

Invited Speaker Abstract

IS3

Estrogen Mediate Osteoprotective Effects by Controlling Osteoclast Life Cycle

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Sex steroids, estrogens and androgens, display an osteoprotective effect and prevent bone loss associated with post-menopausal osteoporosis. However, the molecular mechanism of how this is accomplished remains to be elucidated. We have generated Cathepsin K-Cre recombinase knock-in mice (Ctsk-Cre) to generate osteoclast specific conditional knock-out mice. We then selectively ablated estrogen receptor ($ER\alpha$) in differentiated osteoclasts using Ctsk-Cre mice mating with $ER\alpha$ floxed mice ($ER\alpha^{\Delta Oc/\Delta Oc}$). $ER\alpha^{\Delta Oc/\Delta Oc}$ females exhibited clear bone loss in plain X-ray and 3D-CT, similar to the osteoporotic bone phenotype. Also in DEXA, femurs of $ER\alpha^{\Delta Oc/\Delta Oc}$ females showed low bone mineral density. Bone histomorphometric analysis revealed a significant increase in osteoclast surface, osteoclast number and eroded surface in with increased MAR and BFR. These results showed that $ER\alpha^{\Delta Oc/\Delta Oc}$ females exhibit high turnover osteoporotic phenotypes.

Then, the genechip analysis was done in the femurs of $ER\alpha^{\Delta Oc/\Delta Oc}$ females to find the ER target genes, leading to the identification of Fas ligand (FasL) gene. In *in vitro* primary cultured osteoclasts from bone marrow cells, 17β -estradiol and tamoxifen, potentiated FasL gene expression with osteoclastic apoptosis only in osteoclasts from wild type, but not $ER\alpha^{\Delta Oc/\Delta Oc}$ mice. From these findings, we presume that the osteoprotective actions of estrogens are mediated at least in part through osteoclastic $ER\alpha$ in female.

Reference; Nakamura et al., Cell, 130, 811, 2007