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Human induced pluripotent stem cell-derived mesenchymal stem cell therapy effectively reduced brain infarct volume and preserved neurological function in rat after acute intracranial hemorrhage

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Intracerebral hemorrhage (ICH) causes 10%-20% of all strokes and results in higher mortality compared to other subtypes of cerebral stroke. Although early surgical intervention can clear the expanding hematoma, clinical outcomes following ICH have not significantly improved over the decades. Since ICH elicits neuroinflammation to exacerbate brain edema, damage the blood-brain barrier (BBB), lead to secondary neuronal injury, anti-inflammatory may be a critical therapeutic strategy. Mesenchymal stem cell (MSC) therapy processes anti-inflammatory, immunomodulatory and tissue regenerative properties, suggesting that MSC therapy could be an effective therapy for ICH. Therefore, this study tested the hypothesis that human induced pluripotent stem cell-derived mesenchymal stem cell (iPSC-MSC) therapy could effectively reduce brain-infract volume (BIV) and improve neurological function in rat after acute ICH induced by a weight-drop device. Adult male SD rats (n=40) were equally divided into group 1 (sham-operated control), group 2 (ICH), group 3 (ICH + hyaluronic acid (HA)/intracranial injection/3h after ICH), group 4 [ICH + HA + iPSC-MSC (1.2x10^6 cells/intracranial injection/3h after ICH)] and euthanized by day 28 after ICH procedure. In vitro study showed that hemorrhagic-brain tissue augmented protein expressions of inflammation (HMGB1/MyD88/TLR-4/TLR-2/NF-κB/TNF-α/iNOS/iL-1β) in cultured neurons that were significantly inhibited by iPSC-MSC treatment (all p<0.001). By days 7/14 after ICH procedure, circulating inflammatory levels of TNF-α/iL-6/MPO expressed were lowest in group 1, highest in group 2 and significantly lower in group 4 than in group 3 (all p<0.0001). By day 14 after ICH procedure, neurological function and BIV expressed an opposite pattern, whereas protein expressions of inflammation (HMGB1/MyD88/TLR-4/TLR-2/NF-κB/I-kB/TNF-α/iNOS/iL-1β/MMP-9), oxidative stress (NOX-1/NOX-2/oxidized protein) and apoptosis (mitochondrial-Bax/cleaved-caspase-2/PARP) in brain exhibited an identical pattern to circulating inflammation among the four groups (all p<0.001). Microscopy demonstrated that the number of vascular remodeling/GFAP+/53BP1+/?H2AX+ cells displayed an identical pattern of inflammation, whereas the NeuN+ cells displayed an opposite pattern of inflammation among the four groups (all p<0.001). In conclusion, iPSC-MSC therapy markedly reduced BIV and preserved neurological function mainly by inhibiting inflammatory/oxidative-stress generation.
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