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SIMULATED MICROGRAVITY AND INDUCED MECHANICAL STRESS MODULATE THE CA2+ TRANSPORT THROUGH TRPV4 CHANNELS

Abstract

Mechanotransduction in bone tissue is crucial for proper development of the skeletal system and isolation of specific molecular mechanisms of transduction is important for correcting skeletal anomalies and designing more effective therapies. The drive to understand the basis of mechanical sensitivity in bone is fueled by the unique risk factors contributing to an accelerated decline in bone mass and quality during extended spaceflight and mission operations. Mechanotransduction is an intricate process comprised of multiple interconnected pathways, which limits our ability to discriminate between individual molecular mechanisms converging to significant changes in biological functionalities. Nonetheless, a large body of evidence suggests that modulation of Ca2+ transport is key for understanding the initiation of cellular response to mechanical stress. The identification of Transient Receptor Potential Vanilloid type 4 (TRPV4) as a Ca2+-permeable cation channel and its overall function as a sensor of mechanical and osmotic signals in multiple musculoskeletal tissues is a critical step in linking mechanically triggered molecular signaling and Ca2+ levels as contributors to molecular pathways leading to accelerated osteoclast differentiation. Therefore, we report on the influence of various mechanical stress stimuli on Ca2+ transport through TRPV4 in two eukaryotic cell lines. Our first investigations included direct activation of the TRPV4 channels using transformed Saccharomyces cerevisiae under hypo-osmotic and simulated microgravity conditions. Ca2+ transport was assessed using the luminescence signal generated by the aequorin-coelenterazine system and fluorescence signal by the cell-membrane permeant Ca2+ indicator Fluo-4 AM. Mechanical stress was modulated by introducing the cell culture into a cylindrical High Aspect to Ratio Vessel (HARV) in a horizontal (1g control) or vertical (simulated micro-gravity) position in

the Rotary Cell Culture System. A second set of experiments comprised exposure of the osteocytic cell line MLO-Y4 to multiple mechanical stress conditions, such as simulated microgravity, osmotic stress and stretching. Optical and electrical data provided here demonstrates that mechanical stress and simulated microgravity conditions induce measurable changes in Ca2+ transport by activation of TRPV4 channels. This work paves the way for understanding the molecular basis of osteoporosis in bed-ridden patients or astronauts exposed to the true microgravity of space during extended space flight. Also, this work presents insight into how mechanotranduction, implying Ca2+ transport, may interfere with crucial physiological functions of cardiac or immune cells.