

On the regulation of immune responses to dietary and self antigens

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Regulatory mechanisms are necessary to avoid the misdirected aggressive immune responses responsible for the pathology seen in autoimmunity and allergy. Thymic-derived CD4⁺CD25⁺ regulatory T cells are indispensable for this regulation. We investigated if CD4⁺CD25⁺ Treg prevents auto-reactive responses in adult peripheral blood and cord blood. Mononuclear cells, as well as CD4⁺ T cells isolated from peripheral blood of adults or from cord blood, were stimulated with self-antigens and recall antigens in the absence or presence of CD25⁺ cells. We demonstrate that adult human CD25⁺ cells regulate the response to myelin oligodendrocyte glycoprotein (MOG), while cord blood CD25⁺ cells are not equally efficient in the inhibition of responses to self-antigens. We conclude that activation of self-reactive T cells in normal healthy individuals is prevented by the presence of self-antigen-specific CD25⁺ regulatory T cells and that the majority of these cells mature after birth.

T cells with regulatory properties can also be induced in the periphery, for example in response to a fed antigen. The physiological requirements and localization of the tolerance induction are largely unknown. We studied the antigen-specific activation and induction of regulatory T cells from naïve CD4⁺ T cells in different lymphoid compartments following oral administration of a protein antigen. A significantly higher proportion of antigen-specific CD4⁺ T cells developed into the putative regulatory phenotype in the liver-draining celiac lymph node (CLN), compared to other sites. This suggests that induction of regulatory T cells in the CLN may be relevant for the generation of tolerance to dietary antigens.

Oral tolerance is impaired in germfree animals, which indicates a role of the enteric flora. Using a mouse model of allergic airway inflammation, we investigated how a natural adjuvant from the commensal microflora, *Staphylococcus aureus* enterotoxin A (SEA), aids in the tolerogenic processing of antigens. We found that recipients of serum from SEA-treated and ovalbumin-fed donors were better protected against allergic airway inflammation with diminished influx of eosinophils into the lungs and reduced antigen-induced production of interleukin-5 and interleukin-13 compared to controls. This was associated with increased density of CD8 α ⁺ intraepithelial lymphocytes in gut-sections from SEA treated donors. Our results suggest that SEA promotes oral tolerance by facilitating tolerogenic processing of dietary antigens, possibly via activation of intraepithelial lymphocytes acting on the absorptive intestinal epithelium.

Intestinal epithelial cells have the capacity to sample and package environmental antigens into exosomes, which are found in the serum-fraction that mediates antigen-specific tolerance when transferred to naïve recipients. Exosomes isolated from the murine small intestinal epithelial cell line IEC4.1 were characterized by flow cytometry, electron microscopy and their immunomodulatory capacity was explored in a mouse model of ovalbumin-induced allergic airway inflammation. The exosomes were found to carry MHC class I, MHC class II, CD9 and MFGE-8. When antigen-pulsed exosomes from IEC4.1 cells stimulated with low level of IFN- γ were given to naïve mice they were able to partly prevent the allergic sensitisation.

Keywords: *Tolerance, regulatory T cells, self antigens, oral tolerance, dietary antigens, intestinal epithelial cells, exosomes, Staphylococcus aureus enterotoxin A.*

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- I. Kajsa Wing, Susanne Lindgren, Gittan Kollberg, Anna Lundgren, Robert A Harris, Anna Rudin, Samuel Lundin, Elisabeth Suri-Payer. CD4 T cell activation by myelin oligodendrocyte glycoprotein is suppressed by adult but not cord blood CD25+ T cells. *Eur J Immunol.* 2003 Mar;33(3):579-87.
- II. Susanne Hultkrantz, Sofia Östman, Esbjörn Telemo. Induction of antigen-specific regulatory T cells in the liver-draining celiac lymph node following oral antigen administration. *Immunology.* 2005 Nov;116(3):362-72.
- III. Susanne Lindgren, Nina Almqvist, Anna Lönnkvist, Sofia Östman, Carola Rask, Esbjörn Telemo *, Agnes E Wold*. Oral exposure to Staphylococcus aureus enterotoxin A promotes tolerogenic processing of a fed antigen. *In manuscript.*
- IV. Susanne Lindgren*, Nina Almqvist*, Ulf Gehrmann and Esbjörn Telemo. Characterization and immunomodulatory role of intestinal epithelial cell derived exosomes. *In manuscript.*

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