

# Characteristics and Consequences of Thymic Involution in Inflammatory Bowel Disease.

## Experimental studies in *Gai2*-deficient and DSS-induced Colitis as well as in IBD patients

Akademisk avhandling

Som för avläggning av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i föreläsningssal Karl Kylberg, Medicinargatan 9A, Göteborg

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av

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Avhandlingen baseras på följande delarbeten:

- I. Kristina Elgbratt, Malin Bjursten, Roger Willén, Paul W. Bland and Elisabeth Hultgren Hörnquist. Aberrant T-cell ontogeny and defective thymocyte and colonic T-cell chemotactic migration in colitis-prone *Gai2*-deficient mice. *Immunology* 2007, 122 (2), 199–209.
- II. Maria Fritsch Fredin, Kristina Elgbratt, David Svensson, Liselotte Jansson, Silvia Melgar and Elisabeth Hultgren Hörnquist. Dextran sulfate sodium-induced colitis generates a transient thymic involution – impact on thymocyte subsets. *Scandinavian Journal of Immunology* 2007. 65 (5), 421-429.
- III. Kristina Elgbratt, Göran Kurlberg, Mirjana Hahn-Zohric, and Elisabeth Hultgren Hörnquist. Increased TRECs (T cell Receptor Excision Circle) levels in inflamed mucosa and decreased levels in peripheral blood in IBD patients indicate rapid migration of thymic emigrants to the gut. *Manuscript*
- IV. Kristina Elgbratt, Sarah Peterson, and Elisabeth Hultgren Hörnquist. Thymic atrophy in *Gai2*-deficient colitis is associated with reduced levels of recent thymic emigrant in the gut-associated lymphoid tissue. *Manuscript*

## **Characteristics and Consequences of Thymic Involution in Inflammatory Bowel Disease. Experimental studies in *Gai2*-deficient and DSS-induced Colitis as well as in IBD patients**

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Inflammatory Bowel Disease (IBD) is a chronic relapsing inflammatory disorder of the gastrointestinal tract, comprising ulcerative colitis and Crohn's disease. Alterations in T cell subsets, an important cell type in cell-mediated immune responses in the adaptive immune system, are certainly an element contributing to disease development. The relationship between disease and T-cell maturation in the thymus is, however, poorly understood. The present study investigates intrathymic changes as well as the consequence of thymic involution by analysis of recent thymic emigrants in peripheral blood and lymphoid tissue in two different mouse models for colitis; *Gai2*-deficient mice and mice with DSS-induced colitis, as well as in IBD patients.

Before the onset and during colitis, *Gai2*<sup>-/-</sup> mice demonstrate thymic involution, whereas in DSS-induced colitis the thymic atrophy is transient, being evident during the acute phase of colitis but reversed during the chronic phase. The frequency of medullary mature thymocytes was increased in both models, but the intrathymic changes were mainly seen in the cortex and involved reduced both frequencies and absolute numbers of cortical thymocyte subsets as well as impaired chemotactic responses towards the chemokines CXCL12 and CCL25. The impaired migration was not limited to the thymus as reduced responsiveness to CXCL12 was seen also in colonic lymphocytes from *Gai2*<sup>-/-</sup> mice. In mice with DSS-induced colitis, an increased frequency of the most immature subpopulation of double negative (DN) thymocytes and a proportional decrease in the most mature DN thymocytes correlated with the severity of colitis. These results strongly indicate that an aberrant T cell ontogeny is associated with development of colitis.

It is unknown whether thymic atrophy is evident also in IBD patients. Due to the unavailability of human thymus tissue from IBD patients for such studies, one aspect of thymus function was evaluated by analysis of the levels of T cell receptor excision circles (TRECs), a marker for recent thymic emigrants (RTEs), in T lymphocytes from peripheral blood and the intestinal mucosa. This analysis revealed reduced levels of RTEs in peripheral blood from IBD patients, irrespective of the expression of the mucosal homing receptor integrin  $\alpha_4\beta_7$ . In strong contrast to peripheral blood, an increased level of TRECs was found in the intestinal mucosa, indicative of an instant recruitment of recent thymic emigrants into the intestine. These results were seen in both UC and CD -patients but were more pronounced in UC patients, and could not be explained by enhanced extrathymic T cell maturation within the mucosa. Preliminary data also indicate that the TRECs levels in the mucosa are not influenced by the activity of the disease. A similar analysis of TRECs levels was performed in colitic *Gai2*<sup>-/-</sup> mice but decreased levels were found both in peripheral blood and intestinal mucosa. However, a massive proliferation of memory/effector T cells, especially in the mucosa, disguised the true level of recent thymic emigrants in this compartment.

Thus, chronic intestinal inflammation in IBD is clearly associated with changes in T cell ontogeny and thymic output. It is likely that this influences the peripheral T cell population and further studies would reveal whether this leads to lower ability for T cell mediated immunoregulation and/or the presence of autoreactive T cell clones.

**Key words:** Inflammatory bowel disease, *Gai2*<sup>-/-</sup> mice, dextran sodium sulfate, thymocytes, T cell receptor excision circles (TRECs), recent thymic emigrants.  
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