Göteborg, 2020

Immunological, vascular and metabolic actions of androgens

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, den 27:e March, klockan 9:00

av Marta Lantero Rodriguez

Fakultetsopponent:

Assistant Professor Ilze Bot

Leiden University, The Netherlands

Avhandlingen baseras på följande delarbeten

I. Wilhelmson A.S, Lantero Rodriguez M, Stubelius A, Fogelstrand P, Johansson I, Buechler M.B, Lianoglou S, Kapoor V.N, Johansson M.E, Fagman J.B, Duhlin A, Tripathi P, Camponeschi T, Porse B.T, Rolink A.G, Nissbrandt H, Turley S.J, Carlsten H, Mårtensson I.L, Karlsson M.C.I and Tivesten Å. **Testosterone is an Endogenous Regulator of BAFF and Splenic B cell Number.** *Nat Commun. 2018 May 25;9(1):2067.*

II. Wilhelmson A.S, Lantero Rodriguez M, Svedlund Eriksson E, Johansson I, Fogelstrand P, Stubelius A, Lindgren S, Fagman J.B, Hansson G.K, Carlsten H, Karlsson M.C.I, Ekwall O and Tivesten Å. **Testosterone Protects against Atherosclerosis in Male Mice by Targeting Thymic Epithelial Cells**. *Arterioscler Thromb Vasc Biol. 2018 Jul; 38(7):1519-1527.*

III. Lantero Rodriguez M, Wilhelmson A.S, Svedlund Eriksson E, Fagman J.B, Alexandersson C, Johansson I, Movérare-Skrtic S, Ohlsson S, Karlsson M.C.I, Langenskiöld M and Tivesten Å. **Depletion of the Androgen Receptor in Osterix-Expressing Bone Cells Protects Against Abdominal Aortic Aneurysms in Male Mice.** *Manuscript*

IV. Lantero Rodriguez M*, Schilperoort M*, Johansson I, Svedlund Eriksson E, Palsdottir V, Kroon J, Ståhlman M, Kooijman S, Ericson M, Borén J, Jansson J.O, Levin M.C, Rensen P.C.N, Tivesten Å. **Testosterone Reduces Brown Fat Activity in Male Mice.** ***C**ontributed equally. Manuscript*

SAHLGRENSKA AKADEMIN

INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

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Immunological, vascular and metabolic actions of androgens

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Abstract

Men have higher prevalence of cardiovascular disease (CVD) but lower risk of autoimmune disorders than women. The actions of sex steroids may be involved in the sexual dimorphism of these diseases. Although testosterone, the main androgen, seems to protect against autoimmunity, its role in CVD is contradictory and disease-dependent. Androgens, acting mainly via the ubiquitously expressed androgen receptor (AR), regulate multiple physiological processes (e.g. reproduction, immunity, and energy homeostasis) and are potent anabolic hormones. However, the target cells and mechanisms involved in these effects remain poorly defined. The aim of this thesis was to define effects, target cells and mechanisms involved in the actions of androgens on splenic B cell numbers, atherosclerosis, abdominal aortic aneurysms and brown fat activity in male mice.

The main findings were that androgens/AR: 1) control splenic B cell numbers via nervous regulation of splenic stroma and the cytokine BAFF, 2) protect against atherosclerosis in a T cell-dependent manner and that thymic epithelial cells is a likely AR target for atheroprotection, 3) increase angiotensin II-induced aortic neutrophil infiltration and abdominal aortic aneurysms by targeting bone marrow mesenchymal/stromal cells, and 4) reduce brown fat activity and core body temperature in male mice.

In conclusion, our studies support that many immunological actions of androgens are mediated by targeting the stroma of lymphoid organs. Further, these immunological actions contribute to beneficial (atherosclerosis) as well as deleterious (abdominal aortic aneurysms) effects on vascular pathology. We also show that androgens are important regulators of brown adipose tissue thermogenesis in male mice. These findings elucidate androgen actions of potential importance for cardio-metabolic and immunological diseases and may have implications for future development of selective AR modulators.

Keywords: androgens, androgen receptor, immune system, atherosclerosis, abdominal aortic aneurysm, brown fat, mice.

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