The role of estrogen receptor α in the regulation of bone and growth plate cartilage

Akademisk avhandling

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**The role of estrogen receptor α in the regulation of bone and growth plate cartilage**

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**Abstract**

Estrogens are important endocrine regulators of skeletal growth and maintenance in both females and males. Studies have demonstrated that the estrogen receptor (ER)-α is the main mediator of these estrogenic effects in bone. Therefore, estrogen signaling via ERα is a target both for affecting longitudinal bone growth and for bone remodeling. However, treatment with estradiol (E2) would lead to an increased risk of side effects such as venous thromboembolism and breast cancer. An improved understanding of the signaling pathways of ERα will therefore be essential in order to find better bone specific treatments with minimal adverse effects for different estrogen-related bone disorders. The aim of this thesis was to characterize the intracellular ERα signaling pathways in bone versus other tissues by studying different domains of ERα, and also to find which target cells that are important for the ERα mediated regulation of bone.

The intracellular signaling via ERα activation function (AF)-2 in mice was shown to be crucial for the estrogenic effects on all parameters evaluated, whereas the ERα AF-1 signaling was tissue dependent: with a crucial role in uterus but not in cortical bone. Thus, SERMs activating ERα AF-1 minimally could retain beneficial effects in cortical bone while minimizing effects on reproductive organs.

Further studies of ERα signaling in mice showed that ERα was indispensable for the reduction of longitudinal bone growth and reduced growth plate height in old mice (resembling growth plate closure in humans). In addition, it was shown that specific inactivation of ERα AF-1 results in a hyperactive ERα, since old mice lacking ERα AF-1 displayed fused growth plates. Studies using mice with cartilage specific inactivation of ERα revealed that local ERα in the growth plate chondrocytes is not involved in the regulation of the early pubertal longitudinal bone growth, while it is crucial for the effects of E2 to reduce longitudinal growth in sexually mature mice.

By examining mice lacking ERα in neuronal cells it was found that central ERα has an effect on bone. It was shown that, although peripheral ERα signaling is positive for the bone, centrally expressed ERα in nervous tissue has a negative impact on bone. Thereby, neuronal cells are important targets for estrogen, mediating ERα signaling pathways that affect bone remodeling.

The studies presented in this thesis have characterized signaling pathways of estrogen in bone versus other tissues. A better knowledge about the estrogenic signaling pathways may in turn facilitate the design of new, bone specific treatment strategies with minimal adverse effects.

**Keywords:** estrogen receptor α, bone, growth plate, estrogen