Cancer Immunotherapy

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Tumor-host interactions in human colorectal cancer

Colorectal cancer (CRC) is a leading cause of cancer-related death. Non-transformed cells in CRC microenvironment, including tumor-associated mesenchymal stromal cells (TASCs) and immune cells, have been recognized to play key roles in disease progression. Whereas infiltration by specific immune cell types is significantly associated with prolonged patient survival, TASC abundance predicts unfavorable prognosis. Mechanisms leading to recruitment of these cell populations and underlying their effects on clinical outcome remain to be clarified.
CRC arises in an environment populated by the gut microflora. Commensal bacteria translocate across the dysfunctional neoplastic epithelium into the lamina propria, thus possibly stimulating stromal and immune cells. The potential impact of these events on tumor development and progression remains to be fully elucidated.
We are interested in investigating interactions occurring between tumor, stromal and immune system in CRC and their modulation by the gut microflora. Understanding the complex network of tumor-host interactions in CRC may allow the identification of novel prognostic biomarkers and potential new areas of therapeutic intervention.

Main Projects

Role of CRC infiltrating IL-17-producing T cells: Phenotypes and prognostic relevance of tumor infiltrating IL-17-producing T cells (Th17) in CRC are still debated. Upon *ex vivo* analysis, and *in vitro* and *in vivo* experiments we found that CRC infiltrating Th17 are polyfunctional effector cells able to produce, in addition to IL-17, a spectrum of cytokine/chemokines ultimately leading to recruitment of beneficial CD8+ T cells and neutrophils. Our study reveals a positive role played by tumor infiltrating Th17 in CRC, thus calling for caution when envisaging novel IL-17/Th17 targeted therapies.

Monocytes-Th17 cells crosstalk: Monocytes (Mo) promote differentiation of naïve cells into Th17. However, their impact on pre-differentiated Th17 cells, such those infiltrating CRCs, is unknown. We assessed the ability of classical (cMo) and non-classical monocytes (ncMo) to promote expansion of memory Th17 cells *in vitro*. We found that in the absence of microbial stimulation ncMo are more efficient stimulators of Th17 than cMo, and their ability is counteracted by LFA-1/ICAM-1 interaction. These data highlight ncMo as potential new therapeutic targets in IL-17-mediated inflammation.

Immune cell recruitment into CRC: Chemotactic factors leading to CRC infiltration by beneficial immune cells are still unclear. Upon *ex vivo* analysis of human CRC specimens, we identified a panel of chemokine genes underlying tumor infiltration by favorable immune cell subsets. Stimulation of CRC cells by gut microbiota markedly enhanced the expression of these chemokines *in vitro* and *in vivo*, and led to increased T cell recruitment into tumor xenografts. Importantly, in human CRC specimens, bacterial loads correlated with chemokine expression levels and extent of T cell infiltration. Our findings identify the gut microbiota as critical modulator of immune cell trafficking into CRCs.

Impact of TASCs on CRC progression: Mechanisms underlying the negative prognostic significance of TASCs in CRC are not fully understood. By *in vitro* and *in vivo* experiments, we found that upon tumor conditioning, TASCs acquire surface TGF-β expression and induce epithelial-to-mesenchymal transition (EMT) in CRC cells (see Figure 1). This results in higher numbers of circulating tumor cells, ultimately leading to increase metastasis formation. These data reveal a novel mechanism of tumor-stroma interaction and may suggest novel therapeutic interventions.

3D culture models for primary CRC tissues: In collaboration with the Tissues Engineering group, we developed an innovative 3D system, based on a perfused bioreactor, for culturing freshly isolated CRC specimens. This system proved capable of preserving all components of CRC microenvironment, including tumor, mesenchymal and immune cells, up to five days, and might therefore be suitable for testing the efficacy of innovative anti-cancer compounds targeting the tumor or the tumor-associated stroma.

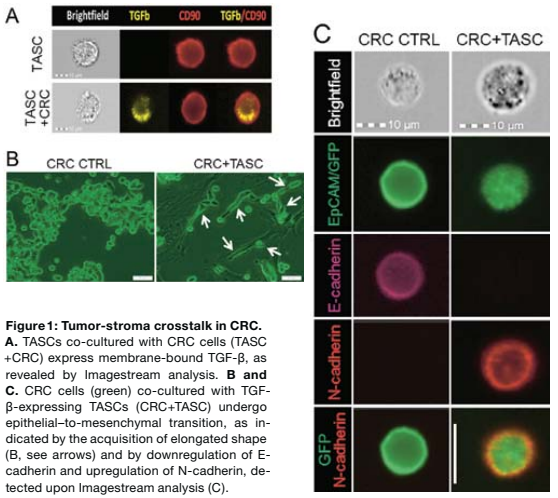

Figure 1: Tumor-stroma crosstalk in CRC. **A.** TASCs co-cultured with CRC cells (TASC +CRC) express membrane-bound TGF-β, as revealed by Imagestream analysis. **B and C.** CRC cells (green) co-cultured with TGF-β-expressing TASCs (CRC+TASC) undergo epithelial–to-mesenchymal transition, as indicated by the acquisition of elongated shape (B, see arrows) and by downregulation of E-cadherin and upregulation of N-cadherin, detected upon Imagestream analysis (C).

Connection to Clinical Practice

Prof. Daniel Oertli
Department of Surgery, University Hospital Basel

Immunotherapeutic intervention in human colorectal cancer

The Cancer Immunotherapy group is closely connected to the Department of Surgery of the University Hospital Basel, led by Prof. Daniel Oertli. Several surgeons, including young doctors in training, have been involved in the planning and development of our research projects. Our ultimate goal is the identification of novel targets for immunotherapeutic intervention in colorectal cancer.
Furthermore, we have established a collaborative network with the surgical units of other Swiss hospitals, including St. Claraspital Basel (Dr. M. Bolli), Kantonsspital Olten (Prof. Markus Zuber), Kantonsspital Arau (Prof. Walter Marti), Kantonsspital St. Gallen (Dr. Michel Adamina), and Ospedale Civicio di Lugano (Prof. Raffaele Rosso), ensuring regular access to clinical samples.
We have also established a proficient collaboration with the Institute of Pathology, of the University of Basel. The availability in this unit of the tissue-microarray technology has allowed the rapid evaluation of the clinical relevance of putative novel prognostic markers on large cohorts of patients. Furthermore, the mutual exchange of specific know-hows has resulted in the generation of significant synergies.

Selected Publications

Amicarella F, Muraro MG, Hirt C, Cremonesi E, Padovan E, Mele V, Governa V, Han J, Huber X, Droeser RA, *et al.* (2015) Dual role of tumor infiltrating T-helper 17 cells in human colorectal cancer. Gut. 2017, 66:692–704. (doi: 10.1136/gutjnl-2015-310016)

Traunecker E, Gardner R, Fonseca J, Polido-Pereira J, Seitz M, Villiger PM, Iezzi G, Padovan E. (2015) Blocking of LFA-1 enhances expansion of Th17 cells induced by human CD14(+) CD16(++) nonclassical monocytes. Eur. J. Immunol. 45:1414–25

Hirt C, Papadimitropoulos A, Muraro MG, Mele V, Panopoulos E, Cremonesi E, Ivanek R, Schultz-Thater E, Droeser RA, Mengus C, *et al.* Bioreactor-engineered cancer tissue-like structures mimic phenotypes, gene expression profiles and drug resistance patterns observed *"in vivo"* (2015). Biomaterials 62:138–46

Mele V, Muraro MG, Calabrese D, Pfaff D, Amatruda N, Amicarella F, Kvinlaug B, Bocelli-Tyndall C, Martin I, Resink TJ, *et al.* (2014) Mesenchymal stromal cells induce epithelial-to-mesenchymal transition in human colorectal cancer cells through the expression of surface-bound TGF-beta. Int. J. Cancer 134:2583–94

Sadallah S, Amicarella F, Eken C, Iezzi G, Schifferli J. (2014) Ectosomes released by platelets induce the differentiation of CD4+ T cells into T regulatory cells. Thromb Haemost 112:1219–29