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СОБЛЮДЕНИЕ ЭТИЧЕСКИХ СТАНДАРТОВ

В настоящей работе не проводили какие-либо исследования с использованием животных или людей в качестве объектов.

КОНФЛИКТ ИНТЕРЕСОВ

Авторы заявляют, что у них нет конфликта интересов.

СПИСОК ЛИТЕРАТУРЫ

Андреева Е.Р., Буравкова Л.Б. 2013. Паракринная активность мультипотентных мезенхимальных стромальных клеток и ее особенности в условиях гипоксии. Физиол. человека. Т. 39. № 3. С. 104. (*Andreeva E.R., Buravkova L.B.* 2013. Paracrine activity of multipotent mesenchymal stromal cells and its modulation in hypoxia. Human Physiol. 2013. V. 39. № 3. P. 315. https://doi.org/ https://doi.org/10.7868/S0131164613030041)

Буравкова Л.Б., Андреева Е.Р., Григорьев А.И. 2012. Роль кислорода как физиологического фактора в проявлении функциональных свойств мультипотентных мезенхимальных стромальных клеток человека. Физиол. человека. Т. 38. № 4. С. 1. (*Buravkova L.B., Andreeva E.R., Grigoriev A.I.* 2012. The impact of oxygen in physiological regulation of human multipotent mesenchymal cell functions. Hum. Physiol. V. 38. № 4. P. 444.)

Ездакова М.И., Зорникова К.В., Буравков С.В., Андреева Е.Р. 2020. Функциональная активность непролиферирующих мезенхимных стромальных клеток, культивируемых в различной плотности. Клет. тех. биол. мед. № 4. С. 247. (*Ezdakova M.I., Zornikova K.V., Buravkov S.V., Andreeva E.R.* 2021. Functional activity of non-proliferating mesenchymal stromal cells cultured at different densities. Bull. Exper. Biol. Med. V. 170. P. 537. https://doi.org/10.47056/1814-3490-2020-4-247-254)

Успенская Ю.А., Малиновская Н.А., Салмина А.Б. 2021. Межклеточный транспорт митохондрий: молекулярные механизмы и роль в поддержании энергетического гомеостаза в тканях. Цитология. Т. 63. № 6. С. 513. (*Uspenskaya Yu.A., Malinovskaya N.A., Salmina A.B.* 2021. Intercellular mitochondrial transfer: molecular mechanisms and role in maintaining the energy homeostasis in tissues. Tsitologiya. V. 63. № 6. P. 513. https://doi.org/10.31857/S0041377121060110)

Anand R.J., Dai S., Gribar S.C., Richardson W., Kohler J.W., Hoffman R.A., Branca M.F., Li J., Shi X.H., Sodhi C.P., Hackam D.J. 2008. A role for connexin43 in macrophage phagocytosis and host survival after bacterial peritoneal infection. J. Immunol. V. 181. P. 8534. https://doi.org/10.4049/jimmunol.181.12.8534

Andreeva E.R., Pugach I.M., Gordon D., Orekhov A.N. 1998. Continuous subendothelial letwork formed by pericyte-like cells in human vascular bed. Tiss. Cell. V. 30. P.127. https://doi.org/10.1016/s0040-8166(98)80014-1

Batra N., Kar R., Jiang J.X. 2012. Gap junctions and hemichannels in signal transmission, function and development of bone. Biochim. Biophys. Acta. V. 1818. P. 1909. https://doi.org/10.1016/j.bbamem.2011.09.018

Bousquenaud M., Schwartz C., Léonard F., Rolland-Turner M., Wagner D., Devaux Y. 2012. Monocyte chemotactic protein 3 is a homing factor for circulating angiogenic cells. Cardiovasc. Res. V. 94. P. 519. https://doi.org/10.1093/cvr/cvs140

Brink P.R., Valiunas V., Gordon C., Rosen M.R., Cohen I.S. 2012. Can gap junctions deliver? Biochim. Biophys. Acta. V. 1818 P. 2076. https://doi.org/10.1016/j.bbamem.2011.09.025

Caplan A.I. 2017. Mesenchymal stem cells: time to change the name! Stem Cells Transl. Med. V. 6. P. 1445. https://doi.org/10.1002/sctm.17-0051

Castellano P., Eugenin E.A. 2014. Regulation of gap junction channels by infectious agents and inflammation in the CNS. Front. Cell Neurosci. V. 8. P. 122. https://doi.org/10.3389/fncel.2014.00122

Caunt M., Hu L., Tang T., Brooks P.C., Ibrahim S., Karpatkin S. 2006. Growth-regulated oncogene is pivotal in thrombin-induced angiogenesis. Cancer Res. V. 66. P. 4125. https://doi.org/10.1158/0008-5472.CAN-05-2570

Chanson M., Derouette J.P., Roth I., Foglia B., Scerri I., Dudez T., Kwak B.R. 2005. Gap junctional communication in tissue inflammation and repair. Biochim. Biophys. Acta. V. 1711. P. 197. https://doi.org/10.1016/j.bbamem.2004.10.005

Cupler E.J., Danon M.J., Jay C., Hench K., Rapka M., Dalakos M.C. 1995. Early features of zidobudine-associated myopathy: histopathological findings and clinical correlations. ActaNeuropathol. V. 90. P. 1. https://doi.org/10.1007/BF00294452

Dorshkind K., Green L., Godwin A., Fletcher W.H. 1993. Connexin-43-type gap junctions mediate communication between bone marrow stromal cells. Blood. V. 82. P. 38.

Duffy H.S., John G.R., Lee S.C., Brosnan C.F., Spray D.C. 2000. Reciprocal regulation of the junctional proteins claudin-1 and connexin43 by interleukin-1beta in primary human fetal astrocytes. J. Neurosci. V. 20. P. RC114. https://doi.org/10.1523/JNEUROSCI.20-23-j0004.2000

Greco S.J., Rameshwar P. 2013. Analysis of the transfer of circulating microRNA between cells mediated by gap junction. Methods Mol. Biol. V. 1024. P. 87. https://doi.org/10.1007/978-1-62703-453-1_7

Harris A.L. 2007. Connexin channel permeability to cytoplasmic molecules. Prog. Biophys. Mol. Biol. V. 94. P. 120. https://doi.org/10.1016/j.pbiomolbio.2007.03.011

Kayakabe K., Kuroiwa T., Sakurai N., Ikeuchi H., Kadiombo A.T., Sakairi T., Nojima Y. 2012. Interleukin-6 promotes destabilized angiogenesis by modulating angiopoietin expression in rheumatoid arthritis. Rheumatol. V. 51. P. 1571. https://doi.org/10.1093/rheumatology/kes093

Lamb R., Bonuccelli G., Ozsvári B., Peiris-Pagès M., Fiorillo M., Smith D.L., Bevilacqua G., Mazzanti C.M., McDonnell L.A., Naccarato A.G., Chiu M., Wynne L., Martinez-Outschoorn U.E., Sotgia F., Lisanti M.P. 2015. Mitochondrial mass, a new metabolic biomarker for stem-like cancer cells: understanding WNT/FGF-driven anabolic signaling. Oncotarget. V. 6. P. 30453. https://doi.org/10.18632/oncotarget.5852

Lee C.F., Liu C.Y., Hsieh R.H., Wei Y.H. 2005. Oxidative stress-induced depolymerization of microtubules and alteration of mitochondrial mass in human cells. Ann. NY Acad. Sci. V. 1042. P. 246. https://doi.org/10.1196/annals.1338.027

Lee C., Yin P.H., Lu C.Y., Chi C.W., Wei Y.H. 2000. Increase of mitochondrial DNA in response to oxidative stress in human cells. Biochem. J. V. 348. P. 425.

Li A., Dubey S., Varney M.L., Dave B.J., Singh R.K. 2003. IL-8 directly enhanced endothelial cell survival, proliferation, and matrix metalloproteinases production and regulated angiogenesis. J. Immunol. V. 170. P. 3369. https://doi.org/10.4049/jimmunol.170.6.3369

Li X., Nagy J.I., Li D., Acott T.S., Kelley M.J. 2020. Gap junction connexin43 is a key element in mediating phagocytosis activity in human trabecular meshwork cells. Int. J. Physiol. Pathophysiol. Pharmacol. V. 12. P. 25

Limoli C.L., Giedzinski E., Morgan W.F., Swarts S.G., Jones G.D.D., Hyun W. 2003. Persistent oxidative stress in chromosomally unstable cells. Cancer Res. V. 63. P. 3107.

Mancini M., Anderson B.O., Caldwell E., Sedghinasab M., Paty P.B., Hockenbery D.M. 2005. Mitochondrial proliferation and paradoxical membrane depolarization during terminal differentiation and apoptosis in a human colon carcinoma cell line. J. Cell Biol. V. 138. P. 449. https://doi.org/10.1083/jcb.138.2.449

Murphy M.B., Moncivais K., Caplan A.I. 2013. Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Exper. Mol. Med. V. 45. P. 54. https://doi.org/10.1038/emm.2013.94

Murray I.R., Péault B. 2015. Mesenchymal stem cells – where do they come from and is it important? BMC Biol. V. 13. P. 99. https://doi.org/10.1186/s12915-015-0212-7

Orekhov A.N., Andreeva E.R., Bobryshev Y.V. 2016. Cellular mechanisms of human atherosclerosis: role of cell-to-cell communications in subendothelial cell functions. Tissue Cell. V. 48. P. 25. https://doi.org/10.1016/j.tice.2015.11.002

Papetti M., Herman I.M. 2002. Mechanisms of normal and tumor-derived angiogenesis. Am. J. Physiol.: Cell Physiol. V. 282. P. C947. https://doi.org/10.1152/ajpcell.00389.2001

Plotnikov E.Y., Babenko V.A., Silachev D.N., Zorova L.D., Khryapenkova T.G., Savchenko E.S., Pevzner I.B., Zorov D.B. 2015. Intercellular transfer of mitochondria. Biochemistry (Mosc). V. 80. P. 542. https://doi.org/10.1134/S0006297915050041

Talbot J., Brion R., Lamora A., Mullard M., Morice S., Heymann D., Verrecchia F. 2018. Connexin43 intercellular communication drives the early differentiation of human bone marrow stromal cells into osteoblasts. J. Cell. Physiol. V. 233. P. 946. https://doi.org/10.1002/jcp.25938

Tan L., Liu X., Dou H., Hou Y. 2020. Characteristics and regulation of mesenchymal stem cell plasticity by the microenvironment-specific factors involved in the regulation of MSC plasticity. Genes Dis. V. 9. P. 296. https://doi.org/10.1016/j.gendis.2020.10.006

Tarzemany R., Jiang G., Larjava H., Häkkinen L. 2015. Expression and function of connexin 43 in human gingival wound healing and fibroblasts. PLoS One. V. 10. P. e0115524. https://doi.org/10.1371/journal.pone.0115524

Udartseva O.O., Zhidkova O.V., Ezdakova M.I., Ogneva I.V., Andreeva E.R., Buravkova L.B., Gollnick S.O. 2019. Low-dose photodynamic therapy promotes angiogenic potential and increases immunogenicity of human mesenchymal stromal cells. J. Photochem. Photobiol. B. V. 199. P. 111596. https://doi.org/10.1016/j.jphotobiol.2019.111596

Wei L.H., Kuo M.L., Chen C.A., Chou C.H., Lai K.B., Lee C.N., Hsieh C.Y. 2003. Interleukin-6 promotes cervical tumor growth by VEGF-dependent angiogenesis via a STAT3 pathway. Oncogene. V. 22. P. 1517. https://doi.org/10.1038/sj.onc.1206226

Yu J., Wu J., Bagchi I.C., Bagchi M.K., Sidell N., Taylor R.N. 2011. Disruption of gap junctions reduces biomarkers of decidualization and angiogenesis and increases inflammatory mediators in human endometrial stromal cell cultures. Mol. Cell. Endocrinol. V. 344. P. 25. https://doi.org/10.1016/j.mce.2011.04.011

Zachar L. Bačenková D., Rosocha J. 2016. Activation, homing, and role of the mesenchymal stem cells in the inflammatory environment. J. Inflamm. Res. V. 9. P. 231. https://doi.org/10.2147/JIR.S121994

Homotypic Regulation of Functional Activity of Multipotent Mesenchymal Stromal Cells: The Role of Gap Junctions

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Perivascular multipotent mesenchymal stromal cells (MSCs) are considered as most likely putative depot for MSCs' mobilization in case of tissue damage. Here, we analyzed the involvement of direct homotypic gap junctional intercellular communication (GJIC) in realization of MSC functions requested in tissue healing and repair: the state of intracellular compartments, paracrine, in particular angiogenic activity, the migration and phagocytosis. GJIC in growth arrested MSCs was suppressed with specific inhibitor, carbenoxolone. Using flow cytometry, a two-fold increase in mitochondrial mass (MitoTracker Green) was shown in MSCs with blocked GJ. The transmembrane mitochondrial potential (JC-1) and the ROS levels (CM-H2DCFDA probe), as well as the activity of the lysosomes (LysoTracker Green) did not change. MSCs with blocked GJs migrated less actively in the "scratch wounding" model. The phagocytosis of latex beads was reduced. According to multiplex immunofluorescence assay, the levels of pleiotropic cytokines IL-6, IL-8, and MCP-3 were significantly lower in the conditioned medium from MSCs with blocked GJs. This medium did not stimulate the non-targeted migration of endothelial cells and the growth of the tubule complexes in the chorioallantoic membrane of the quail embryo. It is supposed, that a decrease in the efficacy of direct MSC-MSC intercellular communication *in vivo* may negatively affect stromal cells' functions on site as well as their mobilization from tissue depots.

Keywords: multipotent mesenchymal stromal cells, homotypic gap junctions, inhibitor, intracellular compartments, phagocytosis, migration, soluble mediators, angiogenesis *in ovo*