Paper ID: 44817
student

IAF/IAA SPACE LIFE SCIENCES SYMPOSIUM (A1)
Biology in Space (8)

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SIMULATED MICROGRAVITY ENHANCES ANGIOGENIC ACTIVITY OF MESENCHYMAL STROMAL CELLS

Abstract

Progenitor cells such as mesenchymal stem/stromal cells (MSCs) are an important member of the stem cell family and can be found in most postnatal organs and tissues. As a source of trophic mediators, MSCs secrete a range of growth factors and other chemokines to induce cell functions. It was shown earlier that the production of cytokines were susceptible to real and simulated microgravity. A subset of MSCs *in vivo* is located in the perivascular niche being strongly involved in endothelial cells (ECs) regulation. A number of studies are focusing on the impact of microgravity on ECs, but there are no data on MSC angiogenic activity under real or simulated microgravity. For this reason, a goal of present paper was to characterize MSC angiogenic potential under simulated microgravity.

A desktop Random Positioning Machine (RPM) (Dutch Space, Netherlands) was used to simulate microgravity effects. Samples were run on the RPM for 96 hours. We use static and dynamic controls to compare and estimate the contribution of medium stirring. Conditioned medium from all samples was collected for further analysis, including chorioallantoic membrane assay in ovo, capillarylike tube formation, nontargeted cell migration assay, analysis of MSC secreted proteins. Total RNA was extracted from MSCs for PCR analysis of gene expression.

The conditioned medium from RPMexposed MSCs stimulated the formation of vessel network in ovo, EC capillarylike network of tubule complexes and nondirected EC migration *in vitro*. These effects were driven by alteration of both angiogenesisrelated gene and protein expression. The elevation of angiogenic regulators Serpin E1, Serpin F1, IGFBP, VEGF, IL8 was detected in MSC conditioned medium after RPM exposure by using Proteome Profiler Human Angiogenesis Array Kit (RD, USA). Additionally, transcription of genes encoding growth factors with proangiogenic activity was upregulated including *BDNF, CXCL1, VEGFc, DKK1, FGF5, GDF10, VEGFa*. These data evidenced that besides direct effect on ECs, microgravity could provoke MSC mediating specific microenvironment for ECs supporting their functions i.e., proliferation and migration via increased production of IL8 and VEGF as well as other paracrine factors involved in angiogenesis regulation.

This study was supported by the Russian Science Foundation (project no. 161510407).