STEM CELL THERAPY IN TRAUMATIC BRAIN INJURY

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ABSTRACT

Traumatic brain injury (TBI), which is the most common cause of death and disability after trauma, is accompanied with altered vasculo--neuronal properties due to a variety of inflammatory complications and cognitive dysfunction. Recent studies show that progression of disease may be ameliorated by increased numbers of stem/progenitor cells, which may restore impaired property of neurons and possibly blood vessels and even regenerate them in pericontusional area. The ability of stem cells to self-regenerate and differentiate may contribute to amelioration of physiological dysfunction and possibly cognitive impairments after TBI. The focus of this review is to explore the role and use of stem/progenitor cells in post-TBI healing process.

Key words: Traumatic brain injury, stem/progenitor cells, endothelial progenitor cells, stromal vascular fraction, vasculo-neuronal unit.

TRAUMATIC BRAIN INJURY; VASCULO-NEURONAL UNIT

Traumatic brain injury (TBI) is a devastating public health problem worldwide. It is the leading cause of death and disability after trauma. The harmful effects of TBI occur during primary injury and secondary complications. Primary damage is induced by a mechanical force which results in compression and physical damage of neuro-vascular unit (NVU)[1,2], which consists of cerebral microvessels, glial cells (astroglia, microglia, oligodendroglia), and neurons forming an integrated network that regulates important physiological functions. The secondary complications that may occur hours or days after the injury can be a result of ischemia, inflammation[2,3] and may involve blood- brain barrier (BBB) impairment. BBB is the regulated interface between the peripheral circulation and the central nervous system[3]. Since any vascular or/and blood flow dysfunction, such as regulation of ion balance, homeostasis, changes

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in oxygen and nutrition supply, transport of neurotransmitters and hormones, leads to or/and exacerbates neuronal abnormalities, a term "vasculo-neuronal" dysfunction seems to be more appropriate to define primary source and direction of complications leading to cognitive impairments[3]. However, "neuro--vascular" alterations should define functional impairments originated from damaged neurons and glial cells that affect vasculature.

The treatment of TBI implies active therapeutic approach in the acute phase and the management of long--term posttraumatic complications. The acute care is mostly a complex symptomatic treatment to maintain adequate cerebral perfusion. The aim of long-term therapy is rehabilitation to improve motor function as well as cognitive skills[2]. The main goal of TBI therapy is to achieve the regeneration of damaged vasculo-neuronal unit. Since ability of neurons to repair is very poor, no effective treatment exists other than supportive care, and therefore treatment of TBI still remains a challenge.

Recently, many preclinical and clinical research studies have shown that stem/progenitor cell transplantation has a potential benefits and positive regenerative effects resulting in physiological and functional improvement in many disorders including TBI[4,5].

STEM/PROGENITOR CELLS; NEURONAL STEM CELLS

Commonly used stem/progenitor cells are pluripotent and/or multipotent cells. While pluripotent cells can give rise to most of the cell types that make up the body, multipotent cells can develop into more than one cell type, but this is more limited than that of pluripotent cells. Thus, multipotent cells have an ability of self--renewal and pluripotent cells have the capacity to generate differentiated cells[6-9]. There are two main stem cells types: embryonic stem cells (found in early embryo), and adult (somatic) stem cells. The main sources of somatic stem cells are blood, skin, umbilical cord blood, bone marrow, and adipose tissue.

Neural stem cells (NSCs) are the most commonly used cells in the treatment of neurological disorders including TBI. NSCs are mostly derived from embryonic stem cells[2,6]. It was shown that NSCs were differentiated in neurons and glial cell lines[10]. Treatment of brain injured rats by NSCs showed that these cells may differentiate into neurons and also improve cognitive function[11]. Reduced neurologic deterioration, decreased inflammatory infiltration, and brain edema formation were also reported after NSCs treatment[2].

The majority of research studies is focused on stem cell therapy targeting neuronal regeneration[4] and less is known about their role in vascular repair. Further we will focus on use of stem cells in cerebrovascular repair/regeneration after TBI.

ENDOTHELIAL PROGENITOR CELLS; STROMAL VASCULAR FRACTION

It is known that angiogenesis is crucial for tissue repair and recovery after TBI. Endothelial progenitor

cells (EPCs) have a pivotal role in neovascularization that improves cerebral perfusion and attenuates secondary complications[12]. As a self-defensive mechanism, the number of EPCs is significantly increased in blood 4 days after TBI[13,14]. They migrate toward the injured area and peripheral cerebral tissues to promote neovascularization[12]. Chen et al demonstrated that intravenously administrated spleen-derived EPCs aggregated in the injured area and restored cerebral blood perfusion diminishing the level of brain injury in rats with TBI[12]. Clinical studies also showed that the number of circulated EPCs along with vascular endothelial growth factor (VEGF) and Angiopoetin-1 were increased and positively correlated to Glasgow outcome scale in patients 7 days after severe TBI compared with the healthy controls[14,15]. Park et al showed that bone-marrow derived EPCs treatment had an effect not only on vascular but also on neuronal tissue. Application of EPCs protected secondary post-ischemic axonal and vascular damage in rats after TBI[16]. Comparative studies were done on adipose tissue and bone-marrow derived EPCs[17]. The data showed that both type of EPCs almost equally participated in brain neovascularization and tissue repair. Behavioral improvement was also demonstrated[17].

TBI is accompanied with an increased cerebrovascular permeability to blood proteins caused by impaired endothelial cell properties. We tested the hypothesis that TBI-induced an increase in cerebrovascular permeability can be ameliorated by elevation of EPC numbers. Permeability of pial venules in pericontusional area of mild injury was studied in C57BL/6J mice. After induction of mild TBI, mice were infused with bone marrow-derived EPCs in 100 ml of phosphate buffered saline (PBS) or with PBS alone (control group) through an external jugular vein. After 14 days, pial venular permeability was assessed in these mice by measuring the extravascular accumulation of fluorescein isothiocyanate-labeled bovine serum albumin using an intravital fluorescence microscope. Cerebrovascular leakage was decreased in mice infused EPCs compared to that in mice infused with PBS alone. These results suggest that TBI-induced increased cerebrovascular permeability can be ameliorated by enhancing the number of EPCs, which can restore impaired property of vascular endothelium in pericontusional area[18].

Adipose tissue is a very abundant source of mesenchymal stem cells and surgically easily accessible [19]. The stromal vascular fraction (SVF) from adipose tissue is very heterogeneous cell isolate and a rich source of regenerative cells, including mesenchymal stem cells[19]. SVF also contains endothelial, smooth muscle, blood, and other stromal/mesenchymal cells[19,20]. Used either as an allogeneic or autologous preparation, SVF cell therapy has a complex healing effect on the vasculature. LeBlanc et al demonstrated that treatment with the SVF after an acute myocardial infarction caused increased microvascular perfusion in the peri-infarct area and improved functional flow reserve, even without changing microvessel density, resulting in ameliorated cardiac dysfunction post-MI[19]. So far, there are no studies

published on the effect of SVF after TBI. Our preliminary data showed that macromolecular permeability was lessened in mice infused with SVF compared to that in mice infused with PBS alone (unpublished data).

CONCLUSION

Presently treatment of TBI is challenging and mainly is based on repair of damaged NVU. While this approach seems promising, targeting vasculo-neuronal unit in anticipation of improvement of overall brain function should also be used. Stem/progenitor cell therapy is the most promising treatment in post-TBI based on their ability of self-regeneration and differentiation. Similarly, transplantation of SVFs has a great potential because of their homologues affinity. However, mechanisms of stem cells proliferation, regeneration, survival and function must be fully understood to be freely used in the future in post--TBI treatment.

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REFERENCES

1. Moppett, I. (2007). Traumatic brain injury: assessment, resuscitation and early management. British Journal of Anaesthesia 99, 18-31.
2. Walker, P.A., Shah, S.K., Harting, M.T. and Cox, C.S. (2009). Progenitor cell therapies for traumatic brain injury: barriers and opportunities in translation. Disease Models & Mechanisms 2, 23-38.
3. Muradashvili, N. and Lominadz, D. (2013). Role of fibrinogen in cerebrovascular dysfunction after traumatic brain injury. Brain Injury 27, 1508--1515.
4. Lindvall, O. and Kokaia, Z. (2006). Stem cells for the treatment of neurological disorders. Nature 441, 1094-1096.
5. Tajiri, N., Acosta, S.A., Shahaduzzaman, M., Ishikawa, H., Shinozuka, K., Pabon, M., Hernandez--Ontiveros, D., Kim, D.W., Metcalf, C., Staples, M., Dailey, T., Vasconcellos, J., Franyuti, G., Gould, L., Patel, N., Cooper, D., Kaneko, Y., Borlongan, C.V. and Bickford, P.C. (2014). Intravenous transplants of human adipose-derived stem cell protect the brain from traumatic brain injury--induced neurodegeneration and motor and cognitive impairments: cell graft biodistribution and soluble factors in young and aged rats. Journal of Neuroscience 34, 313-326.
6. Weiner, L.P. (2008). Definitions and criteria for stem cells. Methods in Molecular Biology 438, 3-8.
7. Walker, P.A., Aroom, K.R., Jimenez, F., Shah, S.K., Harting, M.T., Gill, B.S. and Cox, C.S., Jr. (2009). Advances in progenitor cell therapy using scaffolding constructs for central nervous system injury. Stem Cell Reviews 5, 283-300.
8. Walker, P., Harting, M., Shah, S., Day, M., El Khoury, R., Savitz, S., Baumgartner, J. and Cox, C. (2010). Progenitor cell therapy for the treatment of central nervous system injury: a review of the state of current clinical trials. Stem cells international 2010.
9. Maegele, M. and Schaefer, U. (2008). Stem cell--based cellular replacement strategies following traumatic brain injury (TBI). Minimally Invasive Therapy & Allied Technologies: Mitat 17, 119--131.
10. Reynolds, B. and Weiss, S. (1992). Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 255, 1707-1710.
11. Gao, J., Prough, D.S., McAdoo, D.J., Grady, J.J., Parsley, M.O., Ma, L., Tarensenko, Y.I. and Wu, P. (2006). Transplantation of primed human fetal neural stem cells improves cognitive function in rats after traumatic brain injury. Experimental Neurology 201, 281-292.
12. Chen, X., Yin, J., Wu, X., Li, R., Fang, J., Chen, R., Zhang, B. and Zhang, W. (2013). Effects of magnetically labeled exogenous endothelial progenitor cells on cerebral blood perfusion and microvasculature alterations after traumatic brain injury in rat model. Acta Radiologica 54, 313-323.
13. Wei, H.J., Jiang, R.C., Liu, L. and Zhang, J.N. (2010). Circulating endothelial progenitor cells in traumatic brain injury: an emerging therapeutic target? Chinese Journal of Traumatology 13, 316--318.
14. Gong, D., Hao, M., Liu, L., Liu, C., Dong, J., Cui, Z., Sun, L., Su, S. and Zhang, J. (2012). Prognostic relevance of circulating endothelial progenitor cells for severe traumatic brain injury. Brain Injury 26, 291-297.
15. D, G., Zhang, S., Liu, L., Dong, J., Guo, X., Hao, M., Tu, Y., Diao, Y. and Zhang, J. (2011). Dynamic changes of vascular endothelial growth factor and angiopoietin-1 in association with circulating endothelial progenitor cells after severe traumatic brain injury. J Trauma 70, 1480-1484.
16. Park, K.J., Park, E., Liu, E. and Baker, A.J. (2014). Bone marrow-derived endothelial progenitor cells protect postischemic axons after traumatic brain

injury. Journal of Cerebral Blood Flow & Metabolism 34, 357-366.
17. Xue, S., Zhang, H.T., Zhang, P., Luo, J., Chen, Z.Z., Jang, X.D. and Xu, R.X. (2010). Functional endothelial progenitor cells derived from adipose tissue show beneficial effect on cell therapy of traumatic brain injury. Neuroscience Letters 473, 186-191.
18. Muradashvili, N., Tyagi, R., O'Toole, T., Tyagi, S. and Lominadze, D. (2014). Amelioration of traumatic brain injury-induced increased cerebrovascular permeability by endothelial progenitor cells in mice. J Neurotrauma 31, A14-A15.
19. Leblanc, A.J., Touroo, J.S., Hoying, J.B. and Williams, S.K. (2012). Adipose stromal vascular fraction cell construct sustains coronary microvascular function after acute myocardial infarction. American Journal of Physiology – Heart & Circulatory Physiology 302, H973--982.
20. Nunes, S.S., Maijub, J.G., Krishnan, L., Ramakrishnan, V.M., Clayton, L.R., Williams, S.K., Hoying, J.B. and Boyd, N.L. (2013). Generation of a functional liver tissue mimic using adipose stromal vascular fraction cell-derived vasculatures. Sci. Rep. 3, 2141.