

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

Osterix: inhibition of Wnt signaling

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The recent identification of the genes responsible for several human genetic diseases affecting bone homeostasis and the characterization of mouse models for these diseases indicated that canonical Wnt signaling plays a critical role in the control of bone mass [1]. A recent study [2] reports that the osteoblast-specific transcription factor Osterix (*Osx*), which is required for osteoblast differentiation, inhibits Wnt pathway activity. In calvarial cells of *Osx*-null embryos, expression of the Wnt antagonist *Dkk1* was abolished, and that of Wnt target genes *c-Myc* and *cyclin D1* was increased. Moreover, these studies demonstrated that *Osx* bound to and activated the *Dkk1* promoter. In addition, *Osx* inhibited β -catenin-induced reporter activity and β -catenin-induced secondary axis formation in *Xenopus* embryos. Importantly, data from calvaria of *Osx*-null embryos indicate that *Osx* inhibited the Wnt pathway in osteoblasts *in vivo*. This study further shows that *Osx* disrupts binding of transcription factor TCF to DNA. This provides a likely mechanism for the inhibition by *Osx* of β -catenin transcriptional activity. *Osx* decreased also osteoblast proliferation. Indeed, *Osx*-null calvaria showed greater BrdU incorporation than wild-type calvaria and *Osx* overexpression in C2C12 mesenchymal cells inhibited cell growth. Because Wnt signaling has a major role in stimulating osteoblast proliferation, the authors speculate that *Osx*-mediated inhibition of osteoblast proliferation is a consequence of the *Osx*-mediated control of Wnt/ β -catenin activity.

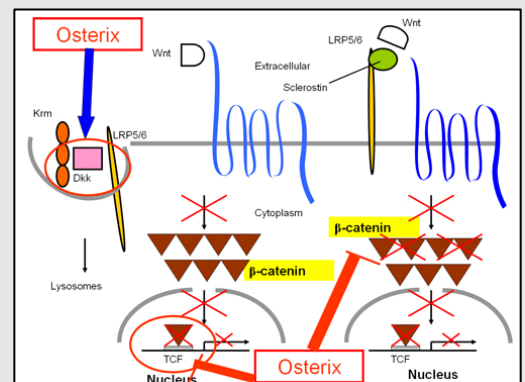
1. Piters E et al. *Arch Biochem Biophys*. 2008;473:112-116.
2. Zhang C et al. *Proc Natl Acad Sci USA*. 2008;105:6936-6941.

Osterix: inhibition of Wnt signaling

Activation of the Wnt/ β -catenin pathway is essential to bone development. Binding of Wnt to Frizzled protein triggers β -catenin-induced gene transcription in the nucleus. This step involves the transcription factor TCF which binds to DNA (adapted from [1]).

LRP5 is a mandatory coreceptor of Wnt, which can also bind to Wnt antagonists Kremen and Dkk. In that case, Wnt is no longer signaling and β -catenin is degraded by the proteasome. This degradation also occurs when Lrp5 binds sclerostin. Osterix is a transcription factor which up-regulates the Wnt inhibitor Dkk. Furthermore, Osterix inhibits the binding of TCF to DNA

Because Wnt signaling has a major role in stimulating osteoblast proliferation, it can be proposed that *Osx*-mediated inhibition of osteoblast proliferation is a consequence of the *Osx*-mediated control of Wnt/ β -catenin activity.



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