Arthritis and immune-mediated bone loss
-role of estrogen signaling pathways

Akademisk avhandling

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av

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This thesis is based on the following papers;

I. Cecilia Engdahl, Caroline Jochems, Sara H Windahl, Anna E Börjesson, Claes Ohlsson, Hans Carlsten, Marie K Lagerquist
Amelioration of collagen-induced arthritis and immune-associated bone loss through signaling via estrogen receptor alpha and not estrogen receptor beta or G protein-coupled receptor 30
Arthritis Rheum. 2010 Feb; 62(2): 524-33

II. Cecilia Engdahl, Anna E Börjesson, Annica Andersson, Alexandra Stubelius, Andree Krust, Pierre Chambon, Ulrika Islander, Claes Ohlsson, Hans Carlsten, Marie K Lagerquist
The role of total and cartilage-specific ERα expression for the ameliorating effect of estrogen on arthritis
Manuscript

III. Cecilia Engdahl, Catharina Lindholm, Alexandra Stubelius, Claes Ohlsson, Hans Carlsten, Marie K Lagerquist
Periarticular bone loss in antigen-induced arthritis
Manuscript

IV. Cecilia Engdahl, Caroline Jochems, Jan-Åke Gustafsson, Paul T van der Saag, Hans Carlsten, Marie K Lagerquist
In vivo activation of gene transcription via oestrogen response elements by a raloxifene analogue
Journal of Endocrinology. 2009 Dec; 203(3): 349-56

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Arthritis and immune-mediated bone loss
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Abstract

Objective: Rheumatoid arthritis (RA) is associated with immune-mediated bone loss and thereby increased risk for fractures. Estrogen and selective estrogen receptor modulators (SERMs) ameliorate not only the incidence and progression of experimental RA but also the immune-mediated bone loss. The aim of this thesis was to elucidate estrogen signaling pathways in arthritis and the associated immune-mediated bone loss.

Methods: Arthritis and bone mineral density (BMD) were evaluated in two experimental models of arthritis, collagen-induced arthritis (CIA) and antigen-induced arthritis (AIA). Specific estrogen receptor (ER) agonists and transgenic mouse models (total ERα knockout (KO), cartilage-specific ERα KO and ERE-luciferase reporter mice) were used, and the resulting phenotypes were examined by histological evaluation and peripheral quantitative computerized tomography.

Results: The ameliorating effect of estrogen on arthritis and associated bone loss was mediated via ERα, as determined by CIA using a specific ERα agonist and confirmed in total ERα KO mice using AIA. Furthermore, the amelioration of joint destruction was mediated via ERα in non-chondrocytes but for synovitis via ERα in chondrocytes. AIA resulted not only in bone erosions, but also in decreased periarticular BMD and can be used as a model to study periarticular bone loss. The SERM raloxifene exerted its effects by inducing the classical genomic estrogen signaling pathway in bone in vivo.

Conclusions: ERα mediates estrogens ameliorating effect on arthritis and immune-mediated bone loss. Estrogen ameliorates joint destruction and synovitis via ERα by two different mechanisms. Long-term treatment with estrogen is associated with significant side effects. Thus increased understanding of the mechanisms behind the beneficial effects of estrogen and SERMs is important in the search for novel treatments of arthritis, including postmenopausal RA, and immune-mediated bone loss.

Keywords: Arthritis, Bone, Estrogen

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