DOCTORAL THESIS

Increased CKIP-1 suppresses Smad-dependent BMP signaling to inhibit bone formation during aging

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Abstract

Emerging evidence indicates that the dysregulation of protein ubiquitination plays a crucial role in aging-associated diseases. Smad-dependent canonical BMP signaling pathway is indispensable for osteoblastic bone formation, which could be disrupted by the ubiquitination and subsequent proteasomal degradation of Smad1/5, the key molecules for BMP signaling transduction. However, whether the dysregulation of Smad1/5 ubiquitination and disrupted BMP signaling pathway are responsible for the age-related bone formation reduction is still underexplored. Casein kinase-2 interacting protein-1 (CKIP-1), also known as Pleckstrin homology domain-containing family O member 1 (PLEKHO1), is a previously identified ubiquitination-related molecule that could specifically target the linker region between the WW domains of Smurf1 to promote the ubiquitination of Smad1/5. Here, we found an age-related increase in the expression of CKIP-1 in bone specimens from either fractured patients or aging rodents, which was associated with the age-related reduction in Smad-dependent BMP signaling and bone formation. By genetic approach, we demonstrated that loss of *Ckip-1* in osteoblasts could promote the Smad-dependent BMP signaling and alleviated the age-related bone formation reduction. In addition, osteoblast-specific *Smad1* overexpression had beneficial effect on bone formation during aging, which could be counteracted after overexpressing *Ckip-1* within osteoblasts. By pharmacological approach, we showed that osteoblast-targeted CKIP-1 siRNA treatment could enhance Smad-

dependent BMP signaling and promote bone formation in aging rodents. Taken together, it suggests that the increased CKIP-1 could suppress Smad-dependent BMP signaling to inhibit bone formation during aging, indicating the translational potential of targeting CKIP-1 in osteoblast as a novel bone anabolic strategy for reversing established osteoporosis during aging.

Table of Contents