Exercise intervention improves bone marrow niche and endothelial progenitor cell defects in stroke

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[Background] Chronically vascular disease, stroke may rely on defective endogenous reparative mechanisms of bone marrow (BM) cells. It is now being recognized that endothelial cells and mesenchymal stromal cells secrete factors such as SDF-1 and SCF that promote BM stem/progenitor cells (HSPC) maintenance in vascular niche. Genetically hypertensive stroke-prone rat (SHRSP) is a model of human hypertension-associated cerebrovascular disease.

[Aim] We examined how the niche change after stroke, what mechanisms regulate the regeneration of HSPC niches after injury by voluntary (rehabilitative) exercise, and to what extent HSPC and niche cells are regulated by long-range signals with systemic physiological changes.

[Methods] SHRSPs were divided into three groups, sedentary (SED) and voluntary exercise (EX), which was started from 5-week-old and continued after stroke, or post-stroke EX combined with SDF-1 treatment after stroke. Changes of number and quality in CD34+ endothelial stem/progenitor cells and niche cells (SDF-1-, SCF-, and leptin receptor-positive) in BM were examined by immunohistochemistry and flow cytometry. Vascular structure and blood supply in BM were measured using fluorescent microspheres. Hypoxic profile was detected by pimonidazole and HIF signaling. Niche factors were determined by ELISA.

[Results] Increased hematopoietic activity of erythrocytes and platelets were found from normotensive young 6-week-old SHRSP, and elevation of peripheral monocytes and neutrophils were detected in the beginning symptoms of stroke. Ex prevented systemic inflammation along with hypertension in SHRSP. SDF-1+ / SCF+ perivascular niche cells, and CD34+ stem/progenitor cells in BM were significantly decreased immediately after stroke in SED and EX rats. Thereafter, spatial changes of SDF-1+ and CD34+ cells were observed toward sinusoidal vascular niche from endosteal region. Their niche cells and CD34+ cells were less in SED than EX at pre- and post-stroke. EX SHRSP prevented the reduction of CD34+ cells in BM, circulating endothelial progenitor cells, and their impaired function. EX SHRSP also extended sinusoidal vascular area and increased FGF-2, PDGF-BB and VEGF expression and hypoxia signaling where most closely interact with sinusoidal microvessels. Furthermore less effective post-stroke EX treatment prolonged survival on combination treatment of SDF-1.

[Conclusion] EX maintains the niche cells and microvessel integrity of BM in recovery from vascular injury.