HIGHLIGHTS

DEVELOPMENT

Dem bones, dem bones…

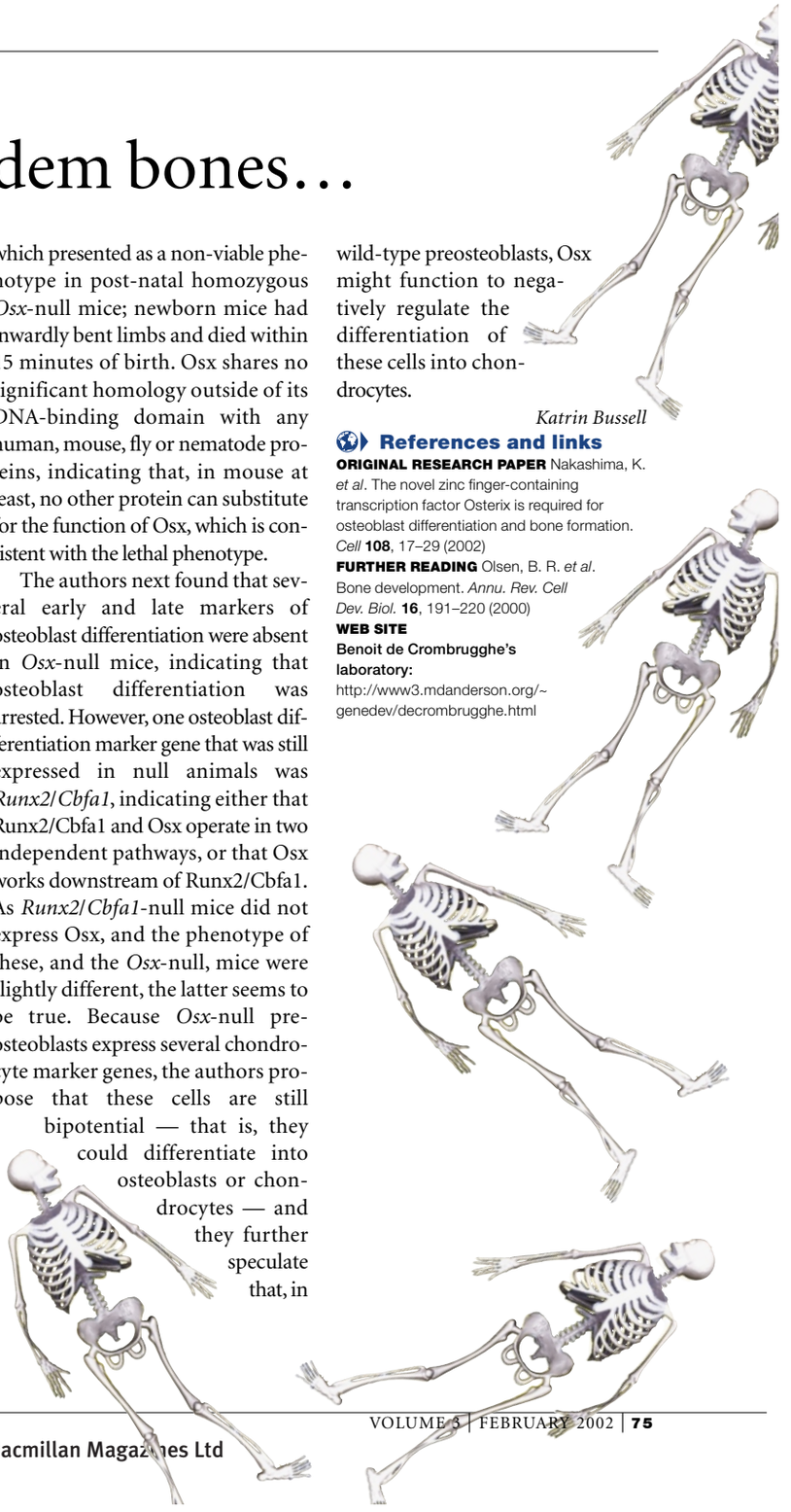
What could Harry Potter do overnight that 'Muggles' take weeks to do and *Osterix*-null mice cannot do at all? Grow bones, of course! Bone formation requires a balance between the building activities of osteoblasts, which secrete the organic matrix of bone, and osteoclasts, which erode this matrix. Nakashima *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/Cbaf1 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 Crombrugghe's laboratory:
http://www3.mdanderson.org/~genedev/decrombrugghe.html