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Sex differences in immune response and  
sex hormone receptor expression  
in healthy individuals and during viral infection

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**Abstract**

There is sex-bias in morbidity and mortality from infectious diseases. Infections kill more men than women and several studies have pointed out differences in the immune system as a reason. The sex hormones estrogen, progesterone and testosterone all shape the effect of the immune response on multiple levels. Women at fertile age have been suggested to have higher proinflammatory responses from inflammatory stimuli compared to men and post-menopausal women, which has been ascribed to their higher estrogen levels. This could possibly lead to a more active pathogen response but may also result in a detrimental immunopathology to infections or development of autoimmune reaction.

The overall aim of this thesis is to study the contribution of sex hormones and sex hormone receptors (SHR) to sex differences in immune response. We focus on peripheral blood mononuclear cells (PBMCs) to study such relationships in healthy individuals, as well as in individuals with asymptomatic Torque Teno Virus infection, and individuals with acute Puumala virus infection.

In **Paper I**, we investigated expression of SHR and immune response genes in PBMC from healthy premenopausal (pre-MP) women during the menstrual cycle. The expression levels were estimated using a qPCR Array (Taqman low-density array, TLDA). SHR expression did not change significantly during the menstrual cycle, but several key immune regulatory genes were significantly more expressed during the ovulatory and mid luteal phase. Further, we separated PBMC into cell subsets (CD4<sup>+</sup> T-cells, CD8<sup>+</sup> T-cells, CD56<sup>+</sup> NK-cells, CD14<sup>+</sup> monocytes and CD19<sup>+</sup> B-cells) and analyzed the expression through qPCR of estrogen receptors (ERs), ER $\alpha$ , ER $\beta$ 1 (wildtype) and the isoform ER $\beta$ 2. For the first time and unexpectedly, we demonstrate that the isoform ER $\beta$ 2 was more abundant than wildtype ER $\beta$ 1. The data from this paper provides new knowledge on the contribution of the menstrual cycle on immune response.

In **Paper II**, we explored the use of Torque Teno Virus as a secondary functional immune marker in men and women. Expression of viral TTV DNA in PBMCs was estimated using a qPCR kit from Argene (R-gene) and analyzed in relation to serum sex hormone levels. The results showed that 50% of the men, 25% the post-MP women, and 18% of the pre-MP women were TTV<sup>+</sup>. Interestingly, all pre-MP women that were TTV<sup>+</sup> had hormonal aberrances and were either anovulatory and/or hypothyroid. TTV<sup>+</sup> pre-MP women also had significantly lower progesterone levels than TTV<sup>-</sup> pre-MP women. This paper indicates that the prevalence of TTV in PBMC differs between men, pre-MP and post-MP women. Furthermore, hormonal aberrances (at least in pre-MP women) will lead to increased prevalence of TTV.

In **Paper III** we investigated the expression of ER $\alpha$ , ER $\beta$ 1 and ER $\beta$ 2 in PBMC from patients with Nephropathia epidemica, the viral zoonotic disease caused by Puumala virus, a Hanta virus known to affect more men than women. Expression of ERs in PBMCs and clinical laboratory results during the acute and convalescent phases were analyzed using a principal component analysis (PCA). The results show differences in ER expression and support previous findings that men and women have a different clinical picture

In conclusion, the results in this thesis reveal distinct patterns of immune response related to sex hormone levels, SHR expression and the phases of the menstrual cycle supporting that there is a link between sex hormone levels and immune responses. Further, we show that the ER isoform ER $\beta$ 2 is more abundant in PBMCs than what was previously described. The data in this thesis adds to the knowledge to the sex differences in immune response and exemplifies the importance of taking these differences into account in the clinic.

**Keywords**

Sex differences, sex hormones, infectious disease, Hantavirus, Puumala virus, torque teno virus, immune response, estrogen receptor, peripheral blood mononuclear cells, qPCR.

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