

Study of co-factor function in transgenic mice and knock out mice models

Cofactors are proteins interacting with nuclear receptors either as a coactivator or corepressor thereby modulating the gene activation or repression function of the nuclear receptor. Time- and cell-specific expression of cofactors is of particular interest because it can specify the precise action of nuclear receptors in a specific tissue. The importance of cofactor is revealed by their involvement in fundamental biological processes including cell lineage specification and organ development but also in pathological conditions. For example, we previously demonstrated that Fhl2, a Four and a half LIM domain cofactor enhances the transcriptional activity of the androgen receptor, which is known to play a crucial role in prostate cancer. To corroborate results obtained in tissue culture and different in vitro assays in vivo we generate mice deficient for known and novel cofactors isolated in the laboratory. We also established a core facility to generate transgenic mice. This allows us to analyze the phenotype associated with the absence, overexpression or ectopic expression of cofactors. Crossing our knock out mice with animal models for different diseases enables us to study the role of these coactivators during embryonic development, in tumorigenesis and metastasis formation as well as their function in early onset of Alzheimer disease.

Fhl2 deficiency results in osteopenia due to decreased activity of osteoblasts

Osteoporosis is one of the major health problems today, yet little is known about the loss of bone mass caused by reduced activity of the bone-forming osteoblasts. We show that mice deficient for the transcriptional cofactor four and a half LIM domains 2 (Fhl2) exhibit a dramatic decrease of bone mass in both genders. Osteopenia is caused by a reduced bone formation rate that is solely due to the diminished activity of Fhl2-deficient osteoblasts, while their number remains unchanged. The number and activity of the bone-resorbing cells, the osteoclasts, is not altered. Enforced expression of Fhl2 in differentiated osteoblasts boosts mineralization in cell culture and, importantly, enhances bone formation in transgenic animals. Fhl2 increases the transcriptional activity of runt-related transcription factor 2 (Runx2), a key regulator of osteoblast function, and both proteins interact in vitro and in vivo. In summary, we present Fhl2-deficient mice as a unique model for osteopenia due to decreased osteoblast activity. Our data offer a novel concept to fight osteoporosis by modulating the anabolic activity of osteoblasts via Fhl2.