Göteborg, 2019

Estrogen Receptor α and Bone

Posttranslational modifications and cell-specific deletion

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal 2118, Hus 2 Hälsovetarbacken, Arvid Wallgrens backe 5, Göteborg, fredagen den 22 november, klockan 9.00

av **Karin Gustafsson**

Fakultetsopponent:
Professor Per Magnusson
Institutionen för klinisk och experimentell medicin, Linköpings Universitet

Avhandlingen baseras på följande delarbeten

I. Gustafsson KL, Farman H, Henning P, Lionikaite V, Movérare-Skrtic S, Wu J, Ryberg H, Koskela A, Gustafsson JÅ, Tuukanen J, Levin ER, Ohlsson C, Lagerquist MK. **The role of membrane ERα signaling in bone and other major estrogen responsive tissues.** *Scientific Reports,* 2016 Jul 8;6:29473

II. Ohlsson C*, Gustafsson KL*, Farman HH, Henning P, Lionikaite V, Movérare-Skrtic S, Sjögren K, Andersson A, Islander U, Bernardi AI, Chambon P, Lagerquist MK. **Phosphorylation site S122 in estrogen receptor α has a tissue-dependent role in female mice.** *Manuscript in preparation.* *Contributed equally

III. Gustafsson KL*, Farman HH*, Nilsson KH, Henning P, Movérare-Skrtic S, Lionikaite V, Lawenius L, Engdahl C, Ohlsson C, Lagerquist MK. **Methylation at site R264 in estrogen receptor alpha is dispensable for the regulation of the skeleton and other estrogen responsive tissues in mice.** *Manuscript in preparation.* *Contributed equally

IV. Gustafsson KL, Nilsson KH, Farman HH, Andersson A, Lionikaite V, Henning P, Wu J, Windahl SH, Islander U, Movérare-Skrtic S, Sjögren K, Carlsten H, Gustafsson JÅ, Ohlsson C, Lagerquist MK. **ERα expression in T lymphocytes is dispensable for estrogenic effects in bone.** *Journal of Endocrinology* 2018; 20: 121-133.

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Posttranslational modifications and cell-specific deletion

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Abstract

Estrogen is involved in the regulation and development of reproductive organs. In addition, estrogen regulates several other organs including the skeleton, immune system, and adipose tissue. Estrogen treatment protects against osteoporosis and some other hormone-related diseases, but this treatment is associated with an increased risk of cancer in reproductive organs and venous thrombosis. Because of these side effects it is important to elucidate the mechanisms behind estrogenic effects in different organs, to aid the development of tissue-specific estrogen treatments. The estrogenic effect in the skeleton and several other hormone-sensitive tissues, including adipose tissue, is mainly mediated by estrogen receptor alpha (ERα). ERα is subjected to posttranslational modifications (PTMs) that can affect receptor signaling in a tissue-specific manner. Therefore, the first aim of this thesis was to evaluate whether targeting of three different ERα PTMs –palmitoylation at site C451 – phosphorylation at site S122 – methylation at site R264 –, results in tissue-specific estrogenic effects.

ERα is classically described as a transcription factor that affects the cell via nuclear (genomic) signaling. However, ERα can also be associated to the membrane and exert non-genomic signaling. To study the role of membrane-initiated ERα (mERα) signaling for the estrogenic response, we used mice lacking palmitoylation at site C451, which is crucial for membrane localization. Our study showed that the importance of mERα signaling is tissue-specific, with the trabecular bone in the axial skeleton being strongly dependent on functional mERα signaling, while adipose tissue is mainly mERα-independent. We also demonstrated that phosphorylation at site S122 in ERα has a tissue-dependent role with an impact specifically on fat mass in female mice. Finally, we found that methylation at site R264 in ERα has no effect on estrogenic regulation of the skeleton or other estrogen-sensitive tissues.

ERα is expressed in several different cell types and ERα expression in bone cells has been shown to affect the skeleton. It is also known that T lymphocytes are involved in the regulation of bone mass. Therefore, the second aim of this thesis was to evaluate whether ERα expression in T lymphocytes is involved in the protective effect of estrogen in the skeleton. We identified that ERα expression in T lymphocytes is dispensable for normal estrogenic regulation of bone mass.

In conclusion, this thesis has increased our knowledge of estrogen signaling mechanisms. Specifically, this thesis shows that mERα is important for estrogen signaling and has a tissue-specific role. In addition, phosphorylation at site S122 modulates the activity of ERα in a tissue-dependent manner. This thesis also shows that methylation at site R264 is dispensable for estrogenic regulation of the skeleton and other estrogen-responsive tissues and that T lymphocytes are not direct target cells for ERα-mediated estrogenic skeletal effects.

Keywords: Estrogen receptor α, bone**,** osteoporosis, adipose tissue, estrogen, posttranslational modifications

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