Exosomes Derived from Multipotent Mesenchymal Stromal Cells Improve Functional Recovery After Experimental Intracerebral Hemorrhage in the Rat

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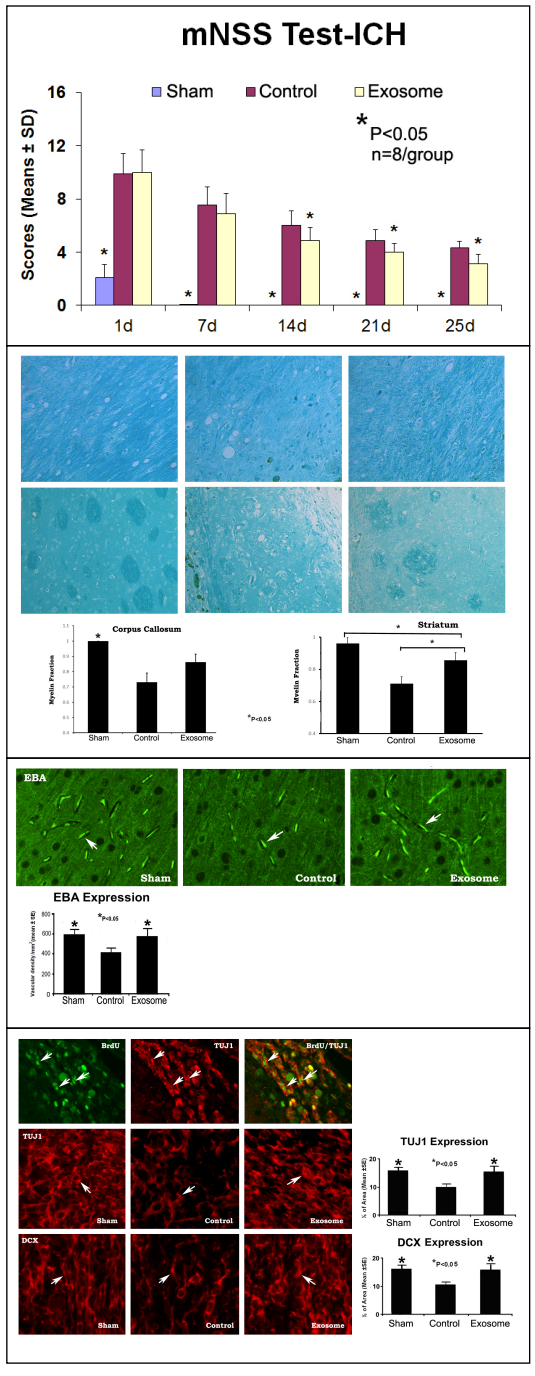
CNS 2017 ANNUAL MEETING
BOSTON, MASSACHUSETTS
OCTOBER 7–11, 2017

Introduction

Our previous studies have demonstrated that transplanted multipotent mesenchymal stromal cells (MSCs) improve functional recovery in rats after experimental intracerebral hemorrhage (ICH). Exosomes are membrane-contained vesicles with cytoplasmic components and cargo proteins which are released into the surrounding interstitial fluid. Their contents are protected from degradative extracellular enzymes. In this study we tested a novel hypothesis that administration of cell -free exosomes generated from MSCs promotes functional recovery and neurovascular remodeling and neurogenesis in rats after ICH.

Methods

Male Wistar rats were subjected to ICH followed 24 hours later by tail vein injection of 100 µg protein of exosomes derived from MSCs or an equal volume of vehicle phosphate-buffered saline (n = 8/group). To evaluate cognitive and sensorimotor functional recovery, the modified neurological severity score (mNSS), the modified Morris water maze test, and a social odor-based novelty recognition test were performed after ICH. Animals were sacrificed 28 days after ICH. Immunohistochemical analysis was performed for measurements of



Results

ICH rats treated with exosomes exhibited significantly increased white matter density in the striatum (lower right slide in the first histology figure), EBA blood vessel density, and markers of proliferating and mature neurons near the SVZ, although the lesion volume was similar in exosome and non-treated rats. The exosome group had significantly improved motor function in the mNSS test starting at day 14 compared to control group, and performed better on the Morris Water maze and social-odor test.

Discussion

ICH rats gradually improve on behavioral tests over 1 month, but when given exosome treatment, this recovery is greatly enhanced, especially in the social-odor test. Exosomes may improve functional recovery of the animals after ICH by augmenting the mutualism/sharing of growth factors between proliferating cell types, which then results in more functioning blood vessels, neurons, and oligodendrocytes after 1 month.

Conclusions

MSC-generated exosomes effectively improve neurological outcome after experimental ICH, at least in part, by promoting endogenous angiogenesis and neurogenesis. MSC-generated cell free exosomes may be a novel therapy to improve recovery after ICH.

Learning Objectives

By the conclusion of this session, participants should be able to describe the histological findings in the experimental model of ICH and the importance of cellular remodeling after treatment, specifically with with MSC derived exosomes.

References

Seyfried D, Ding J, Han Y, Li Y, Chen J, Chopp M. Effects of intravenous administration of human bone marrow stromal cells after intracerebral hemorrhage in rats. J Neurosurg. 2006;104(2):313-8. doi: 10.3171/jns.2006.104.2.313. PubMed PMID: 16509507.