Paper ID: 24468
poster
student

SPACE LIFE SCIENCES SYMPOSIUM (A1)
Poster Session (P)

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SIMULATED MICROGRAVITY INDUCES EPIGENETIC CHANGES BY DEPLETING DNMT1 IN MURINE MONOCYTES

Abstract

PURPOSE: DNA methylation is an epigenetic mechanism involved in gene expression regulation. Astronauts are constantly being exposed to different stress factors, which include radiation, microgravity, and confinement. These environmental stressors are responsible for bone loss, decrease in muscle mass, and suppression of immune function. One of the mechanisms for these deleterious changes could be epigenetic changes induced by environmental stressors. Abnormal epigenetic events have been reported in human diseases like cancers and immunological disorders. To test the hypothesis whether modeled microgravity induces epigenetic changes, the expression of the proteins known to regulate gene expression, specifically the DNA Methyltransferases (DNMT1, DNMT3a, and DNMT3b) and Histone Deacetylase (HDAC1) was examined. METHODS: DNA demethylation studies were carried out using the demethylating agent 5-aza-2-deoxycytidine (DAC) in the presence and absence of microgravity. Western blot and ELISA assays were carried out on whole cell protein extracts using specific primary antibodies for DNMT1, DNMT3a/3b and HDAC1. Whole cell protein was extracted from mouse monocytes cultured in sterile RPMI 1640 medium supplemented with fetal bovine serum and antibiotics and exposed to normal and simulated microgravity conditions with and without DAC. Western blot was done to examine whether DAC treatment altered protein expression in simulated microgravity conditions when compared to that of untreated cells. Cells were examined to ensure proper morphology of cells as well as ensure cell survival. RESULTS: Normal levels of DNMT and HDAC were detected in cells grown under normal gravity however, cells exposed to simulated microgravity showed decreased DNMT and HDAC expression. Alternatively, cells exposed to both simulated microgravity and a DNA methyltransferase inhibitor DAC showed increased levels of DNMT3a and DNMT3b but significantly less DNMT1 and HDAC proteins. CONCLUSIONS: These studies suggest that DNA methylation cannot be ruled out as a cause of cellular apoptosis and senescence in eukaryotic cells when exposed to microgravity.