Paper ID: 69281
interactive
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IAF/IAA SPACE LIFE SCIENCES SYMPOSIUM (A1)
Interactive Presentations - IAF/IAA SPACE LIFE SCIENCES SYMPOSIUM (IP)

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INFLUENCE OF SIMULATED MICROGRAVITY ON MATRISOME MESENCHYMAL STROMAL CELLS IN VITRO

Abstract

Accelerated bone resorption in microgravity is one of the serious risks of long-term orbital flights and future interplanetary missions. The cellular and molecular mechanisms of bone remodeling continue to be actively studied. Particular attention is paid to mesenchymal stromal cells (MSCs), which are multipotent precursors of osteoblasts and produce extracellular matrix (ECM), the main structural bone substance and important component of MSC's niche. Cellular (cytoskeleton) and ECM structures are considered gravisensitive and play important role in mechanotransduction. This work aimed to unveil the influence of simulated microgravity on MSCs' matrisome (structural components of ECM and ECM-associated molecules) in vitro. Human adipose tissue-derived MSCs (3-5 passages) in a monolayer were divided into 2 groups: static control and simulated microgravity on random position machine (RPM). After 10-day exposure, histological staining, real-time PCR, dot blotting, and multiplex analysis were used to analyze different matrisome molecules. After 10-day of RPM exposure, a semi-quantitative analysis of core-matrisome proteins revealed a decrease in collagenous and an increase in non-collagenous ECM components. The genes encoded ECM structural proteins: collagen type XXI (*COL11A1*) and glycoproteins - laminin 3 (*LAMB3*), tenascine (*TNC*) and thrombospondins (*THBS1, THBS2, THBS3*) were upregulated. Increased expression of tenascin and thrombospondins can cause a weakening of cell-ECM adhesion and lead to a deterioration in mineralization and osteogenic differentiation of MSCs, respectively. Among matrisome-associated molecules, a particular attention was paid to regulators (proteases) and soluble mediators. In the conditioned medium the levels of metalloproteinases (MMP-1,-2,-3) and catepsins (A, B, D) was increased. At the transcriptional level, a downregulation of protease inhibitor (*TIMP-1, TIMP-3*) genes has been detected. The alteration of the protease/antiprotease balance in MSCs may be a reason for the lower collagen content in the ECM under10-day microgravity simulation. A proinflammatory shift in soluble mediators' profile was detected in MSCs' conditioned medium after 10-day exposure on RPM manifested as increased VEGF, IL-8, IL-12, CXCL1, CXCL9 and M-CSF. Thus, simulated microgravity during 10 days provoked changes in the MSCs' matrisome, including decrease in collagen content, activation of proteolytic processes and increase in pro-inflammatory cytokine secretion. These changes may contribute to the negative alterations in bone tissue (osteopenia) during long-term space flights. This work was supported by project 65.3 of the Fundamental Research Program of the IMBP of RAS.