

The Exosomes of Stem Cells Derived from Older Adults Impair Mitochondrial Bioenergetics in the Cerebrovascular Endothelial Cells

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Background: Aging increases risk for the development of vascular cognitive impairment. Impaired bioenergetics, mitochondrial oxidative phosphorylation (OxPhos) and glycolysis, in the brain microvascular endothelium induce neurovascular uncoupling, which is one of the underlying mechanisms of vascular cognitive decline. Bone marrow-derived adult CD34⁺ stem/progenitor cells are mobilized into the blood stream in physiological conditions and maintain endothelial health and regeneration via paracrine angiogenic mechanisms largely mediated by exosomes. Aging is associated with impaired endothelial regeneration and vascular repair by CD34⁺ stem cells due to paracrine dysfunctions. This study tested the hypothesis that CD34⁺ stem cell-derived exosomes (CD34-Exo) of older adults impair bioenergetics in the human brain microvascular endothelial cells (hBMVECs).

Methods: CD34⁺ cells were isolated from peripheral blood mononuclear cells derived from subjects, 18 - 35 (Young) or > 60 (Old) years of age. Exosomes were collected from the cell-supernatants by ultracentrifugation. The size distribution of exosomes was analyzed by using a Nanosight and exosome-imaging was carried out by using an Atomic force microscope. Cultured hBMVECs (passage 6 or 7) were exposed to exosomes and angiogenesis was evaluated by carrying out Matrigel assay. Agilent Seahorse bioanalyzer was used to determine OxPhos and glycolysis. 'n' represents the number of subjects the CD34-Exos were derived from.

Results: Old CD34-Exos impaired angiogenesis in hBMVECs (decreased tube length and the number branches and branch points, $P < 0.05$, $n = 6/\text{group}$) while Young Exos potentiated which was not statistically significant. OxPhos was impaired by Old-Exos with decreased basal and maximal respiration and ATP generation ($P < 0.05$) but no change in the nonmitochondrial respiration or the proton leak was noted in comparison with that produced by Young Exos, $n = 6/\text{group}$ while Young Exos showed no effect. Basal glycolysis, proton efflux rate and compensatory glycolysis were decreased by Old CD34-Exos ($P < 0.05$, $n = 10/\text{group}$) compared to the untreated BMVECs was not affected by either group of exosomes.

Conclusion: The study infers that Old CD34-Exos impair mitochondrial and glycolytic metabolism, and angiogenesis in hBMVECs, which collectively contribute to vascular cognitive decline in aging.

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