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THE MECHANOSENSITIVE PIEZO1 CHANNEL MEDIATES OSTEOBLAST MECHANOTRANSDUCTION AND BONE FORMATION

Abstract

PurposeMechanical load of the skeleton system is essential for the development, growth, and maintenance of the structure and strength of the bone, which is evidenced by the severe loss of bone mass during long-term bedridden or microgravity conditions. However, the molecular mechanism by which mechanical stimuli are converted into osteogenesis and bone formation remains unclear. Here we identify Piezo1 as a key mechanotransducer for mediating mechanical responses of osteoblasts and consequently determining bone formation. MethodologyThe changes of mechanically sensitive Piezo1 current and the expression of Piezo1 protein in osteoblasts under simulated microgravity were detected by tail suspension simulated microgravity and rotary simulated microgravity model. Osteoblast-specific Piezo1 gene knockout mice were constructed and their bone phenotypes were analyzed to determine the effect of Piezo1 on bone formation. To determine whether Piezo1-mediated mechanical response of osteoblasts is responsible for mechanical unloading-induced bone loss, we employed the commonly used hindlimb suspension (HS) model to examine the bone remodeling process in response to the weight-bearing unloading of the WT and cKO mice. To examine whether mechanical unloading directly alters Piezo1 expression in osteoblasts, we utilized a cell rotation system to simulate the effect of microgravity on osteoblast. ResultsPiezo1 is expressed in osteoblasts and mediates mechanically evoked cationic currents. Osteoblast-specific knockout of Piezo1 disrupts the mechanical response and differentiation of osteoblasts and severely impairs bone structure and strength. Wild type mice subjected to hindlimb suspension-induced mechanical unloading show decreased expression of Piezo1 and defective osteogenesis and bone formation, which is blunted in the Piezo1 knockout mice. Intriguingly, simulated microgravity treatment reduces the mechanical response and differentiation of osteoblasts via suppressing the expression of Piezo1. Osteoporosis patients show reduced expression of Piezo1, which is closely correlated with osteoblast dysfunction. ConclusionsPiezo1 functions as a key mechanotransducer for conferring osteoblast mechanosensitivity and determining mechanical-load-dependent osteogenesis and bone formation. And targeting osteoblast-expressed Piezo1 might represent a therapeutic potential for treating osteoporosis or mechanical unloading-induced severe bone loss during long-term bedridden or spaceflight.