Sclerosteosis and van Buchem disease are two rare, closely related skeletal disorders characterized by a substantial increase in bone mass. Sclerosteosis is due to premature termination mutations in the SOST gene on chromosome 17q12-q21, whereas in van Buchem disease a 52 kb homozygous deletion downstream of the SOST gene was identified. The SOST gene encodes a protein, named sclerostin, of which the expression in the adult is highly restricted to osteocytes. In particular, sclerostin is localized in mature osteocytes in mineralized cortical and cancellous bone. Sclerostin expression is absent in the bones of both patients with sclerosteosis and van Buchem disease. Increase in bone mass is due to increased osteoblast activity as demonstrated by the predominance of cuboidal, active-appearing osteoblasts, increased double tetracycline labeling spacing, and increased osteoid levels that mineralize normally, in bone biopsies of affected individuals. Osteoclast numbers seem not to be affected. In vitro studies confirmed that sclerostin is a negative regulator of bone formation. Moreover, transgenic mice with overexpression of sclerostin are osteopenic.

In vitro studies of osteoblastic cultures indicated that sclerostin specifically affects BMP and Wnt signaling out of many other growth signaling pathways. Sclerostin, however, did not inhibit stimulation of direct BMP target genes and the observed effect of sclerostin on BMP signaling is, therefore, probably indirect. Recently, sclerostin was found to antagonize canonical Wnt signaling by binding to the Wnt co-receptors LRP5 and LRP6. This Wnt antagonistic activity of sclerostin may explain the inhibitory effect of sclerostin on BMP-stimulated bone formation, since Wnts cooperate with BMPs in stimulating bone formation. Activation of Wnt reporter constructs by BMPs and constitutive active BMP receptors in osteoblastic cells was antagonized by sclerostin, suggesting that it indeed antagonized Wnt activity. This was confirmed by an antagonistic effect of sclerostin on Wnt-stimulated activation of the Wnt reporter construct in these osteoblastic cells.

In conclusion, sclerostin is an osteocyte-expressed protein that inhibits the activity of osteoblasts and prevents them from promoting excessive bone formation. Sclerostin inhibits BMP-stimulated bone formation, but does not effect BMP signaling. Instead, it antagonizes Wnt signaling in osteoblastic cells. High bone mass in sclerosteosis and van Buchem disease may, therefore, result from increased Wnt signaling.

The authors have no conflict of interest.

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