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MODIFICATION OF HEMATOPOIETIC NICHE UNDER LONG-TERM SIMULATED MICROGRAVITY IN VITRO

Abstract

It is well known that microgravity adversely affects the bone homeostasis and hematopoiesis. Multipotent mesenchymal stromal cells (MSCs), which are gravisensitive, play a crucial role in the regulation of these processes. In addition, the interaction between hematopoietic stem and progenitor cells (HSPCs) and MSCs is governing the processes of hematopoiesis. Changes in the functional state of these components of the hematopoietic niche may be involved in the disturbances observed during long-term space flights. Therefore, the aim of this work was to study the influence of simulated microgravity (SMG) on the cellular components of the hematopoietic niche. We have demonstrated that short-term (up to 3 days) SMG using RPM altered the gene expression of intercellular adhesion molecules and extracellular matrix of MSCs, and also increased the level of angiogenic regulators. Prolonged SMG exposure has provoked a decrease in collagenous proteins and an increase in non-collagenous components in the extracellular matrix. At the same time, SMG has stimulated the proteolytic activity of MSCs. We have applied co-culture of human MSCs and HSPCs as an in vitro model of the hematopoietic niche. During long-term SMG (up to 14 days), the ratio of different hematopoietic lineages has been changed. The HSPC commitment was resulted in suppression of monocyte, lymphocyte and erythroid lineages, but activation of the granulocyte lineage. This is consistent with data on changes in the cellular composition of peripheral blood during spaceflight. In MSCs, the genes encoding molecules of intercellular adhesion and extracellular matrix genes were downregulated. The altered transcription of genes encoding cytokines responsible for the balance of hematopoietic primitive/committed cells and regulation of MSC differentiation was detected. In MSCs co-cultured with HSPCs, SMG has provoked downregulation of non-canonical Wnt signaling while genes encoding canonical Wnt components were upregulated. This may be the reason of the osteogenic commitment of MSCs during cell-to-cell interaction. The stromal function of osteocommited MSCs in co-culture with HSPCs has been attenuated under SMG. This may be an explanation for hematopoietic disorders during space flight. The data presented contribute into elucidation of the hematopoietic niche alteration under microgravity. In addition, these may be helpful in development of countermeasures for preventing adverse changes in hematopoiesis and bone homeostasis during spaceflight. This study was supported by the Program of Basic Research of IBMP RAS FMFR-2024-0032