

Regulatory T cells and lymphocyte migration into intestinal tumors

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i sal Karl Isaksson, Medicinaregatan 16, den 26 januari, klockan 9.00

av

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Fakultetsopponent:

Professor Alexandre Corthay

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Avhandlingen baseras på följande delarbeten

- I. Akeus P, Langenes V, von Mentzer A, Yrlid U, Sjöling Å, Saksena P, Raghavan S, and Quiding-Järbrink M. "Altered Chemokine Production and Accumulation of Regulatory T Cells in Intestinal Adenomas of APC^{Min/+} Mice." *Cancer Immunology, Immunotherapy*, 2014;63(8):807-819. doi:10.1007/s00262-014-1555-6.
- II. Akeus P, Langenes V, Kristensen J, von Mentzer A, Sparwasser T, Raghavan S, and Quiding-Järbrink M. "Treg-Cell Depletion Promotes Chemokine Production and Accumulation of CXCR3(+) Conventional T Cells in Intestinal Tumors." *European Journal of Immunology*, 2015;45(6):1654-66. doi:10.1002/eji.201445058.
- III. Akeus P, Ahlmanner F, Sundström P, Alsen S, Gustavsson B, Sparwasser T, Raghavan S, Quiding-Järbrink M, "Regulatory T cells control endothelial chemokine production and migration of T cells in intestinal tumors". Manuscript in preparation

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN**



Regulatory T cells and lymphocyte migration into intestinal tumors

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Abstract

Tumor-infiltrating lymphocytes (TIL) are crucial for anti-tumor immunity. However, regulatory T cells (Treg) often accumulate in tumor tissue and are able to reduce both lymphocyte activity and transendothelial migration and thereby reduce the local anti-tumor immunity. The aim of this thesis was to investigate the anti-tumor immune response in intestinal tumors *in vivo* with a special emphasis on Treg function and lymphocyte recruitment. First, the APC^{Min/+} mouse model of intestinal tumors was used to investigate tumor-associated lymphocyte subsets and their modes of accumulation into intestinal tumors. We could show that the tumors of APC^{Min/+} mice harbour an increased number of Treg, which was also confirmed in human colon cancer and colon adenomas. Furthermore, a decrease of conventional T cells was observed.

By breeding APC^{Min/+} mice with DEREK mice, which harbour a high affinity diphtheria toxin receptor under the control of the FoxP3 promoter, we were able to deplete Treg in tumor-bearing mice. Treg depletion resulted in an accumulation of effector T cells in the intestinal tumors, as a consequence of both higher proliferation and increased migration into the tumors. Furthermore, an increase of the Th1 associated chemokine receptor CXCR3 on T cells and increased levels of IFN- γ was found in the absence of Treg. One important mechanism for TIL migration in the absence of Treg was the increased secretion of the CXCR3 ligands CXCL9 and 10. We could also demonstrate that CXCR3 is crucial for migration into intestinal tumors.

In conclusion, this thesis demonstrates that Treg inhibit a Th1 associated anti-tumor response in intestinal tumors partly by reducing effector T cell accumulation. Strong Th1 responses have been correlated to improved patient outcome in colon cancer. Therefore, the results of this thesis indicate that eliminating Treg or reducing their suppressive mechanisms would constitute a viable anti-tumor therapy, not only increasing effector T cell activity but also their recruitment into tumors.

Keywords: Regulatory T cells, CRC, Tumor infiltrating lymphocytes, CXCR3

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