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TRANSCRIPTIONAL ACTIVITY OF WNT SIGNALING PATHWAY IN MESENCHYMAL STROMAL CELLS UNDER LONG-TERM SIMULATION OF MICROGRAVITY AND CO-CULTIVATION WITH HEMATOPOIETIC PRECURSORS

Abstract

Bone loss is a one of the most negative effects of microgravity on the human body. Gravisensitive mesenchymal stromal cells (MSCs) play an important role in the formation of osteogenic cells. It is known that under simulated microgravity (Smg), the osteodifferentiation potential of MSCs decreases. MSCs are also an important component of the bone marrow hematopoietic niche. MSCs and hematopoietic stem and progenitor cells (HSPCs) interaction in vitro enhances osteogenic commitment of MSCs, therefore, this system is of particular interest for studying the Smg effect. The canonical and noncanonical Wnt signal pathways regulate the osteogenic differentiation of MSCs. In this regard, the aim of this work was to evaluate the transcriptional activity of the canonical and non-canonical Wnt pathways genes in MSCs under Smg and co-cultivation with HSPC. A suspension of cord blood mononuclear cells containing HSPCs was added to MSCs isolated from adipose tissue and co-cultivated for 72 h. After removal of non-adherent cells, flasks containing MSCs with adherent HSPCs were completely filled with growth medium and cultured in static control (1g) or on a random positioning device Gravite (Space bio-laboratories, Japan) (Smg) for 21 days. Expression of 84 Wnt signaling associated genes was assessed in MSC monoculture and MSC co-cultured with HSPCs by Real-time PCR. Predominantly, a downregulation in the expression of negative regulators of the canonical Wnt pathway, such as FZD4, WNT5B, FBXW11, and a downregulation in the expression of non-canonical pathway genes, such as AXIN2, NFATC1, KREMEN1, were noted in MSC monoculture. Upregulation in the expression of a canonical pathway component WNT8A was also revealed. This may indicate a positively modulating of the canonical pathway strength under Smg. In MSCs co-cultured with HSPCs, fewer changes were detected. Under Smg, the expression of canonical pathway positive regulators, such as FZD1, LRP6, WNT1, upregulated, and the expression of the Wnt/-catenin pathway negative regulator CXXC4 downregulated. In addition, the expression of the target gene of this pathway, CCN4, the product of which positively regulates osteogenesis, downregulated. Thus, the Wnt signaling pathway genes transcription analysis in MSCs apparently indicates upregulation in the canonical component under Smg, which may explain the decrease in osteogenesis in microgravity. MSCs and HSPCs co-cultivation retains increased activity of the canonical Wnt signaling pathway. This work was supported in part by Program of Basic Research of IMBP RAS (Project No.65.3) and by the Russian Foundation for Basic Research No. 19-29-04026.