論 文 要 旨

BMP-induced Atoh8 attenuates osteoclastogenesis by suppressing Runx2 transcriptional activity and reducing the Rankl/Opg expression ratio in osteoblasts

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Adult bone structural integrity is maintained by remodeling via the coupling of osteoclastic bone resorption and osteoblastic bone formation. Osteocytes or osteoblasts express receptor activator of nuclear factor κ-B ligand (Rankl) or osteoprotegerin (Opg) to promote or inhibit osteoclastogenesis, respectively. Bone morphogenetic protein (BMP) is a potent bone inducer, but its major role in adult bone is to induce osteocytes to upregulate sclerostin (Sost) and increase the Rankl/Opg expression ratio, resulting in promotion of osteoclastogenesis. However, the precise effect of BMP-target gene(s) in osteoblasts on the Rankl/Opg expression ratio remains unclear. In the present study, we identified atonal homolog 8 (Atoh8), which is directly upregulated by the BMPSmad1 axis in osteoblasts. In vivo, Atoh8 was detected in osteoblasts but not osteocytes in adult mice. Although global Atoh8- knockout mice showed only a mild phenotype in the neonate skeleton, the bone volume was decreased and osteoclasts were increased in the adult phase. Atoh8-null marrow stroma cells were more potent than wild-type cells in inducing osteoclastogenesis in marrow cells. Atoh8 loss in osteoblasts increased Runx2 expression and the Rankl/Opg expression ratio, while Runx2 knockdown normalized the Rankl/Opg expression ratio. Moreover, Atoh8 formed a protein complex with Runx2 to inhibit Runx2 transcriptional activity and decrease the Rankl/Opg expression ratio. These results suggest that bone remodeling is regulated elaborately by BMP signaling; while BMP primarily promotes bone resorption, it simultaneously induces Atoh8 to inhibit Runx2 and reduce the Rankl/ Opg expression ratio in osteoblasts, suppressing osteoclastogenesis and preventing excessive BMP-mediated bone resorption.

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