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Abstract:

Connexin (Cx) proteins are essential for cell differentiation, function and survival in all tissues with Cx43 being the most studied in bone. We now report that Cx37, another member of the connexin family of proteins, is expressed in osteoclasts, osteoblasts and osteocytes. Mice with global deletion of Cx37 (Cx37-/-) exhibit higher BMD, cancellous bone volume, and mechanical strength compared to wild type littermates. Osteoclast number and surface are significantly lower in bone of Cx37-/- mice. In contrast, osteoblast number and surface and bone formation rate in bones from Cx37-/- mice are unchanged. Moreover, markers of osteoblast activity ex vivo and in vivo are similar to those of Cx37+/+ littermates. sRANKL/M-CSF treatment of non-adherent Cx37-/- bone marrow cells rendered a 5-fold lower level of osteoclast differentiation compared to Cx37+/+ cell cultures. Further, Cx37-/- osteoclasts are smaller and have fewer nuclei per cell.

Expression of RANK, TRAP, cathepsin K, calcitonin receptor, MMP9, NFATc1, DCSTAMP, ATP6v0d1 and CD44, markers of osteoclast number, fusion or activity, is lower in Cx37-/- osteoclasts compared to controls. In addition, non-adherent bone marrow cells from Cx37-/- mice exhibit higher levels of markers for osteoclast precursors, suggesting altered osteoclast differentiation. The reduction of osteoclast differentiation is associated with activation of Notch signaling. We conclude that Cx37 is required for osteoclast differentiation and fusion and its absence leads to arrested osteoclast maturation and high bone mass in mice. These findings demonstrate a previously unrecognized role of Cx37 in bone homeostasis that is not compensated for by Cx43 in vivo.

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