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# Hypoxia disturbs the Migration and Adhesion factors profile of Mesenchymal Stem Cells

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**ABSTRACT**

Mesenchymal stem cells (MSCs) have been successfully used in treating many diseases which are being verified through many preclinical and clinical trials. Despite the exciting therapeutic potential of MSCs, multiple challenges are encountered those hinder researchers from achieving successful clinical translations. Many studies have shown that moderate hypoxia (1-7% $O_2$) is considered an important regulator of MSCs homing, migration, and differentiation. Additionally, low oxygen tension levels have been implicated in the maintenance of MSCs quiescence and plasticity in general. On the other hand, severe hypoxia (<1% $O_2$) negatively affects the in vitro therapeutic potential of MSCs and causes their poor survival. Using the ELISA assay we assessed some major adhesion markers secreted by MSCs that play a role in cell-cell and cell-matrix adhesion under normoxia (21% $O_2$) and severe hypoxia (0.5% $O_2$). These markers include SDF1-α, CXCR4, FAK, VEGF and ICAM-1. The results showed a significant drop in the adhesion markers in MSCs under severe hypoxia compared to normoxia, which causes a disruption in the cell-cell adhesion abilities of MSCs and ultimately can affect the incorporation of MSCs at the host site. These findings can open a new avenue to improve the attachment of MSCs at the transplantation site by targeting the adhesion and chemokines markers.

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## Introduction

Stem cell therapy is becoming more credible in treating degenerative diseases compared to conventional medicine (1). Mesenchymal stem cells (MSCs) represent an attractive avenue in the cell therapy field targeting many degenerative and chronic diseases. Human MSCs exert their therapeutic effects through direct multi-lineage differentiation or indirectly by secreting paracrine factors (2). The use of MSCs for tissue regeneration is under extensive investigation worldwide. MSCs can be obtained from adult tissues such as bone marrow, adipose tissue, skeletal muscle, dental pulp and umbilical cord (3) and they can be isolated, expanded in culture, and characterized *in vitro* (4) and *in vivo* (5).

Numerous in vitro and in vivo studies have been conducted in the last two decades to observe the complex environmental factors that affect MSCs maintenance and survival. Several studies showed that controlling oxygen partial pressure in vitro by reducing atmospheric oxygen from 20% to moderate hypoxic levels (usually 2–9% $O_2$ concentration) influenced the MSCs behavior positively (6). MSCs are normally found within niches where the oxygen gradient is around 6-7% $O_2$ (moderate hypoxic condition) (7). For example, hypoxic condition within the bone marrow enhances the proliferation of MSCs and elucidates protection against senescence and apoptosis (8,9). Furthermore, it has been reported that maintaining MSCs in an undifferentiated state may require a moderate hypoxic environment primarily. On the other hand, several studies showed that severe hypoxia (less than 1% $O_2$) reduces proliferation of MSCs and induces their senescence and apoptosis. (10–12)

Despite the imposing potential of MSC-based therapy, several obstacles have been encountered (13), including, the poor viability of MSCs after cell transplantation (14). The absence of proper adhesion with the surroundings is probably one of the major causes of poor MSCs survival after transplantation. Cell-cell adhesion through the extracellular matrix is critical to maintaining major cell activities, proliferation, and survival (15), whereas, a low propensity to adhere to the host cells due to a loss of matrix anchorage may induce the death of the transplanted MSCs.

In this work, we assessed the level of the following major adhesion factors: stromal-derived factor 1 alpha (SDF1-α), C-X-C chemokine receptor type 4 (CXCR4), focal adhesion kinase (FAK), vascular endothelial growth factor (VEGF) and intercellular adhesion molecule 1 (ICAM-1) in human MSCs under normoxia (21% $O_2$) and severe hypoxia (0.5% $O_2$) and its association with the ability of MSCs to survive under severe hypoxia stress.

## Materials and Methods

### Culturing of human BM-MSCs

Human Bone Marrow MSCs (hMSCs) were commercially purchased from ATCC (Cat# PCS-500-012) and expanded using Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) (16), 0.1 mg/ml streptomycin and 100 units/ml penicillin G. Medium was changed every 48 hrs and cells were sub-cultured when confluence exceeded 60%. For normoxia, hMSCs were cultured in standard cell culture incubators (5% $CO_2$/95% air; 37 °C). For hypoxia, hMSCs were cultured at either 0.5% $O_2$ (5% $CO_2$/remaining $N_2$; 37 °C) using a dedicated hypoxia station (HypOxystation

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H35, HypOxygen, Frederick, MD, USA). For all assays, P3-P5 hMSCs were used.

### Cell viability Assay

The viability of hMSCs under normoxia and severe hypoxia were assessed using Calcein AM Assay Kit ( Abcam, Cat# ab228556). Fluorescent intensity was measured at Ex/Em = 485/530 nm. The measured fluorescence intensity is proportional to the number of viable cells. Fluorescent images were also captured using Cytation 5 (BioTek, USA).

### Quantitative Elisa assays

We seeded the hMSCs cells in two 6-well plates and the cells were allowed to grow until confluency. The next day we exposed one plate to severe hypoxia (0.5% $O_2$) while the other plate was kept under normoxic conditions. After 24 hours, we collected the hMSCs culture supernatant and spun them for 15 minutes at 1500xg to get rid of the debris. We measured the levels of the following markers using ELISA kits; SDF1-α (R&D system, Cat # DSA00), CXCR4 (Abcam, Cat# ab287804), FAK (MyBioSource, Cat # MBS2515396), VEGF (R&D system, Cat # DVE00) and ICAM-1(R&D system, Cat # DCD540). Absorbance was measured according to each kit protocol and the concentrations were calculated by applying the sample absorbance to the standard curve equation.

### Statistical analysis

Data are presented as the mean ±standard deviation. Differences between the groups were analyzed using student's *t*-test and P< 0.05 was considered statistically significant.

## Results

### Severe hypoxia decreases the viability of hMSCs

The viability of hMSCs was assessed under normoxia and severe hypoxia (0.5% $O_2$) using immunostaining with calcein AM, then measuring the fluorescent intensity (Figure 1). It was noted that the viability of MSCs under normoxia is well maintained compared to severe hypoxia where the viability is dropped remarkably (Fig 1 A& B).

### Severe hypoxia is associated with a less attached number of cells and decreases the cell-cell contact

hMSCs showed a reduction in cell viability under severe hypoxia in comparison to normoxia. To see the effect of poor viability on hMSCs cell-cell distance, bright field microscopic images were taken (Fig 2A). The images showed that the MSCs cell-cell adhesion distance increased under severe hypoxia compared to normoxia where cells were attached close to each other (Fig 2B).

The results depicted reduced attachment between adjacent hMSCs under severe hypoxic tension compared to normoxia conditions. This observation prompted us to continue investigating the expression and secretion of major adhesion molecules and chemokines: SDF1-α, CXCR-4, FAK, VEGF, and ICAM-1in hMSCs under normoxia and severe hypoxia.

### Severe hypoxia decreases the level of major adhesion and migration factors

Stromal-derived factor-1 (SDF-1) is a chemokine involved in the homing and recruitment of hMSCs to the site of injury and directing their migration. SDF-1 binds CXCR4 and the SDF-1/CXCR4 axis plays an important role in the regulation of stem cell homing and trafficking (17).

Our results showed a significant reduction in the levels of both SDF-1 and CXCR4 markers in hMSCs under severe hypoxia compared to normal oxygen levels.

We further investigated the levels of three major adhesion factors; focal adhesion kinase (FAK), vascular endothelial growth factor (VEGF), and intercellular adhesion molecule-1 (ICAM-1).

FAK is a non-receptor tyrosine kinase that binds integrins to regulate cell adhesion and migration in various cell lines. VEGF is one of the major factors that facilitate

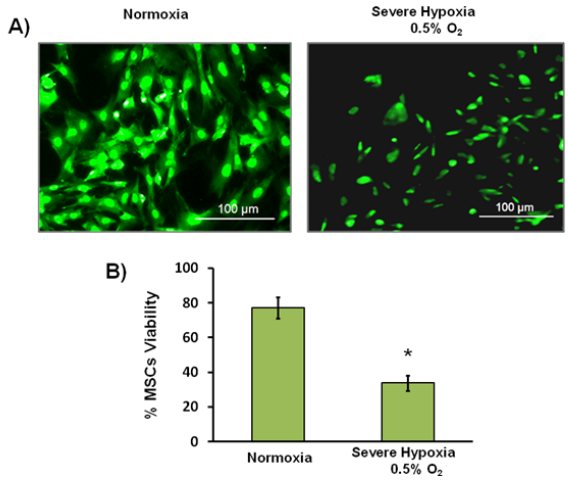


**Figure 1. Exposure to severe hypoxia reduces the viability of hMSCs. (A &B)** Calcein AM viability staining of hMSCs after exposure to normoxia and severe hypoxia (0.5% $O_2$). The fluorescent intensity was measured using Image J, which revealed a reduction in the viability of hMSCs under severe hypoxia in comparison to normoxia; n=4.* $P < 0.05$ compared to normoxic hMSCs.

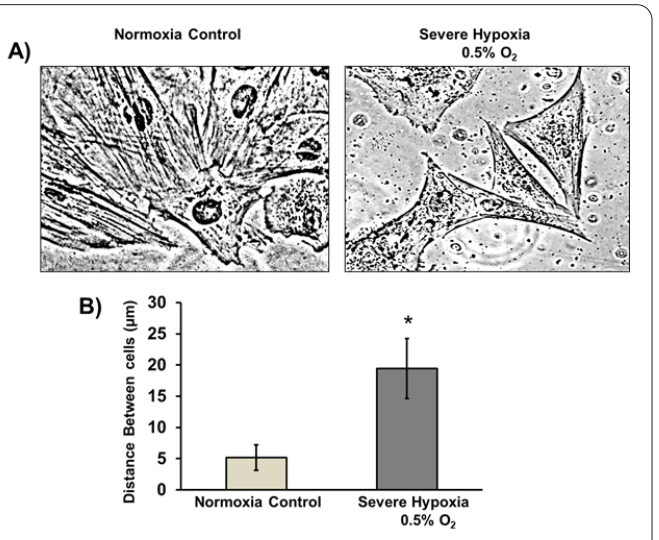


**Figure 2. Bright field images of hMSCs attachment under moderate and severe hypoxia. (A)** Bright-field microscopic images of hMSCs after their treatment with normoxia and severe hypoxia (0.5% $O_2$). The images show that the cells are firmly attached to each other in normoxia, while it appeared that hMSCs are far-off and less attached in severe hypoxia. **(B)** The distance between hMSCs was measured using Image J, the results showed noticeable increase in the distance between hMSCs exposed to severe hypoxia vs. hMSCs under normoxia; n=4. * $P < 0.05$ compared to normoxic hMSCs.

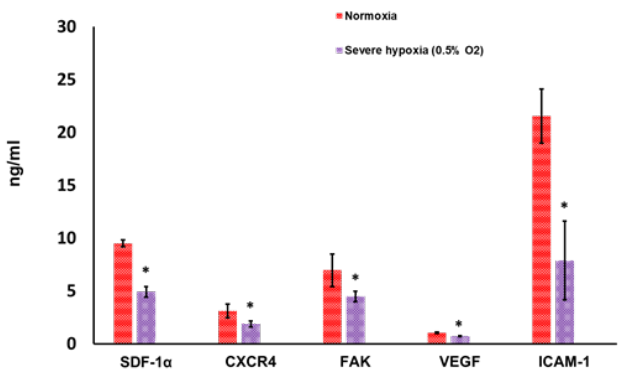


**Figure 3. The concentration of major adhesion and migration factors analyzed by quantitative Elisa assay.** The results showed a significant decrease in the levels of major adhesion and migration factors in hMSCs that were exposed to severe hypoxia weighed against normoxia. * $P < 0.05$ compared with the control group.

adhesion and cell-cell contact which is crucial for the survival and growth of many cells including MSCs. VEGF increases endothelial permeability and induces the release of adhesion molecules mainly FAK and integrin-β1 that are essential for the incorporation of cells at the host site. ICAM-1 is a member of the immunoglobulin superfamily of adhesion molecules that is involved in cell-cell and cell-matrix interactions. Moreover, ICAM-1 has a foremost function in MSCs adhesion and attachment at the host tissue surroundings after transplantation. Our results showed that the levels of FAK, VEGF, and ICAM-1 in MSCs decrease significantly under severe hypoxia compared to normoxia (Fig 3). The low levels of above mentioned migratory and adhesion factors in MSCs after being exposed to severe hypoxia can affect their survival and regenerative abilities. This can explain the poor survival of MSCs in hypoxic microenvironments such as ischemic heart diseases.

## Discussion

It is widely known that MSCs in the bone marrow are located within a niche with low oxygen tension (5-7% $O_2$), which means that moderate hypoxia plays an important role in maintaining MSCs fate, self-renewal and multipotency (18,19). Moreover, *in vitro* studies found that the permanent culture of MSCs under moderate hypoxia (2.5%-15% $O_2$) enhanced the influence of multiple genetic pathways that maintained the cells undifferentiated and multipotent (18,20). Also, under moderate hypoxia, many desirable functional changes of MSC were reported, including increased secretion of molecules like vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6), as well as mobilization and homing by the induction of stromal cell-derived factor-1 expression (SDF-1) (21). On the other hand, severe hypoxia inhibits MSC functions by suppressing the differentiation potential of MSCs and inducing their senescence and apoptosis (10). Together, these findings further substantiate that the oxygen tensions contribute strongly to the regulation of MSCs cellular functions and fate.

In this study, we analyzed the *in vitro* response of hMSCs to hypoxic preconditioning at 0.5% oxygen concentration. We observed that the hMSCs viability significantly decreased in severe hypoxia conditions compared to normal oxygen levels. Moreover, cell-cell distance and the number of cells were significantly lower under severe hypoxia compared to normoxia.

Hypoxia does not have a strict definition in terms of oxygen tension and it depends on cell type and physiological conditions. However, many defined hypoxia as the critical oxygen tension that would permit cell viability and function (22). Hypoxic conditions enhance cell proliferation, and culturing under hypoxia could be an alternative approach without the need for extra additives to stimulate primary culture growth and expansion, yielding a sufficient number of cells to be used for transplantation (23). Hypoxia tension is an important component of the stem-cell niche and provides conducive signals to maintain stem cells cellular functions (24). Moderate hypoxia enhances the proliferation and the expansion of MSCs approximately six- to seven-fold (25). Priming MSCs with moderate hypoxia has been reported to increase the adhesion and migration of MSCs after their engraftment (26). On the other hand, no study so far investigated the effect of severe hypoxia (0.5% $O_2$) on MSCs adhesion and migration. MSCs can face severe hypoxia in many serious diseases mainly acute myocardial infarction leading to their poor survival (27). One of the most important factors that are required to enhance the survival and success rate of MSCs transplantation is the adhesion and integration of MSCs at the host site (28). So it is important to investigate the effect of severe hypoxia (0.5% $O_2$) on the adhesion and homing properties of MSCs. Many studies showed that hypoxia lower than 1% is not a suitable microenvironment to support hMSCs proliferation and growth. Moreover, our study showed that severe hypoxia disturbed the levels of major adhesion and migratory factors that can decrease the chance to survive at the host site.

SDF-1 is an alpha-chemokine that binds the transmembrane domain of the G protein-coupled receptor CXCR4 (29,30). The SDF-1/CXCR4 axis stimulates major signaling pathways that are required for the adhesion and migration of MSCs, including FAK, PI3K, MAPK/Erk kinase (MEK), and Jak/Tyk2 (31). It has been reported that the downregulation of CXCR4 on the surface of MSCs underlined the inefficient homing abilities of MSCs toward damaged tissues, which results in poor MSCs curative effects (32). Moreover, CXCR4 was found to enhance the chemotactic and paracrine therapeutic characteristics of MSCs (32). Our study showed that the levels of SDF-1 and CXCR4 dropped hugely in MSCs after being exposed to severe hypoxia.

Studies showed that FAK plays a significant role in the regulation of cell survival, adhesion, migration, and differentiation in mammalian cells including bone marrow stem cells (33–36). FAK acts as a signal adaptor that interplays with and activates multiple signal transduction pathways that mediate cellular apoptosis, mobility and differentiation (37,38). Several reports showed that FAK can also potentiate the immunosuppression properties of MSCs (39).

VEGF is a potent angiogenic factor and is essential for the survival of many cells (40). VEGF regulates the adhesion of the MSCs by increasing the levels of FAK and integrins (41). It also induces the mobilization of bone marrow-derived MSCs to the injury site and enhances their targeted differentiation (42).

Several studies reported the beneficial role of ICAM-

1 in MSCs. ICAM-1 has the ability to increase the immunosuppression capacity of MSCs and contribute to the migration of MSCs *in vitro* (43,44). Other studies showed that ICAM-1 may play a role in the differentiation of MSCs by modulating the mitogen-activated protein kinase (MAPK) signaling pathway(45). Furthermore, ICAM-1 overexpression was able to modulate the nesting of MSCs in the thyroid gland and lungs (44). Together, these findings indicated that ICAM-1 plays an important role in promoting the homing and immunoregulatory properties of MSCs by potentiating the migration and adhesion of MSCs *in vivo* and *in vitro*. ICAM-1 has been found to facilitate the interaction between MSCs and T-cells which leads to the suppression of TCR signaling and induces immunotolerance by increasing the differentiation of T cells into Tregs (46). Engineering MSCs to overexpress ICAM-1 has been found to prolong their survival post-transplantation in graft-versus-host disease (GVHD) mouse models (46). The levels of FAK, VEGF, and ICAM-1 were reduced significantly in MSCs exposed to severe hypoxia. The results of our screening study are useful in understanding the poor survival of MSCs when there is a severe drop in oxygen tension, like that found in ischemic heart diseases and ischemic limbic diseases, which may reduce the chances of achieving successful therapeutic outcomes. Future studies can investigate the possibility to rescue MSCs in severe hypoxia and prolong their survival by targeting these migratory and adhesion molecules by genetic modifications or using biomaterials.

## Conclusion

In the current screening study, our data demonstrated that severe hypoxic oxygen tension disturbed the adhesion and chemokine factors secretion by hMSCs, which leads to reduced hMSCs attachment and migration to injured tissues and causes the loss of hMSCs at the injection site. However, the normoxia condition maintained sufficient levels of adhesion factors and chemokines in hMSCs leading to prolong the incorporation of MSCs with host tissues, which may explain the poor survival of MSCs under severe hypoxia compared to normoxia. Further studies need to be done to rule out the mechanistic pathways that regulate these adhesion factors and chemokines in MSCs in different oxygen tension levels, which may help in setting up various approaches to improve the homing and integration of transplanted MSCs with the host tissues and enhance their survival rate.

## Conflict of interest

Authors declare no conflict of interest.

## Authors Contributions

R.R.K and E.A.E.R conceptualized the study; R.R.K designed the experiments; carried out the experiments, R.R.K acquired and analyzed the data; R.R.K interpreted the data and performed statistical analyses; R.R.K and E.A.E.R wrote the manuscript. E.A.E.R revised and corrected the grammatical and spelling typos in the final version of the manuscript. The authors have read and approved the final version of the manuscript.

## References


1. Huang GTJ, Gronthos S, Shi S. Mesenchymal stem cells derived from dental tissues vs. those from other sources: their biology and role in regenerative medicine. J Dent Res. 2009 Sep;88(9):792–806.
2. Bayraktar B, Yucesir I, Ozturk A, Cakmak A, Taskara N, Kale A, et al. Change of quadriceps angle values with age and activity. Saudi Med J. 2004;25(2):756–60.
3. Macrin D, Joseph JP, Pillai AA, Devi A. Eminent Sources of Adult Mesenchymal Stem Cells and Their Therapeutic Imminence. Stem Cell Rev Rep. 2017 Dec 1;13(6):741–56.
4. Phinney D, Kopen G, Isaacson R, Prockop D. Plastic adherent stromal cells from the bone marrow of commonly used strains of inbred mice: variations in yield, growth, and differentiation. J Cell Biochem. 1999;72(4):570–85.
5. Pittenger Mark F., Martin Bradley J. Mesenchymal Stem Cells and Their Potential as Cardiac Therapeutics. Circ Res. 2004 Jul 9;95(1):9–20.
6. Carreau A, El Hafny-Rahbi B, Matejuk A, Grillon C, Kieda C. Why is the partial oxygen pressure of human tissues a crucial parameter? Small molecules and hypoxia. J Cell Mol Med. 2011 Jun;15(6):1239–53.
7. Parmar K, Mauch P, Vergilio JA, Sackstein R, Down JD. Distribution of hematopoietic stem cells in the bone marrow according to regional hypoxia. Proc Natl Acad Sci U S A. 2007 Mar 27;104(13):5431–6.
8. Ejtehadifar M, Shamsasenjan K, Movassaghpour A, Akbarzadehlaleh P, Dehdilani N, Abbasi P, et al. The Effect of Hypoxia on Mesenchymal Stem Cell Biology. Adv Pharm Bull. 2015 Jun;5(2):141–9.
9. Fotia C, Massa A, Boriani F, Baldini N, Granchi D. Hypoxia enhances proliferation and stemness of human adipose-derived mesenchymal stem cells. Cytotechnology. 2015 Dec;67(6):1073–84.
10. Cicione C, Muiños-López E, Hermida-Gómez T, Fuentes-Boquete I, Díaz-Prado S, Blanco FJ. Effects of severe hypoxia on bone marrow mesenchymal stem cells differentiation potential. Stem Cells Int. 2013;2013:232896–232896.
11. Xing J, Ying Y, Mao C, Liu Y, Wang T, Zhao Q, et al. Hypoxia induces senescence of bone marrow mesenchymal stem cells via altered gut microbiota. Nat Commun. 2018 May 22;9(1):2020.
12. Khasawneh RR, Abu-El-Rub E, Serhan AO, Serhan BO, Abu-El-Rub H. Cross talk between 26S proteasome and mitochondria in human mesenchymal stem cells' ability to survive under hypoxia stress. J Physiol Sci. 2019 Nov 1;69(6):1005–17.
13. Chang W, Song BW, Hwang KC. Mesenchymal Stem Cell Survival in Infarcted Myocardium: Adhesion and Anti-death Signals. In: Hayat MA, editor. Stem Cells and Cancer Stem Cells, Volume 10: Therapeutic Applications in Disease and Injury [Internet]. Dordrecht: Springer Netherlands; 2013. p. 35–43. Available from: https://doi.org/10.1007/978-94-007-6262-6_4
14. Toma Catalin, Pittenger Mark F., Cahill Kevin S., Byrne Barry J., Kessler Paul D. Human Mesenchymal Stem Cells Differentiate to a Cardiomyocyte Phenotype in the Adult Murine Heart. Circulation. 2002 Jan 1;105(1):93–8.
15. Santos AK, Tonelli FM, Silva DA, Gomes KN, Ladeira LO, Resende RR. Trends in Stem Cell Proliferation and Cancer Research. Springer. 2013;13–49.
16. Khasawneh RR, Al Sharie AH, Abu-El Rub E, Serhan AO, Obeidat HN. Addressing the impact of different fetal bovine serum percentages on mesenchymal stem cells biological performance. Mol Biol Rep [Internet]. 2019 Jun 1; Available from: https://doi.org/10.1007/s11033-019-04898-1
17. Libura J, Drukala J, Majka M, Tomescu O, Navenot JM, Kucia M, et al. CXCR4–SDF-1 signaling is active in rhabdomyosarcoma cells and regulates locomotion, chemotaxis, and adhesion:

Presented at the Annual Meeting of the American Society of Hematology, Orlando, FL, December 7-11, 2001. Blood. 2002 Oct 1;100(7):2597–606.
18. Basciano L, Nemos C, Foliguet B, de Isla N, de Carvalho M, Tran N, et al. Long term culture of mesenchymal stem cells in hypoxia promotes a genetic program maintaining their undifferentiated and multipotent status. BMC Cell Biol. 2011 Mar 30;12:12–12.
19. dos Santos F, Andrade PZ, Boura JS, Abecasis MM, da Silva CL, Cabral JMS. Ex vivo expansion of human mesenchymal stem cells: A more effective cell proliferation kinetics and metabolism under hypoxia. J Cell Physiol. 2010 Apr 1;223(1):27–35.
20. Abu-El-Rub E, Sequiera GL, Sareen N, Yan W, Moudgil M, Sabbir MG, et al. Hypoxia-induced 26S proteasome dysfunction increases immunogenicity of mesenchymal stem cells. Cell Death Dis. 2019 Jan 28;10(2):90.
21. Das R, Jahr H, van Osch GJVM, Farrell E. The Role of Hypoxia in Bone Marrow–Derived Mesenchymal Stem Cells: Considerations for Regenerative Medicine Approaches. Tissue Eng Part B Rev. 2009 Aug 21;16(2):159–68.
22. Murphy KC, Hung BP, Browne-Bourne S, Zhou D, Yeung J, Genetos DC, et al. Measurement of oxygen tension within mesenchymal stem cell spheroids. J R Soc Interface. 2017 Feb;14(127):20160851.
23. Grayson W, Zhao F, Bunnell B, Ma T. Hypoxia enhances proliferation and tissue formation of human mesenchymal stem cells. Biochem Biophys Res Commun. 2007;358(3):948–53.
24. Mohyeldin A, Garzón-Muvdi T, Quiñones-Hinojosa T. Oxygen in Stem Cell Biology: A Critical Component of the Stem Cell Niche. Cell Stem Cell. 2010;7(2).
25. Yamamoto Y, Fujita M, Tanaka Y, Kojima I, Kanatani Y, Ishihara M, et al. Low oxygen tension enhances proliferation and maintains stemness of adipose tissue-derived stromal cells. BioResearch Open Access. 2013 Jun;2(3):199–205.
26. De Becker A, Riet IV. Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy? World J Stem Cells. 2016;26(8):73–87.
27. Saini U, Gumina RJ, Wolfe B, Kuppusamy ML, Kuppusamy P, Boudoulas KD. Preconditioning mesenchymal stem cells with caspase inhibition and hyperoxia prior to hypoxia exposure increases cell proliferation. J Cell Biochem. 2013 Nov 1;114(11):2612–23.
28. Lee S, Choi E, Cha MJ, Hwang KC. Cell adhesion and long-term survival of transplanted mesenchymal stem cells: a prerequisite for cell therapy. Oxid Med Cell Longev. 2015;2015:632902–632902.
29. D'Apuzzo M, Rolink A, Loetscher M, Hoxie JA, Clark-Lewis I, Melchers F, et al. The chemokine SDF-1, stromal cell-derived factor 1, attracts early stage B cell precursors via the chemokine receptor CXCR4. Eur J Immunol. 1997 Jul 1;27(7):1788–93.
30. Kofuku Y, Yoshiura C, Ueda T, Terasawa H, Hirai T, Tominaga S, et al. Structural Basis of the Interaction between Chemokine Stromal Cell-derived Factor-1/CXCL12 and Its G-protein-coupled Receptor CXCR4*. J Biol Chem. 2009 Dec 11;284(50):35240–50.
31. Li M, Sun X, Jin L, Zhang W, Xiao M, Yu Q. SDF-1/CXCR4 axis induces human dental pulp stem cell migration through FAK/PI3K/Akt and GSK3β/β-catenin pathways. Sci Rep. 2017;7(1):40161.
32. Yang JX, Zhang N, Wang HW, Gao P, Yang QP, Wen QP. CXCR4 receptor overexpression in mesenchymal stem cells facilitates treatment of acute lung injury in rats. J Biol Chem. 2015 Jan 23;290(4):1994–2006.
33. An L, Li W, Hu X, Zhang W, Zhao S. Abundant Focal Adhesion Kinase Causes Aberrant Neuronal Migration Via Its Phosphorylation at Tyr925. J Mol Neurosci. 2018 Jan 1;64(1):102–10.
34. Zhao X, Guan JL. Focal adhesion kinase and its signaling pathways in cell migration and angiogenesis. Target Cell Mov Tumor Cardiovasc Dis. 2011 Jul 18;63(8):610–5.
35. Liu L, Luo Q, Sun J, Wang A, Shi Y, Ju Y, et al. Decreased nuclear stiffness via FAK-ERK1/2 signaling is necessary for osteopontin-promoted migration of bone marrow-derived mesenchymal stem cells. Exp Cell Res. 2017 Jun 15;355(2):172–81.
36. Sun J, Zhou Y, Ye Z, Tan WS. Transforming growth factor-β1 stimulates mesenchymal stem cell proliferation by altering cell cycle through FAK-Akt-mTOR pathway. Connect Tissue Res. 2019 Jul 4;60(4):406–17.
37. Lachowski D, Cortes E, Robinson B, Rice A, Rombouts K, Del Río Hernández AE. FAK controls the mechanical activation of YAP, a transcriptional regulator required for durotaxis. FASEB J. 2018 Feb 1;32(2):1099–107.
38. Sun C, Yuan H, Wang L, Wei X, Williams L, Krebsbach PH, et al. FAK Promotes Osteoblast Progenitor Cell Proliferation and Differentiation by Enhancing Wnt Signaling. J Bone Miner Res. 2016 Dec 1;31(12):2227–38.
39. Lee HJ, Diaz MF, Ewere A, Olson SD, Cox CS, Wenzel PL. Focal adhesion kinase signaling regulates anti-inflammatory function of bone marrow mesenchymal stromal cells induced by biomechanical force. Cell Signal. 2017 Oct 1;38:1–9.
40. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis. Genes Cancer. 2011;2(12):1097–105.
41. Avraham H, Lee T, Koh Y, Kim T, Jiang S, Sussman M, et al. Vascular endothelial growth factor regulates focal adhesion assembly in human brain microvascular endothelial cells through activation of the focal adhesion kinase and related adhesion focal tyrosine kinase. J Biol Chem. 2003;278(38):36661–8.
42. Li Q, Xia S, Fang H, Pan J, Jia Y, Deng G. VEGF treatment promotes bone marrow-derived CXCR4+ mesenchymal stromal stem cell differentiation into vessel endothelial cells. Exp Ther Med. 2017;13(2):449–54.
43. Takizawa N, Okubo N, Kamo M, Chosa N, Mikami T, Suzuki K, et al. Bone marrow-derived mesenchymal stem cells propagate immunosuppressive/anti-inflammatory macrophages in cell-to-cell contact-independent and -dependent manners under hypoxic culture. Exp Cell Res. 2017 Sep 15;358(2):411–20.
44. Ma S, Chen X, Wang L, Wei Y, Ni Y, Chu Y, et al. Repairing effects of ICAM-1-expressing mesenchymal stem cells in mice with autoimmune thyroiditis. Exp Ther Med. 2017 Apr;13(4):1295–302.
45. Chen J, Xu F, Zhu H, Li X, Tang B, Liu Y, et al. ICAM-1 regulates differentiation of MSC to adipocytes via activating MAPK pathway. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2014;22(1):160–5.
46. Zheng S, Huang K, Xia W, Shi J, Liu Q, Zhang X, et al. Mesenchymal Stromal Cells Rapidly Suppress TCR Signaling-Mediated Cytokine Transcription in Activated T Cells Through the ICAM-1/CD43 Interaction. Front Immunol [Internet]. 2021;12. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2021.609544