T cells in colon cancer; migration and effector functions

AKADEMISK AVHANDLING

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av **Louis Szeponik**

Fakultetsopponent: Professor **Katharina Lahl**
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Avhandlingen baseras på följande delarbeten

I. Akeus P, Szeponik L, Ahlmanner F, Sundstrom P, Alsen S, Gustavsson B, Sparwasser T, Raghavan S, Quiding-Järbrink M (2018) **Regulatory T cells control endothelial chemokine production and migration of T cells into intestinal tumors of APC$^{Min/+}$ mice.** *Cancer Immunology, Immunotherapy*. doi:10.1007/s00262-018-2161-9

II. Akeus P, Szeponik L, Langenes V, Karlsson V, Sundström P, Bexe-Lindskog E, Tallon C, Slusher BS, Quiding-Järbrink M (2021) **Regulatory T cells reduce endothelial neutral sphingomyelinase 2 to prevent T-cell migration into tumors.** *European Journal of Immunology*. doi:10.1002/eji.202149208

III. Szeponik L, Akeus P, Rodin W, Raghavan S, Quiding-Järbrink M (2020) **Regulatory T cells specifically suppress conventional CD8αβ T cells in intestinal tumors of APC$^{Min/+}$ mice.** *Cancer Immunology, Immunotherapy.* doi:10.1007/s00262-020-02540-9

IV. Szeponik L, Rodin W, Sundström P, Raghavan S, Lindskog E, Wettergren Y, Cosma A, Quiding-Järbrink M. **Unconventional T cells in colon cancer – phenotypic characterization.** *Manuscript.*

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T cells in colon cancer; migration and effector functions

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Abstract

Immune cells are recognised as one of the main players in the tumor microenvironment and targeted by many new cancer therapies. Regulatory T cells (Treg) can suppress tumor infiltrating lymphocytes which are associated with a better patient outcome. Additionally, unconventional T cells have the potential to kill tumor cells through T cell receptor-independent mechanisms and also in a non- major histocompatibility complex restricted manner. The aim of this thesis was to investigate how Treg can supress the T cell migration into intestinal tumors and what type of T cell populations are affected. Furthermore, we characterized different unconventional T cell populations in human colon cancer samples using mass cytometry. We used $APC^{Min/+}$/DEREG mice to deplete Treg in intestinal tumors. We demonstrated that Treg inhibit the transendothelial migration of T cells into tumors dependent on the interaction of CXCR3 with its ligand CXCL10. Endothelial cells increased expression of CXCL10 when Treg were depleted in tumors. Furthermore, Treg inhibited the expression of endothelial neutral sphingomyelinase 2 (nSMase2) through TGF-β and other unknown soluble factors which resulted in reduced expression of adhesion molecules and chemokines, and decreased tumor infiltration of T cells. CD8αβ T cells were specifically affected by Treg depletion which increased their expression of Th1 related molecules, activation, and proliferation, while CD8αα T cells and γδ T cells were unaffected. In human tumors, exhausted mucosal associated invariant T (MAIT) cells were increased compared to unaffected tissue and none of the MAIT cell populations expressed high levels of activating natural killer cell receptors. In addition, γδ T cell subpopulations showed a great diversity, and some populations were patient specific.

In conclusions, this thesis demonstrates that Treg depletion increases the migration of tumor infiltrating T cells associated with a Th1 response. This is partly mediated by nSMase2 inhibition in endothelial cells. Treg depletion could be a viable option to increase beneficial effector T cells in colorectal cancer patients.

Keywords: Treg, CRC, TIL, nSMase2, Transendothelial migration, Unconventional T cells

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