Characteristics and functions of thymic exosomes in human and mouse

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen våning 3, Guldhedsgatan 10A, Göteborg, torsdagen den 25 september 2014, kl. 09:00

av
Gabriel Skogberg

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Avhandlingen baseras på följande arbeten:

I. **Gabriel Skogberg**, Judith Gudmundsdottir, Sjoerd van der Post, Kerstin Sandström, Sören Bruhn, Mikael Benson, Lucia Mincheva-Nilsson, Vladimir Baranov, Esbjörn Telemo, Olov Ekwall. Characterization of Human Thymic Exosomes. *PLoS ONE 8(7): e67554. doi:10.1371/journal.pone.0067554*

II. **Gabriel Skogberg**, Vanja Lundberg, Martin Berglund, Judith Gudmundsdottir, Esbjörn Telemo, Susanne Lindgren and Olov Ekwall. Human thymic epithelial primary cells produce exosomes carrying tissue restricted antigens. *In manuscript.*

III. Vanja Lundberg*, Martin Berglund*, **Gabriel Skogberg**, Susanne Lindgren, Judith Gudmundsdottir, Esbjörn Telemo and Olov Ekwall. Thymic exosomes promote the maturation of developing thymocytes. *In manuscript.* *Equal contribution.

IV. **Gabriel Skogberg**, Vanja Lundberg, Susanne Lindgren, Judith Gudmundsdottir, Kerstin Sandström, Olle Kämpe, Göran Annerén, Jan Gustafsson, Jan Sunnegårdh, Sjoerd van der Post, Esbjörn Telemo, Martin Berglund and Olov Ekwall. Altered Expression of Autoimmune Regulator in Infant Down Syndrome Thymus, a Possible Contributor to an Autoimmune Phenotype. *The Journal of Immunology, 2014, 193: 2187–2195.*

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Characteristics and functions of thymic exosomes in human and mouse

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Thymocytes develop in the thymus to become a functional pool of T-cells in the periphery. To achieve this, the thymocytes go through several steps of maturation and selection within the thymus. The goal is a cell population able to recognize foreign structures, in order to help in the defense against invading pathogens/infectious agents, which at the same time tolerate self-structures and thereby avoid autoimmunity. Exosomes are nano-sized vesicles released into the extracellular space by cells. They carry components such as proteins, micro-RNA and mRNA between cells and are able to participate in inter-cellular communication. We have isolated and characterized exosomes from human thymus and we demonstrate that exosomes are abundant in thymic tissue and that they share features with other exosomes but have their own characteristic niche. Tissue-restricted antigens (of which many are under the control of the autoimmune regulator gene) are antigens expressed by highly specialized medullary thymic epithelial cells. The role of these antigens is to mirror self-antigens found in the periphery, in order to deplete self-reactive thymocytes in the negative selection process. Tissue-restricted antigens were found in exosomes from human thymic tissue and also in exosomes from primary cultures of human thymic epithelial cells. Also, several known autoantigens e.g. myelin basic protein and transglutaminase 2 were found in these exosomes. When studying the effects of exosomes on thymocyte maturation, with an *in vitro* model, we showed that thymic exosomes stimulated the final steps of single-positive CD4+ thymocyte maturation. Finally, since Down syndrome patients share autoimmunity and autoantibodies with patients carrying mutations in the *autoimmune regulator*, and this gene is located on chromosome 21, we investigated the expression of the autoimmune regulator in thymus from Down syndrome patients. The expression was up regulated and also accompanied by other thymic abnormalities such as accumulation of CD11c+ cells in the medulla and an altered protein composition of thymic exosomes.

Keywords: Exosome, thymus, tissue-restricted antigen, Aire, Down Syndrome

ISBN: 978-91-628-9100-8 (print)
978-91-628-9127-5 (pdf)
http://hdl.handle.net/2077/35944