Bone Phenotype of Conditionally Estrogen Receptor Alpha Deleted Mice

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Estrogen is known to participate in regulation of bone homeostasis and estrogen deficiency such as condition caused by menopause in women which can lead to osteoporosis. However, it is mostly unknown how estrogen regulates bone forming osteoblasts and bone resorbing osteoclasts. We have generated genetically manipulated mouse strains where the effect of estrogen receptor alpha (ERα) mediated regulation on bone resorption and formation can be modelled. The conditional gene inactivation is achieved by utilizing bacteriophage derived cre-recombinase catalysed exon deletion in target gene carrying lox recognition sequences. In OSTER mice, the cre-recombinase is expressed under the control of osteocalcin promoter. In TRAPER mice, the cre expression is regulated by tartrate-resistant acidic phosphatase (TRACP) promoter. In both mouse strains, lox recognition sequences are flanking exon 3 of the ERα gene. These genetic modifications lead to inactivation of the ERα gene in osteocytes and osteoblasts in cre positive OSTER mice and in myeloid cells, such as osteoclasts, in cre positive TRAPER mice.

In 3,5 month old female OSTER mice clear cre-dependent phenotype was detected by µCT analysis of the trabecular part of tibia. The trabecular bone volume and density were significantly reduced in cre positive mice when compared to age-matched cre negative mice. In male mice of similar age, no significant differences between cre positive and negative mice could be detected. TRAPER mice did not display prominent differences between untreated cre positive and negative individuals, but ovariectomy appears to induce more severe osteoporosis in cre positive animals.

The findings from OSTER mice fit to the current knowledge about how osteoblasts regulate the function of bone resorbing osteoclasts. Receptor activator of nucleic factor kappa B (RANK) / RANK-ligand signaling is crucial for osteoclast formation and activity. Osteoblasts competitively inhibit RANK/RANK-
L signaling by secreting a decoy molecule osteoprotegerin (OPG). The expression of OPG is upregulated by estrogen. The findings in TRAPER mice are so far not so clearly interpreted, but estrogen is known to inhibit the final maturation of other myeloid cells. Further analysis of the phenotypes of these mice are currently ongoing.