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The role of estrogen receptor α in the regulation of bone mass

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 11 januari 2019, klockan 09:00

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Avhandlingen baseras på följande delarbeten

I. **Farman HH**, Windahl SH, Westberg L, Isaksson H, Egecioglu E, Schele E, Ryberg H, Jansson JO, Tuukkanen J, Koskela A, Xie SK, Hahner L, Zehr J, Clegg DJ, Lagerquist MK, and Ohlsson C. Female mice lacking estrogen receptor-α in hypothalamic proopiomelanocortin (POMC) neurons display enhanced estrogenic response on cortical bone mass. Endocrinology, 2016. 157(8):3242-52.

II. Börjesson AE, **Farman HH**, Engdahl C, Koskela A, Sjögren K, Kindblom JM, Stubelius A, Islander U, Carlsten H, Antal MC, Krust A, Chambon P, Tuukkanen J, Lagerquist MK, Windahl SH, and Ohlsson C. The role of activation functions 1 and 2 of estrogen receptor-α for the effects of estradiol and selective estrogen receptor modulators (SERMs) in male mice. Journal of Bone and Mineral Research, 2013. 28(5):1117-26.

III. **Farman HH**, Wu J, Gustafsson KL, Windahl SH, Kim SH, Katzenellenbogen JA, Ohlsson C, and Lagerquist MK. Extra-nuclear effects of estrogen on cortical bone in males require ERαAF-1. Journal of Molecular Endocrinology, 2017. 58(2):105-111.

IV. **Farman HH**, Gustafsson KL, Henning P, Grahnemo L, Lionikaite V, Movérare-Skrtic S, Wu J, Ryberg H, Koskela A, Tuukkanen J, Levin ER, Ohlsson C, and Lagerquist MK. Membrane estrogen receptor-α is essential for estrogen signaling in the male skeleton. Journal of Endocrinology, 2018. 239(3):303-312.

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The role of estrogen receptor α in the regulation of bone mass

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Abstract

Estrogens are major regulators of skeletal growth and maintenance in both females and males. Estrogen receptor α (ERα) is the main mediator of estrogenic effects in bone. Thus, estrogen signaling via ERα is a target for treatment of estrogen-related bone diseases including osteoporosis. However, treatment with estrogen leads to side effects in both genders. The aim of this thesis was to characterize different ERα signaling pathways in order to increase the knowledge regarding the mechanisms behind the protective effects of estrogen on bone mass versus adverse effects in other organs.

We have evaluated the role of ERα expression in two distinct hypothalamic nuclei. Female mice lacking ERα expression in proopiomelanocortin (POMC) neurons, mainly found in the arcuate nucleus, displayed substantially enhanced estrogenic response on cortical bone mass while lack of ERα in the ventromedial nucleus revealed no effects on bone mass. We therefore propose that the balance between inhibitory effects of central ERα activity in hypothalamic POMC neurons and stimulatory peripheral ERα-mediated effects in bone determines cortical bone mass in female mice.

We have also evaluated the role of ERα signaling pathways in males. We found that the ERα activation function (AF)-2 was required for the estrogenic effects on all evaluated parameters. In contrast, the role of ERαAF-1 was tissue specific, where trabecular bone was dependent on ERαAF-1, while effects on cortical bone did not require ERαAF-1. In addition, all evaluated effects of the selective estrogen receptor modulators (SERMs) were dependent on a functional ERαAF-1.

In addition to nucleus, ERα is also located at the plasma membrane, where it can initiate extra-nuclear signaling. We found that extra-nuclear ERα signaling affects cortical bone mass in males and that this effect is dependent on a functional ERαAF-1. To further determine the role of membrane-initiated ERα signaling, we used a mouse model lacking an ERα palmitoylation site, which is crucial for membrane localization of ERα. We showed that membrane ERα signaling is essential for normal development and maintenance of trabecular and cortical bone, and is crucial for normal estrogen response in both trabecular and cortical bone in male mice.

The studies presented in this thesis have increased our knowledge regarding estrogen signaling pathways in both females and males and may contribute to the design of new, bone-specific treatment strategies that maintain the protective effects of estrogen but minimize the adverse effects.

Keywords: estrogen receptor α, bone, estrogen

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