effect of SDF-1 on the Migration of Mesenchy-mal Stem Cells under Hypoxia[J]. Systems Medicine. 3(15), 13-15. DOI:10.19368/j.cnki.2096-1782.2018.15.013.

[24] Shao, Y.T. (2020). The role of Aj-msil, Aj-lgr5, Aj-sdf2 and Aj-kif3a in the intestinal regeneration of Apostichopus japonicus[D]. Master thesis, Liaoning: Liaoning Normal University.

[25] Shen, W., Bendall, L. J., Gottlieb, D. J., & Bradstock, K. F. (2001). The chemokine receptor CXCR4 enhances integrin-mediated in vitro adhesion and facilitates engraftment of leukemic precursor-B cells in the bone marrow. Experimental hematology, 29(12), 1439-1447. DOI: 10.1016/S0301-472X(01)00741-X.

[26] Peled, A., Kollet, O., Ponomaryov, T., Petit, I., Franitza, S., Grabovsky, V., Slav, M.M., Nagler, A., Lider, O., Alon, R., Zipori, D. & Lapidot, T. (2000). The chemokine SDF-1 activates the integrins LFA-1, VLA-4, and VLA-5 on immature human CD34+ cells: role in transendothelial/stromal migration and engraftment of NOD/SCID mice. Blood, The Journal of the American Society of Hematology, 95(11), 3289-3296. DOI: 10.1182/blood.V95.11.3289.

[27] Peled, A., Petit, I., Kollet, O., Magid, M., Ponomaryov, T., Byk, T., Nagler, A., Ben-Hur, H., Many, A., Shultz, L., Lider, O., Alon, R., Zipori, D., & Lapidot, T. (1999). Dependence of human stem cell engraftment and repopulation of NOD/SCID mice on CXCR4. Science, 283(5403), 845-848. DOI: 10.1126/science.283.5403.845.

[28] Wynn, R. F., Hart, C. A., Corradi-Perini, C., O'Neill, L., Evans, C. A., Wraith, J. E., Fairbairn, L. J. & Bellantuono, I. (2004). A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow. Blood, 104(9), 2643-2645. DOI: 10.1182/blood-2004-02-0526

[29] Sordi, V., Malosio, M. L., Marchesi, F., Mercalli, A., Melzi, R., Giordano, T., Belmonte, N., Giuliana Ferrari, Biagio Leone, E., Bertuzzi, F,, Z.G., Allavena, P., Bonifacio, E. & Piemonti, L. (2005). Bone marrow mesenchymal stem cells express a restricted set of functionally active chemokine receptors capable of promoting migration to pancreatic islets. Blood, 106(2), 419-427. DOI: 10.1182/blood-2004-09-3507

[30] Tang, J.H., Zhang, N.N., Huang,G.L., Long, Y.Z., Cui, T.N., Luo, Q.L., Lang, J.C., Dai, M. & Zhang, L.G. (2023), Biological characteristics of human amniotic mesenchymal stem cells pretreated with different volume fractions of oxygen[J]. Chinese Journal of Tissue Engineering Research, 27(15), 2318-2324.

[31] Qiu, Y.J. & Zhang, M. (2024). Effects of Metrnl on Aortic Remodeling in Type 2 Diabetes Mice and Its Related Mechanisms[J]. Sichuan Medical Journal. 45(3), 250-255. DOI: 10.16252/j.cnki.issn1004-0501-2024.03.006

[32] Zhu, W., Chen, J., Cong, X., Hu, S., & Chen, X. (2006). Hypoxia and serum deprivation-induced apoptosis in mesenchymal stem cells. Stem cells, 24(2), 416-425. DOI: 10.1634/stemcells.2005-0121

[33] Wang, W.Q., Yang, H.Q., Fan, Z.P. & Shi, R.T. (2024). Advances in the study of hypoxia's impact on mitoc hondrial energy metabolism in mesenchymal stem cells[J]. Oral Biomedicine. 15(05), 297-302. DOI: 10.3969 /j.issn.1674-8603.2024.05.010

[34] Guo, T.T., Liu,Y. & Zhou, J. (2023). Effects of physiological hypoxia and anoxia-reoxygenation on proliferation and osteogenic differentiation of mouse bone marrow mesenchymal stem cells[J]. Beijing Journal of Stomatology. 31(02), 82-87. DOI: 10.20049/j.bjkqyx.1006-673X.2023.02.002

[35] Zhang, L.L. (2023). The genes related to ferroptosis in cartilage of knee osteoarthritis were screened and verified by mechanical learning method[D]. Master thesis, Anhui: Anhui Medical University.

[36] Ji, J.K., Li, K.W., Zhang, H.T., Zhang, B.B., Feng, C., Zhaxi Dawa, Wu, L. & Liu, C.Z. (2022). Effects of bone marrow mesenchymal stem cells on cartilage damage and KDM6A/SOX9 signaling pathway in rats with knee osteoarthritis[J]. Chinese Journal of Osteoporosis. 28(04), 486-492. DOI:10.3969/j.issn.1006-7108.2022.04.004.

[37] Wang, P., Li, Y., Meng, T., Zhang, J., Wei, Y., Meng, Z., Lin, Y., Liu, D. & Sui, L. (2018). KDM6A promotes chondrogenic differentiation of periodontal ligament stem cells by demethylation of SOX9. Cell Proliferation, 51(3), e12413. DOI:10.1111/cpr.12413.

[38] Zhang, F. J., Luo, W., & Lei, G. H. (2015). Role of HIF-1α and HIF-2α in osteoarthritis. Joint bone spine, 82(3), 144-147. DOI: 10.1016/j.jbspin.2014.10.003.

[39] Li, D. (2017). Effects of hypoxia microenvironment on tenogenic differentiation of adipose derived mesenchymal stem cells[D]. Master thesis, Sichuan: Southwest Medical University.

[40] Cicione, C., Muiños-López, E., Hermida-Gómez, T., Fuentes-Boquete, I., Díaz-Prado, S., & Blanco, F. J. (2013). Effects of severe hypoxia on bone marrow mesenchymal stem cells differentiation potential. Stem cells international, 2013(1), 232896. DOI: 10.1155/2013/232896.

[41] Zhang, J. (2019). Transcriptional profiling of rat bone marrow mesenchymal stem cells cultured under hypoxic condition[D]. Doctor thesis, Hunan: Hunan Normal University.

[42] Qu. G.J. (2019). Effects of hypoxia on the biological behaviors and paracrine functions of mesenchymal stem cells[D]. Master thesis, Hubei: Wuhan University.

[43] Li, X., Fu, X., Li, H., Gao, Y., Wang, W., Liu, Z., & Shen, Y. (2023). Leptin accelerates BMSC transformation into vertebral epiphyseal plate chondrocytes by activating SENP1-mediated deSUMOylation of SIRT3. FEBS Open bio, 13(2), 293-306. DOI: 10.1002/2211-5463.13539

[44] Iorio, R., Petricca, S., Mattei, V., & Delle Monache, S. (2024). Horizontal mitochondrial transfer as a novel bioenergetic tool for mesenchymal stromal/stem cells: molecular mechanisms and therapeutic potential in a variety of diseases. Journal of Translational Medicine, 22(1), 491. DOI:10.1186/s12967-024-05047-4.