

# Dynamic changes in T cell compartments and new approaches in evaluating DSS induced and $\text{G}\alpha\text{i}2$ deficient colitis

AKADEMISK AVHANDLING

Som för avläggning av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Akademicum, Medicinaregatan 3

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av

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Fakultetsopponent:

Dr Marika Kullberg

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Avhandlingen baseras på följande delarbeten:

- I. **Maria Fritsch Fredin, Kristina Elbratt, David Svensson, Liselotte Jansson, Silvia Melgar and Elisabeth Hultgren Hörnquist, 2007**  
Dextran sulfate sodium induced colitis generates a transient thymic involution - impact on thymocyte subsets. *Scand J Immunol* 2007;65:421-429.
- II. **Maria Fritsch Fredin, Roger Willén, Liselotte Jansson and Elisabeth Hultgren Hörnquist**  
Regional alterations in intraepithelial cells in  $\text{G}\alpha\text{i}2$  deficient colitis and  $\text{RAG}^{-/-}$  recipients of peripheral T cells from colitic donor mice. *Manuscript*
- III. **Maria Fritsch Fredin\*, Alexander Vidal\*, Helena Utkovic, Yu- Yuan Götlind, Roger Willén, Liselotte Jansson, Elisabeth Hultgren Hörnquist and Silvia Melgar**  
*Ex vivo* cultures and its relevance for assessment of treatment of inflammatory bowel disease: Comparative studies in DSS induced and  $\text{G}\alpha\text{i}2$  deficient colitis and human ulcerative colitis. *Submitted*  
*\*Both authors contributed equally*
- IV. **Maria Fritsch Fredin, Leif Hultin, Gina Hyberg, Erika Rehnström, Elisabeth Hultgren Hörnquist, Silvia Melgar and Liselotte Jansson**  
Predicting and monitoring colitis development in mice by Micro-Computed Tomography. *Accepted for publication in Inflammatory Bowel Diseases*

# Dynamic changes in T cell compartments and new approaches in evaluating DSS induced and $G\alpha i2$ deficient colitis

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The overall aim of this thesis was to increase the understanding of the immunopathology of Inflammatory Bowel Disease (IBD). The first aim was to elucidate how the thymus and the gut epithelium were affected by colitis. The second aim was to investigate new ways of assessing and monitoring colitis. Two mouse models of colitis were used, the dextran sodium sulfate (DSS) induced model and the  $G\alpha i2$  deficient ( $G\alpha i2^{-/-}$ ) mouse model, which spontaneously develops colitis. These two models were compared throughout the study.

Colitis-induced changes were analysed in thymocytes and intestinal intraepithelial lymphocytes (IEL). To monitor and evaluate colitis, cultures of mouse and human colonic tissue were set up and the colon wall thickness was measured by micro-Computed Tomography (micro-CT).

During acute DSS induced colitis, the thymocytes were shifted towards a more mature phenotype, with loss of double positive (DP) thymocytes, paralleled by an increase in the absolute number of double negative (DN1) thymocytes. These changes were transient and returned to normal as the mice recovered or progressed into the chronic phase. In colitic  $G\alpha i2^{-/-}$  mice,  $CD4^+$  IELs increased in the large intestine, while  $CD4^+CD8\alpha\alpha^+$  DP IELs increased in the small intestine. The dynamic changes in thymocyte and IEL composition demonstrates that colitis affect other T cell compartments than the colon.

Thymic involution and the increase in immature DN1 thymocytes during acute colitis may result in an increased export of immature T cells to the gut. The different responses in the small and large intestine during colitis suggest that the two microenvironments induce either an uncontrolled inflammation in the large intestine or suppression in the small intestine.

Approximately 75% of the genes detected in DSS induced and  $G\alpha i2^{-/-}$  colitic mice were similarly regulated in *ex vivo* cultures and *in vivo*, and belonged to cytokines and T and B cell markers. A similar gene profile was obtained in human UC *ex vivo* cultures compared to mouse. Measurements of the colon wall in DSS treated mice demonstrated a significantly thicker colon wall during the acute phase of colitis compared to healthy controls, and correlated to the macroscopic scoring of colitis. The similar gene expression profile in mouse and human cultures and the finding that colon wall thickness can be used to identify responding animals support the relevance of these systems in monitoring colitis and evaluating new substances for the treatment of IBD.

Finally, this study points to the fact that chemically induced and spontaneously developing mouse models of colitis have several characteristics in common, such as thymic involution and expression of similar immune-related genes during colitis.

**Key words:** colitis,  $G\alpha i2^{-/-}$  mice, Dextran sodium sulfate, *ex vivo* cultures, micro-Computed Tomography, IEL, thymus, Inflammatory Bowel Diseases