Mechanobiological Reprogramming of Cancer Cells in RPM-Simulated Microgravity: A High-Fidelity Transcriptomic Model for Overcoming Chemoresistance and Therapeutic Regression

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Chemoresistance remains a primary cause of cancer treatment failure and is increasingly attributed to non-genetic regulatory mechanisms. Emerging evidence suggests that three-dimensional chromatin organization and mechanotransduction influence gene expression programs governing DNA damage response and apoptosis. This study investigated whether mechanical unloading via Random Positioning Machine (RPM)-simulated microgravity could disrupt cytoskeletal-nuclear force transmission and alter chromatin organization, thereby influencing cisplatin sensitivity. HEL 92.1.7 Uveal Melanoma cells were exposed to RPM-simulated microgravity, and changes in DNA damage signaling, transcriptional activity, and chromatin organization were evaluated alongside integration of NASA Open Science Data Repository datasets (OSD-665 and OSD-125). Cells exposed to simulated microgravity demonstrated an 82% increase in cisplatin-induced cell death relative to normal gravity controls, indicating enhanced chemosensitivity under conditions of mechanical unloading. Transcriptomic analysis further revealed altered gene expression profiles associated with DNA damage response pathways, while ?H2AX immunofluorescence assays indicated increased DNA damage signaling in microgravity-exposed cells. Collectively, this study proposes that chemotherapy resistance is a mechanically reinforced epigenomic state, and that disrupting these mechanical mechanisms could provide new opportunities for developing more effective cancer treatments.

Awards Won:

Second Award of $2,400