Immunomodulation by estrogen and estren

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet, kommer att offentligen försvaras i föreläsningssalen, våning 3, Guldhedsgatan 10A, Göteborg

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av
Ulrika Islander

Fakultetsopponent:
Professor Rikard Holmdahl
Lunds universitet

Avhandlingen baseras på följande delarbeten:

I. **Malin C. Erlandsson, Charlotte A. Jonsson, Ulrika Islander, Claes Ohlsson and Hans Carlsten.** Oestrogen receptor specificity in oestradiol-mediated effects on B lymphopoiesis and immunoglobulin production in male mice.
Immunology 2003, 108:346-51.

II. **Ulrika Islander, Malin C. Erlandsson, Bengt Hasséus, Charlotte A. Jonsson, Claes Ohlsson, Jan-Åke Gustafsson, Ulf Dahlgren and Hans Carlsten.** Influence of oestrogen receptor alpha and beta on the immune system in aged female mice.
Immunology 2003, 110:149-57.

III. **Ulrika Islander, Malin C. Erlandsson, Tina Chavoshi, Caroline Jochems, Sofia Movérare, Stefan Nilsson, Claes Ohlsson, Jan-Åke Gustafsson and Hans Carlsten.** Estren-mediated inhibition of T lymphopoiesis is estrogen receptor-independent whereas its suppression of T cell-mediated inflammation is estrogen receptor-dependent.
Clinical and Experimental Immunology 2005, 139:210-215.

IV. **Ulrika Islander, Bengt Hasséus, Malin C. Erlandsson, Caroline Jochems, Sofia Movérare Skrtic, Marie Lindberg, Jan-Åke Gustafsson, Claes Ohlsson and Hans Carlsten.** Estren promotes androgen phenotypes in primary lymphoid organs and submandibular glands.
BMC Immunology 2005, 6:16.

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Immunomodulation by estrogen and estren

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Abstract

Estrogen affects the development and regulation of the immune system. Treatment of gonadectomized mice with estrogen results in suppression of T and B lymphopoiesis, as well as decreased delayed type hypersensitivity reaction, granulocyte mediated inflammation and levels of IL-6 in serum. Conversely, immunoglobulin production is stimulated by estrogen. The effects of estrogen are mediated through the estrogen receptors (ER), ERα and ERβ, which are ligand activated transcription factors that induce expression of specific estrogen responsive genes. The aims of this thesis were to investigate the role of ERs on B lymphopoiesis and immunoglobulin production, as well as on the aged immune system. Furthermore, the ER specific effects of the synthetic molecule estren on T and B lymphopoiesis, T cell-mediated inflammation and submandibular glands were studied. ER knock-out mice lacking ERα, ERβ or both ERα and ERβ, were gonadectomized and treated with 17β-estradiol-3-benzoate (E2) or 4-estren-3α,17β-diol (estren).

We found that both ERα and ERβ are required for the estrogen-induced decreased frequency of B lymphopoietic cells in the bone marrow. ERα alone is necessary for the estrogen-mediated, as well as for the age-induced, increased frequency of immunoglobulin producing B cells. We could also show that estren inhibits inflammation through ER-mediated pathways, while the inhibitory effects on T and B lymphopoiesis are not dependent on ERs. Furthermore, estren promotes an androgen phenotype in submandibular glands that is independent of ERs.

In conclusion, our results show that the effects of estrogen on the immune system are mainly mediated via ERα, but signalling through ERβ is necessary for complete inhibitory effect on B lymphopoiesis. Furthermore, estren treatment induces effects on lymphopoiesis and submandibular glands that are not mediated through ERs, but instead possibly through the androgen receptor.

Key words: estrogen receptor knock-out mice, estrogen, estren, estrogen receptor, lymphopoiesis, T cells, B cells, immunoglobulin, inflammation

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