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 microbiota. Commensal bacteria translocate across the dysfunctional neoepithelium 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 microbiota. 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 cytokines/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 naive T cells into Th17. However, their impact on pre-differentiated Th17 cells, such as those infiltrating CRCs, is unknown. We assessed the ability of classical (MoC) 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 MoC, and their ability is counterbalanced 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: Chemokatic 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.

Selected Publications


3D culture models for primary CRC tissues: In collaboration with the Tissues Engineering group, we developed an innovative 3D system, based on a perfused bio-reactor, 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.

Connection to Clinical Practice
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), Kantonshospital Olten (Prof. Markus Zuber), Kantonsspital St. Gallen (Dr. Michel Adamina), and Ospedale Civico di Lugano (Prof. Raffaello 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-how has resulted in the generation of significant synergies.