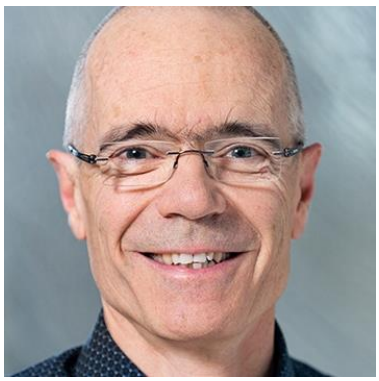
DECRYPTING THE CROSSTALK BETWEEN A DEVELOPING COLORECTAL TUMOR AND ITS MICRO-ENVIRONMENT

ENTSCHLÜSSELUNG DER KOMMUNIKATION ZWISCHEN DARMKREBS UND SEINER (MIKRO)UMGEBUNG



KONRAD BASLER
Institute of Molecular Life Sciences
University of Zurich,

GERHARD ROGLER
Department of Gastroenterology and Hepatology
University Hospital Zurich

KEYWORDS - COLORECTAL CANCER, WNT SIGNALING, CELL-CELL COMMUNICATION, STROMAL CELLS, TUMOR MICROENVIRONMENT

SCHLAGWÖRTER – DICKDARMKREBS, WNT SIGNALWEGE, ZELL-ZELL-KOMMUNIKATION, STROMA, TUMOR-MIKROUMGEBUNG

SUMMARY

The fate of a cancer cell is determined not only by the mutations that it carries but also by its interactions with its host. In the case of colorectal cancer (CRC) the communication between the epithelial-derived tumor cells and the underlying stroma remains cryptic. A better understanding of the crosstalk represents an exciting opportunity for improved treatments. Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths and the lifetime risk of developing CRC is about 1 in 22 for men and 1 in 24 for women. Regarding the role played by the stroma there are many open questions: what is the complement of stroma-derived signals, what are their cellular sources, and what are their roles in orchestrating tumor proliferation and differentiation? The same is true of the signals from the tumor cells. Starting to answer these questions is the goal of the proposed project. One part of the project will reveal the details of the arena; the second part of the project explores an understudied facet of a major player's (Wnt's) involvement in CRC evolution. To chart the arena, we will - with single cell resolution - profile the transcriptomes of cancer cells and in the underlying stroma at different stages of tumorigenesis. We will do this with samples from a metastasizing murine CRC model and from patient biopsies. As well as revealing the signals that are sent, the cellular resolution of the data will allow us to determine between which cellular sub-populations the conversation is happening. Follow up experiments with sm-FISH and IHC will reveal the location of implicated populations in situ. The work may uncover potential prognostic markers that, individually or combined, demarcate stromal and/or CRC sub-populations, which are altered during the course of tumorigenesis. Despite extensive work on the role of elevated Wnt signaling in CRC initiation, the relevance of Wnt ligand mediated crosstalk between the tumor and stroma is a mystery. An important starting question is what, if any, role Wnt secretion from the tumor has? Does it impinge on tumor development and the concordant stromal responses? We will answer these questions. The impetus for the proposed project is this notion that cancer therapies can be improved by targeting stroma-tumor crosstalk. Given the availability of the small molecule inhibitors, Wnt production is an actionable target.