

# HIGHLIGHTS

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## DEVELOPMENT

# Dem bones, dem bones...

What could Harry Potter do overnight that 'Muggles' take weeks to do and *Osterix*-null mice cannot do at all? Grow bones, of course! Bone formation requires a balance between the building activities of osteoblasts, which secrete the organic matrix of bone, and osteoclasts, which erode this matrix. Nakashima *et al.*, reporting in *Cell*, have now identified a transcription factor, *Osterix*, which is specifically expressed in developing bones and is needed for osteoblast differentiation.

The transcription factor *Runx2/Cbfa1* is known to be necessary for multipotent mesenchymal cells to differentiate into osteoblasts, but the authors proposed that additional transcription factors might also be required. So, they screened for osteoblast-specific cDNAs and cloned *Osterix (Osx)*. As the amino-acid sequence of *Osx* predicts that the carboxyl terminus of *Osx* contains three zinc-finger motifs, Nakashima *et al.* tested whether *Osx* could bind DNA. They found that it could, and then showed that it has a transcriptional activation domain and a restricted nuclear localization — all the hallmarks of a transcription factor. Furthermore, transfecting *Osx* into C2C12 muscle progenitor cells induced osteoblast-marker gene expression.

In wild-type mice, *Osx* transcripts were found in all developing bones. So what happens in the absence of *Osx*? Functional inactivation of the *Osx* gene resulted in a null mutation,

which presented as a non-viable phenotype in post-natal homozygous *Osx*-null mice; newborn mice had inwardly bent limbs and died within 15 minutes of birth. *Osx* shares no significant homology outside of its DNA-binding domain with any human, mouse, fly or nematode proteins, indicating that, in mouse at least, no other protein can substitute for the function of *Osx*, which is consistent with the lethal phenotype.

The authors next found that several early and late markers of osteoblast differentiation were absent in *Osx*-null mice, indicating that osteoblast differentiation was arrested. However, one osteoblast differentiation marker gene that was still expressed in null animals was *Runx2/Cbfa1*, indicating either that *Runx2/Cbfa1* and *Osx* operate in two independent pathways, or that *Osx* works downstream of *Runx2/Cbfa1*. As *Runx2/Cbfa1*-null mice did not express *Osx*, and the phenotype of these, and the *Osx*-null, mice were slightly different, the latter seems to be true. Because *Osx*-null preosteoblasts express several chondrocyte marker genes, the authors propose that these cells are still bipotential — that is, they could differentiate into osteoblasts or chondrocytes — and they further speculate that, in

wild-type preosteoblasts, *Osx* might function to negatively regulate the differentiation of these cells into chondrocytes.

Katrin Bussell

## References and links

**ORIGINAL RESEARCH PAPER** Nakashima, K. *et al.* The novel zinc finger-containing transcription factor *Osterix* is required for osteoblast differentiation and bone formation. *Cell* **108**, 17–29 (2002)

**FURTHER READING** Olsen, B. R. *et al.* Bone development. *Annu. Rev. Cell Dev. Biol.* **16**, 191–220 (2000)

## WEB SITE

Benoit de Crombrughe's laboratory:  
<http://www3.mdanderson.org/~genedev/decrombrughe.html>

