

# Sex steroid hormones - roles in adaptive immunity and vascular pathology

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentlig försvaras i hörsal Arvid Carlsson, Academicum, Medicinargatan 3, Göteborg.  
Torsdagen den 23 januari 2014 kl. 09.00

av **Anna Wilhelmson**

**Fakultetsopponent: Professor Jean-François Arnal**

Université Paul Sabatier, Institut National de la Santé et de la Recherche Médicale, Institut des Maladies Métaboliques et Cardiovasculaires, Toulouse, France

Avhandlingen baseras på följande arbeten:

- I:** Anna S. Wilhelmson, Johan Bourghardt-Fagman, Joseph A. Gogos, Per Fogelstrand, and Åsa Tivesten  
**Catechol-O-Methyltransferase Is Dispensable for Vascular Protection by Estradiol in Mouse Models of Atherosclerosis and Neointima Formation**  
*Endocrinology 152: 4683–4690, 2011*
- II:** Johan Bourghardt, Anna S. Wilhelmson, Camilla Alexanderson, Karel De Gendt, Guido Verhoeven, Alexandra Krettek, Claes Ohlsson, and Åsa Tivesten  
**Androgen Receptor-Dependent and Independent Atheroprotection by Testosterone in Male Mice**  
*Endocrinology 151: 5428–5437, 2010*
- III:** Anna S. Wilhelmson, Johan Bourghardt-Fagman, Inger Johansson, Maria E. Johansson, Per Lindahl, Karel De Gendt, Guido Verhoeven, Per Fogelstrand, and Åsa Tivesten  
**Increased Neointimal Hyperplasia Following Vascular Injury in Male Androgen Receptor Knockout Mice**  
*In manuscript*
- IV:** Anna S. Wilhelmson, Alexandra Stubelius, Johan Bourghardt-Fagman, Anna Stern, Stephen Malin, Lill Mårtensson-Bopp, Mikael C. Karlsson, Hans Carlsten, and Åsa Tivesten  
**Testosterone Regulates B cell Homeostasis by Targeting Osteoblasts in Bone and the Survival Factor BAFF in Spleen**  
*In manuscript*
- V:** Anna S. Wilhelmson, Alexandra Stubelius, Johan Bourghardt-Fagman, Ulrika Islander, Hans Carlsten, and Åsa Tivesten  
**Increased T Lymphopoiesis but Unchanged Peripheral T cell Number Following Depletion of the Androgen Receptor in Thymus Epithelial Cells**  
*In manuscript*



UNIVERSITY OF GOTHENBURG

# Sex steroid hormones

## - roles in adaptive immunity and vascular pathology

Anna Wilhelmson

The Wallenberg Laboratory for Cardiovascular and Metabolic Research  
Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

### ABSTRACT

The prevalence of autoimmune diseases is higher in women than men, while for cardiovascular disease, there is a male predominance. The sexual dimorphism of autoimmune and cardiovascular diseases probably relates to a number of factors, e.g. difference in exposure to risk factors and response to therapy, together with the effects of sex steroid hormones on disease pathophysiology. The sex difference and the effect of sex steroid hormones sometimes coincide while sometimes not: male sex and testosterone protect from autoimmune disease while male sex is considered a risk factor for CVD although testosterone is atheroprotective.

Owing to this, it is important to in detail understand the targets and mechanisms for the effects of sex steroid hormones in vascular pathology and adaptive immunity. This thesis aimed to 1) determine the role of catechol-O-methyltransferase (COMT) for the vasculo-protective actions of estradiol, 2) determine the role of the androgen receptor (AR) in the atheroprotection actions of testosterone, 3) investigate the role of the AR in neointimal hyperplasia, 4) determine the mechanisms and target cells for AR-mediated regulation of B cell homeostasis, and 5) determine the mechanisms and target cells for AR-mediated regulation of T cell homeostasis in mice.

Concluding the results in this thesis, we found that testosterone exerts its inhibitory effect on B lymphopoiesis in males by targeting the AR in osteoblasts while the thymic epithelial cells are a target for AR-mediated inhibition of T lymphopoiesis. A distinct regulation of peripheral B and T cell homeostasis may involve non-hematopoietic spleen cells and inhibition of B cell activating factor (BAFF) production. Moreover, testosterone exerts atheroprotection through AR-dependent as well as AR-independent pathways. The AR also mediates protection from neointimal hyperplasia as a response to vascular injury, possibly through regulation of endothelial nitric oxide production leading to reduced proliferatory capacity of vascular smooth muscle cells. Lastly, the COMT enzyme is dispensable for vascular protection by estradiol *in vivo*. Although the conclusions in this thesis increase our understanding of the role of sex steroid hormones in adaptive immunity and vascular pathology, they also raise new questions that warrant further investigation.

**Keywords:** COMT, androgen receptor, testosterone

ISBN: 978-91-628-8825-1

<http://hdl.handle.net/2077/34401>