

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

Lyn is good for bone

N°112 – December 2009

Src family kinases (SFKs) are nonreceptor tyrosine kinases that are promiscuous in their impact on events such as growth, differentiation, cytoskeletal organization, and survival. One member of this family, c-Src kinase, is a rate-limiting activator of osteoclast function and Src inhibitors are therefore candidate antiosteoporosis drugs. By affecting M-CSF-induced signaling, c-Src is central to osteoclast activity, but not differentiation. The authors of a recent study [1] found that Lyn, another member of Src family kinases is, in contrast, a negative regulator of osteoclastic bone resorption.

The absence of Lyn enhances RANKL-mediated differentiation of osteoclast precursors without affecting proliferation and survival, while its overexpression decreases osteoclast formation. In further contrast to c-Src, Lyn deficiency does not impact the activity of the mature cell. Reflecting increased osteoclast development in vitro, Lyn knockout mice undergo accelerated osteoclastogenesis and bone loss, in vivo, in response to RANKL. Mechanistically, Lyn forms a complex with RANK, the tyrosine phosphatase, SHP-1, and the adapter protein, Grb2-associated binder 2 (Gab2). Upon RANKL exposure, Gab2 phosphorylation, JNK, and NF- κ B activation are enhanced in Lyn knockout osteoclasts, all critical events in osteoclast development.

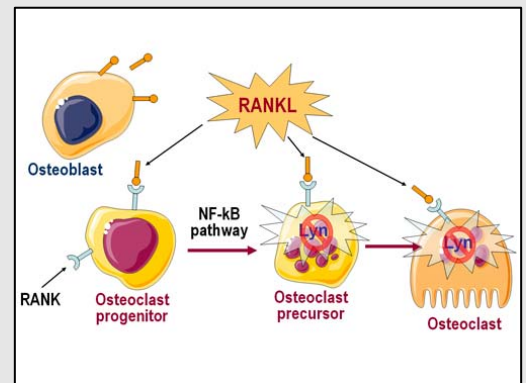
This study therefore established that Lyn regulates osteoclast formation and does it in a manner antithetical to that of c-Src. The most pragmatic aspect of these findings is that successful therapeutic inhibition of c-Src, in the context of the osteoclast, will require its stringent targeting.

1. Kim HJ et al. *PNAS*. 2009; 106:2325–2330.

Lyn is good for bone

Upon activation by RANKL, osteoclasts are recruited and differentiate. The effect of RANKL/RANK is controlled by Src family kinases. One of them, called Lyn, is a negative regulator of osteoclastic bone resorption. In the absence of Lyn, mice have increased osteoclastogenesis and bone loss.

Successful therapeutic inhibition of c-Src, in the context of the osteoclast, would require its stringent targeting.



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