

Regulatory T cells and mucosal-associated invariant T cells in colon adenocarcinomas; Phenotype and function

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Fredagen den 22 Mars, klockan 9.00

av Filip Ahlmanner

Fakultetsopponent:

Professor Fredrik Ivars
Lunds Universitet, Sverige

Avhandlingen baseras på följande delarbeten

- I. CD39⁺ regulatory T cells accumulate in colon adenocarcinomas and display markers of increased suppressive function.
Ahlmanner F, Sundström P, Akeus P, Eklöf J, Börjesson L, Gustavsson B, Lindskog EB, Raghavan S, Quiding-Järbrink M.
Oncotarget. 2018; 9(97): 36993-37007.
- II. Intratumoral CD39⁺ regulatory T cell accumulation may predict disease recurrence in colon cancer patients.
Ahlmanner F, Sundström P, Gustavsson B, Lindskog EB, Wettergren Y, Quiding-Järbrink M.
Manuscript
- III. Human mucosa-associated invariant T cells accumulate in colon adenocarcinomas but produce reduced amounts of IFN- γ .
Sundström P, Ahlmanner F, Akéus P, Sundquist M, Alsén S, Yrlid U, Börjesson L, Sjöling Å, Gustavsson B, Wong SB, Quiding-Järbrink M.
Journal of Immunology. 2015; 195(7): 3472-3481.

APPENDIX

Intratumoral mucosal-associated invariant T cells and disease outcome in colon cancer patients.

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Abstract

In many solid cancers, and also in colon adenocarcinomas, an increased accumulation of lymphocytes is beneficial for the patient. However, tumor-infiltrating immune cells may be either pro- or anti-tumorigenic and the balance between these two counteracting forces partly determines patient outcome. Boosting of the anti-tumor immune response by immunotherapy, e.g. by immune checkpoint blockade, has been highly successful in several types of cancer but less so for colon cancer. In the interest of developing new cancer immunotherapies also for the treatment of colon cancer, additional studies of tumor-infiltrating lymphocytes in colon cancer are warranted. In this study, we used flow cytometry and flow cytometric cell sorting as well as *in vitro* cell culture assays to examine the phenotype and effector functions of two distinct immune cell populations which we have shown to accumulate in tumors of colon cancer patients, CD39⁺ regulatory T cells (CD39⁺ Treg) and mucosal-associated invariant T (MAIT) cells. Treg reduce the activity of other immune cells and can express the surface molecule CD39, an ectoenzyme involved in converting extracellular ATP to immunosuppressive adenosine. MAIT cells recognize bacterial metabolites and are innate-like T cells which are believed to provide a first line defense at epithelial surfaces. This thesis comprises an extensive phenotypic and functional characterization of these two subsets in colon tumors, and also preliminary survival data on their respective impact on patient prognosis.

We show that CD39⁺ Treg constitute a highly activated and immunosuppressive Treg subset. In particular, surface expression of immunomodulatory mediators were increased in the CD39⁺ Treg subset, while cytokine production was similar in CD39⁺ and CD39⁻ Treg. We also present preliminary survival data which suggests a correlation between high levels of CD39 expression on intratumoral Treg and a worse patient prognosis, thus highlighting CD39⁺ Treg as a potential candidate for targeted immunotherapy. With regard to MAIT cells, we could demonstrate accumulation of MAIT cells in colon adenocarcinomas. However, there were reduced frequencies of IFN- γ -producing cells among tumor-associated MAIT cells compared to MAIT cells from unaffected colon tissue. MAIT-cell infiltration into colon tumors has been correlated with poor patient prognosis and in an independent appendix of the thesis, we present preliminary data actually showing a positive impact of MAIT cell infiltration into colon tumors on patient survival.

Keywords: colon cancer, regulatory T cells, CD39, adenosine, immune checkpoint molecules, immunosuppression, MAIT cells, cytokines, cancer-specific survival