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MICROGRAVITY REGULATES ENDOTHELIAL CELL INFLAMMATION AND PYROPTOSIS THROUGH METABOLIC TURNOVER MEDIATED BY THE SIRT3-PDH-NLRP3 SIGNALING PATHWAY

Abstract

Objective: Endothelial cell inflammation induced by microgravity has been identified as a potential contributor to cardiovascular dysfunction in astronauts following spaceflight, thereby increasing the risk of cardiovascular events. However, the precise mechanisms underlying this process remain poorly understood. Sirtuin-3 (SIRT3), a mitochondrial NAD+-dependent deacetylase, regulates critical metabolic pathways. This study aims to investigate the role of SIRT3-mediated metabolic alterations in activating the NLRP3 inflammasome and modulating endothelial cell function under simulated microgravity conditions. Methods: Human umbilical vein endothelial cells (HUVECs) were cultured under two-dimensional rotational simulated microgravity. Western blotting was utilized to assess protein expression levels of SIRT3, NLRP3, and Caspase-1. Enzyme-linked immunosorbent assay (ELISA) was employed to quantify pro-inflammatory cytokine secretion. Flow cytometry was used to evaluate mitochondrial membrane potential (m), cellular reactive oxygen species (ROS) production, and pyroptosis rates. Transmission electron microscopy was applied to examine ultrastructural changes in cells. Co-immunoprecipitation assays were conducted to investigate the interaction between SIRT3 and pyruvate dehydrogenase alpha 1 (PDHA1). Results: Simulated microgravity-induced inhibition of SIRT3 triggered activation of the NLRP3 inflammasome, leading to increased Caspase-1 expression and secretion of pro-inflammatory cytokines IL-1 and IL-18. Overexpression of SIRT3 significantly reduced microgravity-induced ROS production, reversed the decline in m, and suppressed NLRP3 inflammasome activation and cellular pyroptosis. In contrast, SIRT3 knockout exacerbated microgravity-induced mitochondrial dysfunction and promoted a shift toward enhanced glycolytic metabolism in endothelial cells. Mechanistically, SIRT3 deficiency resulted in acetylation of lysine 83 on PDHA1, impairing pyruvate dehydrogenase complex (PDHC) activity. Transfection with PDHA1 alleviated NLRP3 inflammasome activation, Caspase-1 cleavage, glycolytic shift, and mitochondrial dysfunction, restoring m and oxidative phosphorylation. The PDHA1 acetylation mutant (PDHA1-K83R) proved more effective than wild-type PDHA1 in protecting HUVECs from microgravity-induced damage. Conclusion: SIRT3 plays a pivotal role in mitigating endothelial cell inflammation and restoring metabolic homeostasis under microgravity conditions by deacetylating PDHA1 and enhancing PDHC activity. This study highlights SIRT3 as a potential therapeutic target for counteracting NLRP3-mediated inflammatory responses and preserving endothelial cell function in spaceflight-associated cardiovascular

deconditioning. These findings provide critical insights into the mechanisms underlying cardiovascular dysfunction in microgravity and lay the foundation for potential interventions.