ATF4 is a key molecule linking food intake and skeletal development

H. Sowa and G. Karsenty

Department of Genetics and Development, Columbia University, New York, NY, USA

Keywords: ATF4, RSK2, Protein, Osteoblast

RSK2 is a ribosomal kinase that is inactivated in Coffin Lowry Syndrome (CLS), a mental retardation disease with skeletal manifestation that worsens over time. It has been shown that one mechanism whereby RSK2 favors skeletal development and bone formation is by phosphorylating ATF4, a transcriptional factor that itself regulates osteoblast differentiation during development and favors bone formation and osteoclast differentiation post-natally. ATF4 regulates these various processes through two mechanisms, by favoring expression of some genes and by enhancing amino acid import in osteoblasts. To determine the biological importance and medical relevance of this latter mode of action of ATF4 we fed pregnant Atf4+/− and Rsk2+/− mothers with either a normal diet (ND), a high fat diet (HFD) or a high protein diet (HPD). Subsequently Atf4- and Rsk2-deficient pups were kept on the same diet as their mothers received until one month of age. Remarkably HPD rescued the perinatal lethality of Atf4+/− mice, it also restored protein synthesis as measured by phosphorylation of GCN2 and the α subunit of eukaryotic translation initiation factor 2 in both Atf4+/− and Rsk2+/− bones as well as by determining collagen synthesis in bones. Consequently bone mineralization and bone mass was identical between wild type, Atf4+/− and Rsk2+/− mice fed a HPD (Figure 1). Surprisingly, bone mineralization and osteoblast genes expression as analyzed by histological means and in situ hybridization was also corrected in Atf4+/− embryos. Two arguments indicate that this effect of HPD is specific of the function of the RSK2-ATF4 signaling pathway; first a HFD has no effect on bone formation parameters and bone mass, second a HPD did not affect any aspect of the phenotype in the mice lacking Runx2+/− and Osterix−/−, the crucial genes for osteoblasts’ differentiation.

On the other hand, Neurofibromatosis type I (NF1) is a disease caused by loss of function mutations in NF1, a gene encoding the Ras GAP (GTPase Activating Protein) neurofibromin, characterized by nerve tumors and skeletal abnormalities. We showed that in contrast, RSK2 activity, ATF4-dependent collagen synthesis as well as osteoblast number, bone formation ratio and bone mass are increased in mice lacking Neurofibromin in osteoblasts (Nf1+−/− mice). Furthermore, transgenic mice overexpressing Atf4 specifically in osteoblasts (αI(I)-Atf4), displayed increased osteoblast numbers, bone formation ratio and bone mass, which are the same phenotypes observed in Nf1+−/− mice. In agreement with ATF4 function in amino acid import, a low protein diet (LPD) decreased bone protein synthesis, normalized bone

The authors have no conflict of interest.

Corresponding author: Hideaki Sowa, M.D., Ph.D., Columbia University, Department of Genetics and Development, 7012W 168th St, Room 1620, New York, NY 10032, USA
E-mail: hs2353@columbia.edu

Accepted 10 August 2007
formation and bone mass in Nf1ob−/− (Figure 2) and α(I)-Atf4 mice without affecting other organ weight. In addition, increased bone resorption parameters in both mice were not affected with the low protein diet, suggesting LPD corrects bone formation specifically.

In summary, these results illustrate that a simple diet manipulation could alleviate some of the symptoms in patients with genetic bone diseases. They also suggest that the knowledge of the molecular mode of action of a gene involved in a given genetic disease can have therapeutic consequences and provide evidence for a link between food intake and skeletal development.

References