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Abstract Article

Hylonome

Mechanical stimulation *in vivo* reduces osteocyte expression of sclerostin

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Osteocytes are by far the most numerous cell type in bone. Their population density, distribution, extensive communication networks, and fluid-filled lacuno-canalicular environment make these cells ideal mechanosensors in bone's adaptive process. Despite these attributes, very little data have been generated that implicate the osteocyte network as the primary mechanosensory cell type, to the exclusion of the other cell types (e.g., osteoblasts, bone lining cells). The discovery of a mechanically modulated osteocyte-specific factor, particularly a secreted factor that had the propensity to reach effector cell populations, would provide a molecular basis for osteocytic reception and initiation of mechanotransduction.

Sclerostin, the protein product of the SOST gene, is an osteocyte-specific cysteine-knot secreted glycoprotein that is a potent inhibitor of bone formation. Sclerostin can bind and inhibit Lrp5, a Wnt co-receptor that we have shown to be required for mechanotransduction. We investigated the regulation of sclerostin expression in mechanically loaded and control (non-loaded) mouse ulnar diaphyses to determine whether this osteocyte-specific factor was under mechanoregulation. To this end, we subjected the right forelimb of four male 18-week-old C57BL/6 mice to two brief (60 sec) bouts of *in vivo* mechanical loading (60 cycles, 2 Hz, ~1,800 με) using a non-invasive rodent ulna-loading model. Twenty-four hours after the last session, the mice were sacrificed, and the right and left forelimb bones were dissected free, fixed in 4% paraformaldehyde, decalcified in 10% EDTA, embedded in paraffin, sectioned at 8 μm, and immunolabeled for sclerostin. We measured the number of sclerostin-positive osteocyte cell bodies in the medial, lateral and central cortex of each ulnar section, corresponding to different strain environments.

The sections revealed strong reactivity in osteocytes but not in any other cell type (bone lining cells, osteoblasts, marrow cells). Qualitatively, the loaded ulnar sections revealed a clear difference from control ulna sections in the degree of sclerostin staining, particularly in canaliculi. Quantitatively, loading reduced the number of sclerostin-positive osteocyte cell bodies by 76% in the medial cortex but by only 10% in the central cortex. Sclerostin-positive osteocytes were reduced by 30% in the lateral cortex. The degree of reduction in sclerostin expression corresponded to strain distribution in the ulnar midshaft during exogenous loading, suggesting that sclerostin reduction is dose responsive to strain magnitude.

In conclusion, mechanical loading resulted in a clear and significant reduction in sclerostin protein levels in the ulnar diaphysis after 24 hours. Our data have led us to hypothesize that mechanical loading is detected by osteocytes and causes a reduction in sclerostin secretion, which in turn reduces the inhibition of Lrp5 signaling in nearby osteoblasts, ultimately leading to enhanced osteogenesis.

The authors have no conflict of interest.

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