Abstract

Background: Mesenchymal stromal cell (MSC) transplantation therapy is a promising therapy for stroke patients. In parallel, rehabilitation with physical exercise could ameliorate stroke-induced neurological impairment. In this study, we aimed to clarify whether combination therapy of intracerebral transplantation of human modified bone marrow-derived MSCs, SB623 cells, and voluntary exercise with running wheel (RW) could exert synergistic therapeutic effects on a rat model of ischemic stroke.

Methods: Wistar rats received right transient middle cerebral artery occlusion (MCAO). Voluntary exercise (Ex) groups were trained in a cage with RW from day 7 before MCAO. SB623 cells (4.0×10^5 cells/5μl) were stereotactically injected into the right striatum at day 1 after MCAO. Behavioral tests were performed at day 1, 7, and 14 after MCAO using the modified Neurological Severity Score (mNSS) and cylinder test. Rats were euthanized at day 15 after MCAO for mRNA level evaluation of ischemic infarct area, endogenous neurogenesis, angiogenesis, and expression of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). The rats were randomly assigned to one of the four groups: vehicle, Ex, SB623, and SB623+Ex groups.

Results: SB623+Ex group achieved significant neurological recovery in mNSS compared to the vehicle group ($p < 0.05$). The cerebral infarct area of SB623+Ex group

were significantly decreased compared to those in all other groups ($p < 0.05$). The number of BrdU/Doublecortin (Dcx) double-positive cells in the subventricular zone (SVZ) and the dentate gyrus (DG), the laminin-positive area in the ischemic boundary zone (IBZ), and the mRNA level of BDNF and VEGF in SB623+Ex group were significantly increased compared to those in all other groups ($p < 0.05$).

Conclusions: This study suggests that combination therapy of intracerebral transplantation SB623 cells and voluntary exercise with RW achieves robust neurological recovery and synergistically promotes endogenous neurogenesis and angiogenesis after cerebral ischemia, possibly through a mechanism involving the up-regulation of BDNF and VEGF.