Göteborg, 2022

# Thymic exosomes

## Effects on selection and maturation of thymocytes

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreälsningssalen, Klinisk Mikrobiologi, Guldhedsgatan 10A, den 13 maj 2022 klockan 09:00

av Vanja Lundberg Wiraeus

Fakultetsopponent:
Professor Jan Ernerudh
Linköpings Universitet, Sverige

**Avhandlingen baseras på följande delarbeten**

I. Skogberg, G, Lundberg V, Berglund M, Gudmundsdottir J, Telemo E, Lindgren S, Ekwall O. **Human thymic epithelial primary cells produce exosomes carrying tissue-restricted antigens.** Immunology and Cell Biol 2015; 93(8): 727-734.

II. Lundberg V, Berglund M, Skogberg G, Lindgren S, Lundqvist C, Gudmundsdottir J, Thörn K, Telemo E, Ekwall O. **Thymic exosomes promoto the final maturation of thymocytes**. Scientific Report 2016; 6: 36479

III. Lundberg V, Berglund M, Lindgren S, Thörn K, Hennings V, Lemarquis A, Lingman Framme J, Lundqvist C, Telemo E, Ekwall O. **Thymus derived exosomes transfer tissue restricted antigen and affect induction of antigen specific central tolerance in the insHEL-3A9 TCR transgenic mouse model** (in manuscript)

**SAHLGRENSKA AKADEMIN**
**INSTITUTIONEN FÖR MEDICIN**

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# Thymic exosomes

# Effects on selection and maturation of thymocytes

**Vanja Lundberg Wiraeus**

Avdelningen för Reumatologi och Inflammationsforskning, Institutionen för Medicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2022.

**Abstract**

T cell tolerance is primarily shaped in the thymus, through direct and indirect presentation of self-antigens to developing T cells. Medullary thymic epithelial cells (mTECs), producing and expressing self-antigens, together with dendritic cells (DCs) are the key antigen presenting cells in the thymus. In addition to direct presentation of self-antigens by mTECs, antigens are transferred to DCs followed by presentation to developing thymocytes. The underlying mechanism of this antigen transfer is not understood. Extracellular vesicles (EVs), and more specifically exosomes, are known to carry antigens and genomic material with a biological function to target cells. This thesis report thymic exosomes as mediators of antigen transfer important for T cell maturation, negative selection and Treg development. Furthermore, we show that thymic exosomes carry co-stimulatory molecules and MHC II. In the first paper, we report that exosomes derived from primary human thymic epithelial cell cultures carry self-antigens associated with autoimmune diseases. The second paper demonstrates how exosomes from mouse thymic tissue induce the final maturation of thymocytes, independently of antigen presenting cells (APCs), before they egress the thymus as T cells, *in vitro*. In order to study the impact of thymic exosomes on central tolerance *in vivo*, we used the transgenic mouse model insHEL-3A9 TCR, which is well described in studies of central tolerance. We report that thymic exosomes from HEL-mice carry the dominant HEL-peptide in complex with MHC II on their surface. Injection of thymic exosomes from HEL-mice into 3A9 TCR mice resulted in a reduction of HEL-specific thymocytes and expansion of peripheral Tregs, suggesting that thymic exosomes are important for tolerance induction. In conclusion, this thesis reports that thymic exosomes carry self-antigens and are mediators for the induction of central and peripheral tolerance.

**Keywords:** Thymus, T cells, Treg, Exosomes, Extracellular vesicles, central tolerance, negative selection

ISBN: 978-91-8009-699-7 (TRYCK) http://hdl.handle.net/2077/70547
ISBN: 978-91-8009-700-0 (PDF)