

Human umbilical cord blood cell transplantation in neuroregenerative strategies

Galieva L., Mukhamedshina Y., Arkhipova S., Rizvanov A.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2017 Galieva, Mukhamedshina, Arkhipova and Rizvanov. At present there is no effective treatment of pathologies associated with the death of neurons and glial cells which take place as a result of physical trauma or ischemic lesions of the nervous system. Thus, researchers have high hopes for a treatment based on the use of stem cells (SC), which are potentially able to replace dead cells and synthesize neurotrophic factors and other molecules that stimulate neuroregeneration. We are often faced with ethical issues when selecting a source of SC. In addition to precluding these, human umbilical cord blood (hUCB) presents a number of advantages when compared with other sources of SC. In this review, we consider the key characteristics of hUCB, the results of various studies focused on the treatment of neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis), ischemic (stroke) and traumatic injuries of the nervous system and the molecular mechanisms of hUCB-derived mononuclear and stem cells.

<http://dx.doi.org/10.3389/fphar.2017.00628>

Keywords

Human umbilical cord blood cells, Neurodegeneration diseases, Neuroregeneration strategies, Spinal cord injury, Stroke

References

- [1] Aleynik, A., Gernavage, K. M., Mourad, Y. S., Sherman, L. S., Liu, K., Gubenko, Y. A., et al. (2014). Stem cell delivery of therapies for brain disorders. *Clin. Transl. Med.* 3:24. doi: 10.1186/2001-1326-3-24
- [2] Arpinati, M., Green, C. L., Heimfeld, S., Heuser, J. E., and Anasetti, C. (2000). Granulocyte-colony stimulating factor mobilizes T helper 2-inducing dendritic cells. *Blood* 95, 2484-2490
- [3] Au, P., Daheron, L. M., Duda, D. G., Cohen, K. S., Tyrrell, J. A., Lanning, R. M., et al. (2008). Differential in vivo potential of endothelial progenitor cells from human umbilical cord blood and adult peripheral blood to form functional long-lasting vessels. *Blood* 111, 1302-1305. doi: 10.1182/blood-2007-06-094318
- [4] Awad, B. I., Carmody, M. A., and Steinmetz, M. P. (2015). Potential role of growth factors in the management of spinal cord injury. *World Neurosurg.* 83, 120-131. doi: 10.1016/j.wneu.2013.01.042
- [5] Bakhshandeh, B., Soleimani, M., Ghaemi, N., and Shabani, I. (2011). Effective combination of aligned nanocomposite nanofibers and human unrestricted somatic stem cells for bone tissue engineering. *Acta Pharmacol. Sin.* 32, 626-636. doi: 10.1038/aps.2011.8
- [6] Bigini, P., Veglianese, P., Andriolo, G., Cova, L., Grignaschi, G., Caron, I., et al. (2011). Intracerebroventricular administration of human umbilical cord blood cells delays disease progression in two murine models of motor neuron degeneration. *Rejuvenation Res.* 14, 623-639. doi: 10.1089/rej.2011.1197

- [7] Broxmeyer, H. E., Douglas, G. W., Hangoc, G., Cooper, S., Bard, J., English, D., et al. (1989). Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. *Proc. Natl. Acad. Sci. U.S.A.* 86, 3828-3832
- [8] Campagnoli, C., Roberts, I. A., Kumar, S., Bennett, P. R., Bellantuono, I., and Fisk, N. M. (2001). Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. *Blood* 98, 2396-2402
- [9] Chen, C.-T., Foo, N.-H., Liu, W.-S., and Chen, S.-H. (2008). Infusion of human umbilical cord blood cells ameliorates hind limb dysfunction in experimental spinal cord injury through anti-inflammatory, vasculogenic and neurotrophic mechanisms. *Pediatr. Neonatol.* 49, 77-83. doi: 10.1016/S1875-9572(08)60017-0
- [10] Chen, J., Sanberg, P. R., Li, Y., Wang, L., Lu, M., Willing, A. E., et al. (2001). Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats. *Stroke* 32, 2682-2688. doi: 10.1161/his.1101.098367
- [11] Chen, N., Hudson, J. E., Walczak, P., Misiuta, I., Garbuzova-Davis, S., Jiang, L., et al. (2005). Human umbilical cord blood progenitors: the potential of these hematopoietic cells to become neural. *Stem Cells* 23, 1560-1570. doi: 10.1634/stemcells.2004-0284
- [12] Chen, R., and Ende, N. (1999). The potential for the use of mononuclear cells from human umbilical cord blood in the treatment of amyotrophic lateral sclerosis in SOD1 mice. *J. Med.* 31, 21-30
- [13] Chua, S. J., Bielecki, R., Yamanaka, N., Fehlings, M. G., Rogers, I. M., and Casper, R. F. (2010). The effect of umbilical cord blood cells on outcomes after experimental traumatic spinal cord injury. *Spine* 35, 1520-1526. doi: 10.1097/BRS.0b013e3181c3e963
- [14] Dalous, J., Larghero, J., and Baud, O. (2012). Transplantation of umbilical cord-derived mesenchymal stem cells as a novel strategy to protect the central nervous system: technical aspects, preclinical studies, and clinical perspectives. *Pediatr. Res.* 71, 482-490. doi: 10.1038/pr.2011.67
- [15] Danby, R., and Rocha, V. (2014). Improving engraftment and immune reconstitution in umbilical cord blood transplantation. *Front. Immunol.* 5:68. doi: 10.3389/fimmu.2014.00068
- [16] Dasari, V. R., Spomar, D. G., Li, L., Gujrati, M., Rao, J. S., and Dinh, D. H. (2008). Umbilical cord blood stem cell mediated downregulation of fas improves functional recovery of rats after spinal cord injury. *Neurochem. Res.* 33, 134-149. doi: 10.1007/s11064-007-9426-6
- [17] Ding, D.-C., Shyu, W.-C., Chiang, M.-F., Lin, S.-Z., Chang, Y.-C., Wang, H.-J., et al. (2007). Enhancement of neuroplasticity through upregulation of β 1-integrin in human umbilical cord-derived stromal cell implanted stroke model. *Neurobiol. Dis.* 27, 339-353. doi: 10.1016/j.nbd.2007.06.010
- [18] Eglitis, M. A., and Mezey, é. (1997). Hematopoietic cells differentiate into both microglia and macroglia in the brains of adult mice. *Proc. Natl. Acad. Sci. U.S.A.* 94, 4080-4085
- [19] Ende, M., and Shende, N. (1972). Hematopoietic transplantation by means of fetal (cord) blood: a new method. *Va. Med. Mon.* 99, 276-280
- [20] Ende, N., and Chen, R. (2000). Human umbilical cord blood cells ameliorate Huntington's disease in transgenic mice. *J. Med.* 32, 231-240
- [21] Ende, N., and Chen, R. (2002). Parkinson's disease mice and human umbilical cord blood. *J. Med.* 33, 173-180
- [22] Ende, N., Chen, R., and Ende-Harris, D. (2000a). Human umbilical cord blood cells ameliorate Alzheimer's disease in transgenic mice. *J. Med.* 32, 241-247
- [23] Ende, N., Weinstein, F., Chen, R., and Ende, M. (2000b). Human umbilical cord blood effect on sod mice (amyotrophic lateral sclerosis). *Life Sci.* 67, 53-59
- [24] Erices, A., Conget, P., and Minguez, J. J. (2000). Mesenchymal progenitor cells in human umbilical cord blood. *Br. J. Haematol.* 109, 235-242
- [25] Fu, Y.-S., Shih, Y.-T., Cheng, Y.-C., and Min, M.-Y. (2004). Transformation of human umbilical mesenchymal cells into neurons in vitro. *J. Biomed. Sci.* 11, 652-660. doi: 10.1159/000079678
- [26] Garbuzova-Davis, S., Rodrigues, M. C., Mirtyl, S., Turner, S., Mitha, S., Sodhi, J., et al. (2012). Multiple intravenous administrations of human umbilical cord blood cells benefit in a mouse model of ALS. *PLoS ONE* 7:e31254. doi: 10.1371/journal.pone.0031254
- [27] Garbuzova-Davis, S., Sanberg, C. D., Kuzmin-Nichols, N., Willing, A. E., Gemma, C., Bickford, P. C., et al. (2008). Human umbilical cord blood treatment in a mouse model of ALS: optimization of cell dose. *PLoS ONE* 3:e2494. doi: 10.1371/journal.pone.0002494
- [28] Garbuzova-Davis, S., Willing, A. E., Zigova, T., Saporta, S., Justen, E. B., Lane, J. C., et al. (2003). Intravenous administration of human umbilical cord blood cells in a mouse model of amyotrophic lateral sclerosis: distribution, migration, and differentiation. *J. Hematother. Stem Cell Res.* 12, 255-270. doi: 10.1089/152581603322022990
- [29] Glavaski-Joksimovic, A., and Bohn, M. C. (2013). Mesenchymal stem cells and neuroregeneration in Parkinson's disease. *Exp. Neurol.* 247, 25-38. doi: 10.1016/j.expneurol.2013.03.016

- [30] Gluckman, E., Broxmeyer, H., Auerbach, A. D., Friedman, H. S., Douglas, G. W., Devergie, A., et al. (1989). Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N. Engl. J. Med.* 321, 1174-1178
- [31] Gluckman, E., and Rocha, V. (2005). History of the clinical use of umbilical cord blood hematopoietic cells. *Cytotherapy* 7, 219-227. doi: 10.1080/14653240510027136
- [32] Gluckman, E., Rocha, V., Boyer-Chammard, A., Locatelli, F., Arcese, W., Pasquini, R., et al. (1997). Outcome of cord-blood transplantation from related and unrelated donors. *New Engl. J. Med.* 337, 373-381
- [33] Goldstein, G., Toren, A., and Nagler, A. (2007). Transplantation and other uses of human umbilical cord blood and stem cells. *Curr. Pharm. Des.* 13, 1363-1373
- [34] Handschel, J., Naujoks, C., Langenbach, F., Berr, K., Depprich, R. A., Ommerborn, M. A., et al. (2010). Comparison of ectopic bone formation of embryonic stem cells and cord blood stem cells in vivo. *Tissue Eng. A* 16, 2475-2483. doi: 10.1089/ten.TEA.2009.0546
- [35] Hei, W.-H., Almansoori, A. A., Sung, M.-A., Ju, K.-W., Seo, N., Lee, S.-H., et al. (2017). Adenovirus vector-mediated ex vivo gene transfer of brain-derived neurotrophic factor (BDNF) to human umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs) promotes crush-injured rat sciatic nerve regeneration. *Neurosci. Lett.* 643, 111-120. doi: 10.1016/j.neulet.2017.02.030
- [36] Hsieh, J.-Y., Wang, H.-W., Chang, S.-J., Liao, K.-H., Lee, I.-H., Lin, W.-S., et al. (2013). Mesenchymal stem cells from human umbilical cord express preferentially secreted factors related to neuroprotection, neurogenesis, and angiogenesis. *PLoS ONE* 8:e72604. doi: 10.1371/journal.pone.0072604
- [37] Ikeda, Y., Fukuda, N., Mika, W., Matsumoto, T., Satomi, A., Yokoyama, S.-I., et al. (2004). Development of angiogenic cell and gene therapy by transplantation of umbilical cord blood with vascular endothelial growth factor gene. *Hypertens. Res.* 27, 119-128
- [38] Jang, Y., Park, J., Lee, M., Yoon, B., Yang, Y., Yang, S., et al. (2004). Retinoic acid-mediated induction of neurons and glial cells from human umbilical cord-derived hematopoietic stem cells. *J. Neurosci. Res.* 75, 573-584. doi: 10.1002/jnr.10789
- [39] Jiao, F., Wang, J., Dong, Z.-L., Wu, M.-J., Zhao, T.-B., Li, D.-D., et al. (2012). Human mesenchymal stem cells derived from limb bud can differentiate into all three embryonic germ layers lineages. *Cel. Reprogram.* 14, 324-333. doi: 10.1089/cell.2012.0004
- [40] Kang, E. J., Lee, Y. H., Kim, M. J., Lee, Y. M., Mohana Kumar, B., Jeon, B. G., et al. (2013). Transplantation of porcine umbilical cord matrix mesenchymal stem cells in a mouse model of Parkinson's disease. *J. Tissue Eng. Regen. Med.* 7, 169-182. doi: 10.1002/term.504
- [41] Karahuseyinoglu, S., Cinar, O., Kilic, E., Kara, F., Akay, G. G., Demiralp, D. ö., et al. (2007). Biology of stem cells in human umbilical cord stroma: in situ and in vitro surveys. *Stem Cells* 25, 319-331. doi: 10.1634/stemcells.2006-0286
- [42] Kim, E.-J., Kim, N., and Cho, S.-G. (2013). The potential use of mesenchymal stem cells in hematopoietic stem cell transplantation. *Exp. Mol. Med.* 45:e2. doi: 10.1038/emm.2013.2
- [43] Kim, H. J., Seo, S. W., Chang, J. W., Lee, J. I., Kim, C. H., Chin, J., et al. (2015). Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: a phase 1 clinical trial. *Alzheimer's Demen. Transl. Res. Clin. Interv.* 1, 95-102. doi: 10.1016/j.trci.2015.06.007
- [44] Knippenberg, S., Thau, N., Schwabe, K., Dengler, R., Schambach, A., Hass, R., et al. (2011). Intraspinal injection of human umbilical cord blood-derived cells is neuroprotective in a transgenic mouse model of amyotrophic lateral sclerosis. *Neurodegenerative Dis.* 9, 107-120. doi: 10.1159/000331327
- [45] Kögler, G., Sensken, S., Airey, J. A., Trapp, T., Müschen, M., Feldhahn, N., et al. (2004). A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. *J. Exp. Med.* 200, 123-135. doi: 10.1084/jem.20040440
- [46] Langenbach, F., Berr, K., Naujoks, C., Hassel, A., Hentschel, M., Depprich, R., et al. (2011). Generation and differentiation of microtissues from multipotent precursor cells for use in tissue engineering. *Nat. Protoc.* 6, 1726-1735. doi: 10.1038/nprot.2011.394
- [47] Lee, J.-H., Chung, W.-H., Kang, E.-H., Chung, D.-J., Choi, C.-B., Chang, H.-S., et al. (2011). Schwann cell-like remyelination following transplantation of human umbilical cord blood (hUCB)-derived mesenchymal stem cells in dogs with acute spinal cord injury. *J. Neurol. Sci.* 300, 86-96. doi: 10.1016/j.jns.2010.09.025
- [48] Lyons, S. A., and Kettenmann, H. (1998). Oligodendrocytes and microglia are selectively vulnerable to combined hypoxia and hypoglycemia injury in vitro. *J. Cereb. Blood Flow Metab.* 18, 521-530
- [49] Malinin, N. L., Wright, S., Seubert, P., Schenk, D., and Griswold-Prenner, I. (2005). Amyloid- β neurotoxicity is mediated by FISH adapter protein and ADAM12 metalloprotease activity. *Proc. Natl. Acad. Sci. U.S.A.* 102, 3058-3063. doi: 10.1073/pnas.0408237102
- [50] Masgutov, R. F., Masgutova, G. A., Rogojin, A. A., Zhuravleva, M. N., Zakirova, E. Y., Nigmatzyanova, M. V., et al. (2015). Regeneration of rat sciatic nerve using tubulation and allogeneic transplantation of adipose-derived mesenchymal stromal cells. *Gene Cells* 10, 78-82

- [51] Masgutov, R. F., Masgutova, G. A., Zhuravleva, M. N., Salafutdinov, I. I., Mukhametshina, R. T., Mukhamedshina, Y. O., et al. (2016). Human adipose-derived stem cells stimulate neuroregeneration. *Clin. Exp. Med.* 16, 451-461. doi: 10.1007/s10238-015-0364-3
- [52] McGuckin, C. P., and Forraz, N. (2008). Potential for access to embryonic-like cells from human umbilical cord blood. *Cell Prolif.* 41(Suppl. 1), 31-40. doi: 10.1111/j.1365-2184.2008.00490.x
- [53] Mukhamedshina, Y. O., Garanina, E. E., Masgutova, G. A., Galieva, L. R., Sanatova, E. R., Chelyshev, Y. A., et al. (2016a). Assessment of glial scar, tissue sparing, behavioral recovery and axonal regeneration following acute transplantation of genetically modified human umbilical cord blood cells in a rat model of spinal cord contusion. *PLoS ONE* 11:e0151745. doi: 10.1371/journal.pone.0151745
- [54] Mukhamedshina, Y. O., Shaymardanova, G., Garanina, E. E., Salafutdinov, I., Rizvanov, A. A., Islamov, R., et al. (2016b). Adenoviral vector carrying glial cell-derived neurotrophic factor for direct gene therapy in comparison with human umbilical cord blood cell-mediated therapy of spinal cord injury in rat. *Spinal Cord* 54, 347-359. doi: 10.1038/sc.2015.161
- [55] Murohara, T. (2001). Therapeutic vasculogenesis using human cord blood-derived endothelial progenitors. *Trends Cardiovasc. Med.* 11, 303-307
- [56] Nikolic, W. V., Hou, H., Town, T., Zhu, Y., Giunta, B., Sanberg, C. D., et al. (2008). Peripherally administered human umbilical cord blood cells reduce parenchymal and vascular β -amyloid deposits in Alzheimer mice. *Stem Cells Dev.* 17, 423-440. doi: 10.1089/scd.2008.0018
- [57] Pantoni, L., Garcia, J. H., and Gutierrez, J. A. (1996). Cerebral white matter is highly vulnerable to ischemia. *Stroke* 27, 1641-1647
- [58] Petukhova, E., Mukhamedshina, Y., Rizvanov, A., Mukhitov, A., Zefirov, A., Islamov, R., et al. (2014). Transplantation of human cord blood mononuclear cells improves spatial memory in app/ps1 transgenic mice with the Alzheimer's disease model. *Gene Cells* 9, 234-239
- [59] Petukhova, E., Mukhamedshina, Y., Vasilyeva, O., Aksanova, L., Solovyova, V., Garanina, E., et al. (2015). Stimulation of neurogenesis at hippocampus in Alzheimer's disease. *Gene Cells* 10, 54-59
- [60] Pimentel-Coelho, P. M., Rosado-de-Castro, P. H., da Fonseca, L. M. B., and Mendez-Otero, R. (2012). Umbilical cord blood mononuclear cell transplantation for neonatal hypoxic-ischemic encephalopathy. *Pediatr. Res.* 71, 464-473. doi: 10.1038/pr.2011.59
- [61] Rizvanov, A. A., Guseva, D. S., Salafutdinov, I. I., Kudryashova, N. V., Bashirov, F. V., Kiyasov, A. P., et al. (2011). Genetically modified human umbilical cord blood cells expressing vascular endothelial growth factor and fibroblast growth factor 2 differentiate into glial cells after transplantation into amyotrophic lateral sclerosis transgenic mice. *Exp. Biol. Med.* 236, 91-98. doi: 10.1258/ebm.2010.010172
- [62] Robertovich Islamov, R., Anatolyevich Rizvanov, A., Alexandrovich Mukhamedyarov, M., Ildusovich Salafutdinov, I., Evgenevna Garanina, E., Yuryevna Fedotova, V., et al. (2015). Symptomatic improvement, increased life-span and sustained cell homing in amyotrophic lateral sclerosis after transplantation of human umbilical cord blood cells genetically modified with adeno-viral vectors expressing a neuro-protective factor and a neural cell adhesion molecule. *Curr. Gene Ther.* 15, 266-276
- [63] Rocha, V., and Broxmeyer, H. E. (2010). New approaches for improving engraftment after cord blood transplantation. *Biol. Blood Marrow Transplant.* 16(Suppl. 1), S126-S132. doi: 10.1016/j.bbmt.2009.11.001
- [64] Rogers, I., and Casper, R. F. (2004). Umbilical cord blood stem cells. *Best Pract. Res. Clin. Obstet. Gynaecol.* 18, 893-908
- [65] Rowe, D. D., Leonardo, C. C., Recio, J. A., Collier, L. A., Willing, A. E., and Pennypacker, K. R. (2012). Human umbilical cord blood cells protect oligodendrocytes from brain ischemia through Akt signal transduction. *J. Biol. Chem.* 287, 4177-4187. doi: 10.1074/jbc.M111.296434
- [66] Rowe, D., Leonardo, C., Hall, A., Shahaduzzaman, M., Collier, L., Willing, A., et al. (2010). Cord blood administration induces oligodendrocyte survival through alterations in gene expression. *Brain Res.* 1366, 172-188. doi: 10.1016/j.brainres.2010.09.078
- [67] Rubinstein, P., Rosenfield, R. E., Adamson, J. W., and Stevens, C. E. (1993). Stored placental blood for unrelated bone marrow reconstitution. *Blood* 81, 1679-1690
- [68] Ryu, H. H., Kang, B. J., Park, S. S., Kim, Y., Sung, G. J., Woo, H. M., et al. (2012). Comparison of mesenchymal stem cells derived from fat, bone marrow, Wharton's jelly, and umbilical cord blood for treating spinal cord injuries in dogs. *J. Vet. Med. Sci.* 74, 1617-1630
- [69] Santourlidis, S., Wernet, P., Ghanjati, F., Graffmann, N., Springer, J., Kriegs, C., et al. (2011). Unrestricted somatic stem cells (USSC) from human umbilical cord blood display uncommitted epigenetic signatures of the major stem cell pluripotency genes. *Stem Cell Res.* 6, 60-69. doi: 10.1016/j.scr.2010.08.003
- [70] Saporta, S., Kim, J.-J., Willing, A. E., Fu, E. S., Davis, C. D., and Sanberg, P. R. (2003). Human umbilical cord blood stem cells infusion in spinal cord injury: engraftment and beneficial influence on behavior. *J. Hematother. Stem Cell Res.* 12, 271-278. doi: 10.1089/152581603322023007

- [71] Scherjon, S. A., Kleijburg-van der Keur, C., de Groot-Swings, G. M., Claas, F. H., Fibbe, W. E., and Kanhai, H. H. (2004). Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. *Stem Cells* 22, 1338-1345. doi: 10.1634/stemcells.2004-0058
- [72] Schira, J., Gasis, M., Estrada, V., Hendricks, M., Schmitz, C., Trapp, T., et al. (2012). Significant clinical, neuropathological and behavioural recovery from acute spinal cord trauma by transplantation of a well-defined somatic stem cell from human umbilical cord blood. *Brain* 135, 431-446. doi: 10.1093/brain/awr222
- [73] Selkoe, D. J. (2001). Alzheimer's disease: genes, proteins, and therapy. *Physiol. Rev.* 81, 741-766
- [74] Souayah, N., Coakley, K., Chen, R., Ende, N., and McArdle, J. J. (2012). Defective neuromuscular transmission in the SOD1G93A transgenic mouse improves after administration of human umbilical cord blood cells. *Stem Cell Rev. Rep.* 8, 224-228. doi: 10.1007/s12015-011-9281-3
- [75] Stenderup, K., Justesen, J., Clausen, C., and Kassem, M. (2003). Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells. *Bone* 33, 919-926. doi: 10.1016/j.bone.2003.07.005
- [76] Sung, M. A., Jung, H. J., Lee, J. W., Lee, J. Y., Pang, K. M., Yoo, S. B., et al. (2012). Human umbilical cord blood-derived mesenchymal stem cells promote regeneration of crush-injured rat sciatic nerves. *Neural Regen Res.* 7, 2018-2027. doi: 10.3969/j.issn.1673-5374.2012.26.003
- [77] Taguchi, A., Soma, T., Tanaka, H., Kanda, T., Nishimura, H., Yoshikawa, H., et al. (2004). Administration of CD34+ cells after stroke enhances neurogenesis via angiogenesis in a mouse model. *J. Clin. Invest.* 114, 330-338. doi: 10.1172/JCI20622
- [78] Trapp, T., Kögl, G., El-Khattouti, A., Sorg, R. V., Besselmann, M., Föcking, M., et al. (2008). Hepatocyte growth factor/c-MET axis-mediated tropism of cord blood-derived unrestricted somatic stem cells for neuronal injury. *J. Biol. Chem.* 283, 32244-32253. doi: 10.1074/jbc.M800862200
- [79] Vangsness, C. T., Sternberg, H., and Harris, L. (2015). Umbilical cord tissue offers the greatest number of harvestable mesenchymal stem cells for research and clinical application: a literature review of different harvest sites. *Arthroscopy* 31, 1836-1843. doi: 10.1016/j.arthro.2015.03.014
- [80] van Rood, J. J., Stevens, C. E., Smits, J., Carrier, C., Carpenter, C., and Scaradavou, A. (2009). Reexposure of cord blood to noninherited maternal HLA antigens improves transplant outcome in hematological malignancies. *Proc. Natl. Acad. Sci. U.S.A.* 106, 19952-19957. doi: 10.1073/pnas.0910310106
- [81] Veeravalli, K. K., Dasari, V. R., Tsung, A. J., Dinh, D. H., Gujrati, M., Fassett, D., et al. (2009). Stem cells downregulate the elevated levels of tissue plasminogen activator in rats after spinal cord injury. *Neurochem. Res.* 34, 1183. doi: 10.1007/s11064-008-9894-3
- [82] Vendrame, M., Cassady, J., Newcomb, J., Butler, T., Pennypacker, K. R., Zigova, T., et al. (2004). Infusion of human umbilical cord blood cells in a rat model of stroke dose-dependently rescues behavioral deficits and reduces infarct volume. *Stroke* 35, 2390-2395. doi: 10.1161/01.STR.0000141681.06735.9b
- [83] Vendrame, M., Gemma, C., Mesquita, D. D., Collier, L., Bickford, P. C., Sanberg, C. D., et al. (2005). Anti-inflammatory effects of human cord blood cells in a rat model of stroke. *Stem Cells Dev.* 14, 595-604. doi: 10.1089/scd.2005.14.595
- [84] Vercelli, A., Mereuta, O., Garbossa, D., Muraca, G., Mareschi, K., Rustichelli, D., et al. (2008). Human mesenchymal stem cell transplantation extends survival, improves motor performance and decreases neuroinflammation in mouse model of amyotrophic lateral sclerosis. *Neurobiol. Dis.* 31, 395-405. doi: 10.1016/j.nbd.2008.05.016
- [85] Verneris, M. R., and Miller, J. S. (2009). The phenotypic and functional characteristics of umbilical cord blood and peripheral blood natural killer cells. *Br. J. Haematol.* 147, 185-191. doi: 10.1111/j.1365-2141.2009.07768.x
- [86] Wang, H. S., Hung, S. C., Peng, S. T., Huang, C. C., Wei, H. M., Guo, Y. J., et al. (2004). Mesenchymal stem cells in the Wharton's jelly of the human umbilical cord. *Stem Cells* 22, 1330-1337. doi: 10.1634/stemcells.2004-0013
- [87] Wang, X., Wang, S., and Xiao, Y. (2015). An experimental study on repair of sciatic nerve injury by Schwann-like cells derived from umbilical cord blood mesenchymal stem cells. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 29, 213-220
- [88] Willing, A. E., Eve, D. J., and Sanberg, P. R. (2007). Umbilical cord blood transfusions for prevention of progressive brain injury and induction of neural recovery: an immunological perspective. *Regen. Med.* 2:457-464. doi: 10.2217/17460751.2.4.457
- [89] Willing, A., Lixian, J., Milliken, M., Poulos, S., Zigova, T., Song, S., et al. (2003). Intravenous versus intrastriatal cord blood administration in a rodent model of stroke. *J. Neurosci. Res.* 73, 296-307. doi: 10.1002/jnr.10659
- [90] Xiao, J., Nan, Z., Motooka, Y., and Low, W. C. (2005). Transplantation of a novel cell line population of umbilical cord blood stem cells ameliorates neurological deficits associated with ischemic brain injury. *Stem Cells Dev.* 14, 722-733. doi: 10.1089/scd.2005.14.722
- [91] Yin, A. H., Miraglia, S., Zanjani, E. D., Almeida-Porada, G., Ogawa, M., Leary, A. G., et al. (1997). AC133, a novel marker for human hematopoietic stem and progenitor cells. *Blood* 90, 5002-5012

- [92] Zaehres, H., Kögler, G., Arauzo-Bravo, M. J., Bleidissel, M., Santourlidis, S., Weinhold, S., et al. (2010). Induction of pluripotency in human cord blood unrestricted somatic stem cells. *Exp. Hematol.* 38, 809-818, 818.e1-2. doi: 10.1016/j.exphem.2010.05.009
- [93] Zaibak, F., Bello, P., Kozlovska, J., Crombie, D., Ang, H., Dottori, M., et al. (2009). Unrestricted somatic stem cells from human umbilical cord blood grow in serum-free medium as spheres. *BMC Biotechnol.* 9:101. doi: 10.1186/1472-6750-9-101
- [94] Zhu, H., Poon, W., Liu, Y., Leung, G. K.-K., Wong, Y., Feng, Y., et al. (2016). Phase I-II clinical trial assessing safety and efficacy of umbilical cord blood mononuclear cell transplant therapy of chronic complete spinal cord injury. *Cell Transplant* 25, 1925-1943. doi: 10.3727/096368916X691411
- [95] Zola, H., Fusco, M., Macardle, P., Flego, L., and Roberton, D. (1995). Expression of cytokine receptors by human cord blood lymphocytes: comparison with adult blood lymphocytes. *Pediatr. Res.* 38, 397-403