Colonic fibroblasts in tissue homeostasis and cancer

Michael David Brügger, Tomas Valenta, Hassan Fazilaty, George Hausmann and Konrad Basler

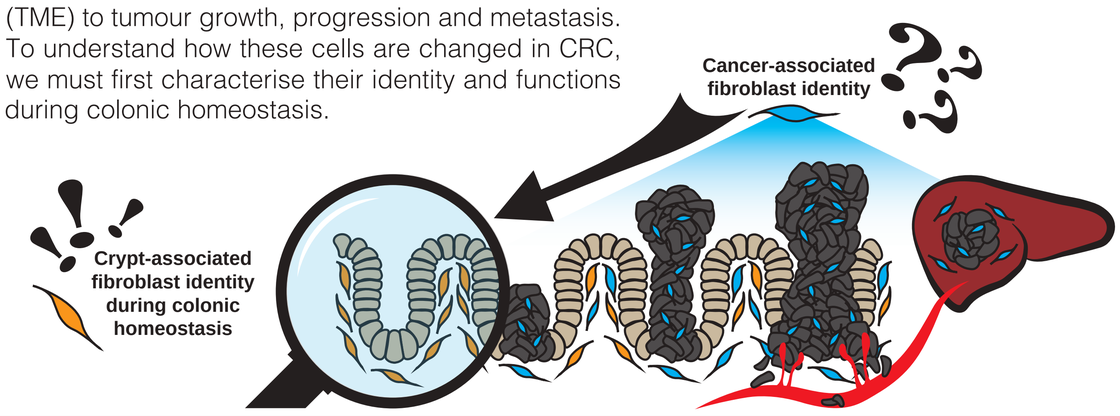
University of Zürich, Switzerland

@MDBScience

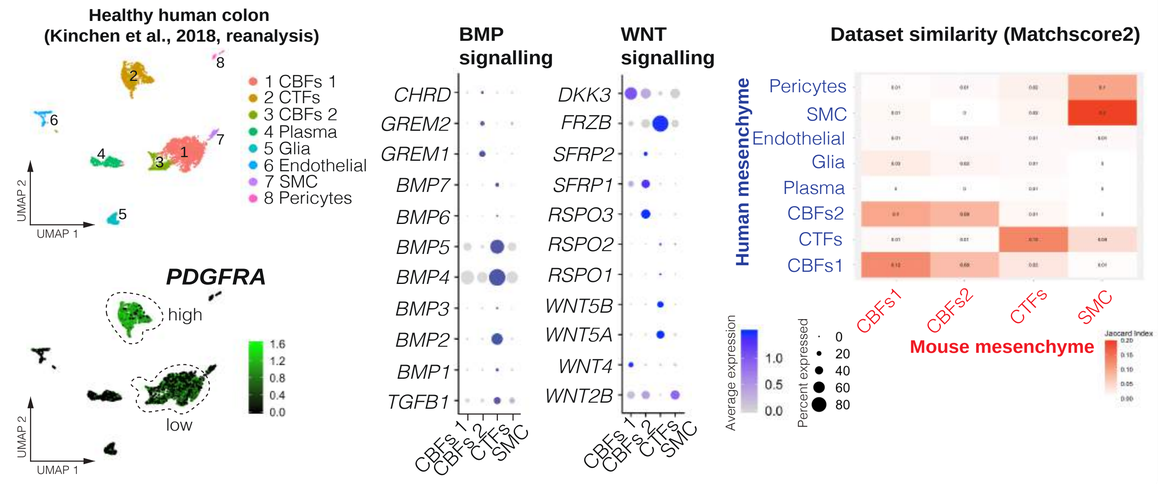
@BaslerLab

Introduction

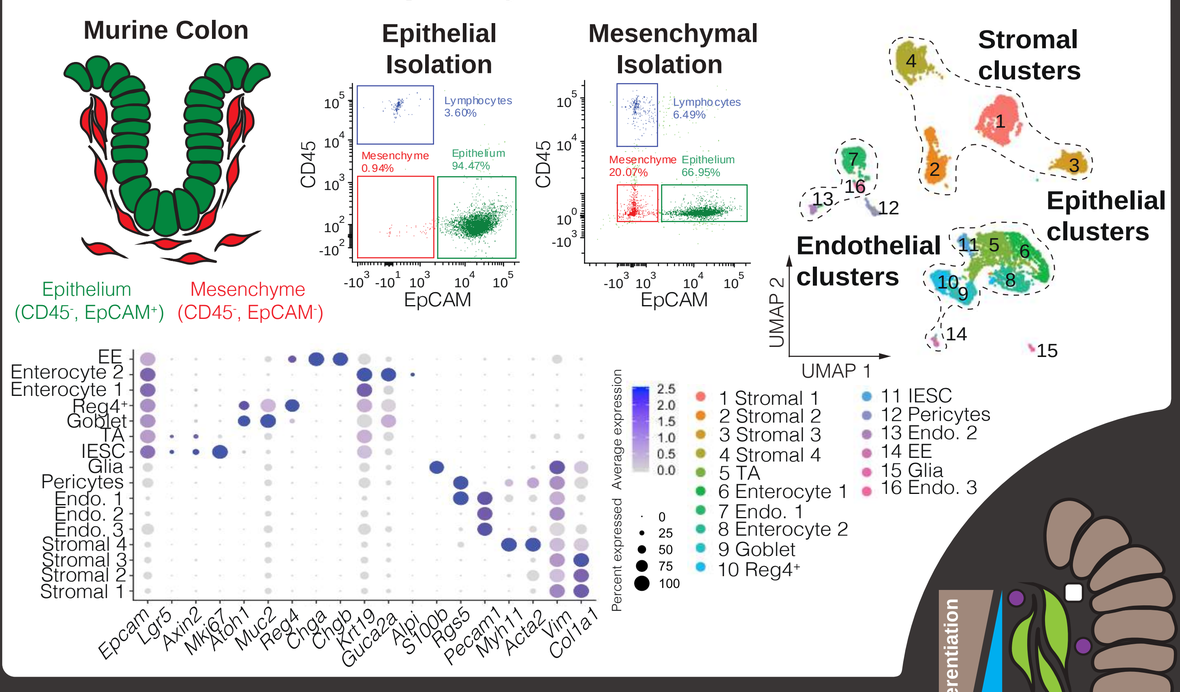
Colorectal cancer (CRC) is among the most prevalent cancers in Switzerland (2nd in women 3rd in men, BFS statistics 2013-2017) and worldwide (3rd in women and men). We are only now starting to appreciate the contribution of not only tumour cells themselves, but also the non-tumour stromal cells of the tumour microenvironment (TME) to tumour growth, progression and metastasis. To understand how these cells are changed in CRC, we must first characterise their identity and functions during colonic homeostasis.



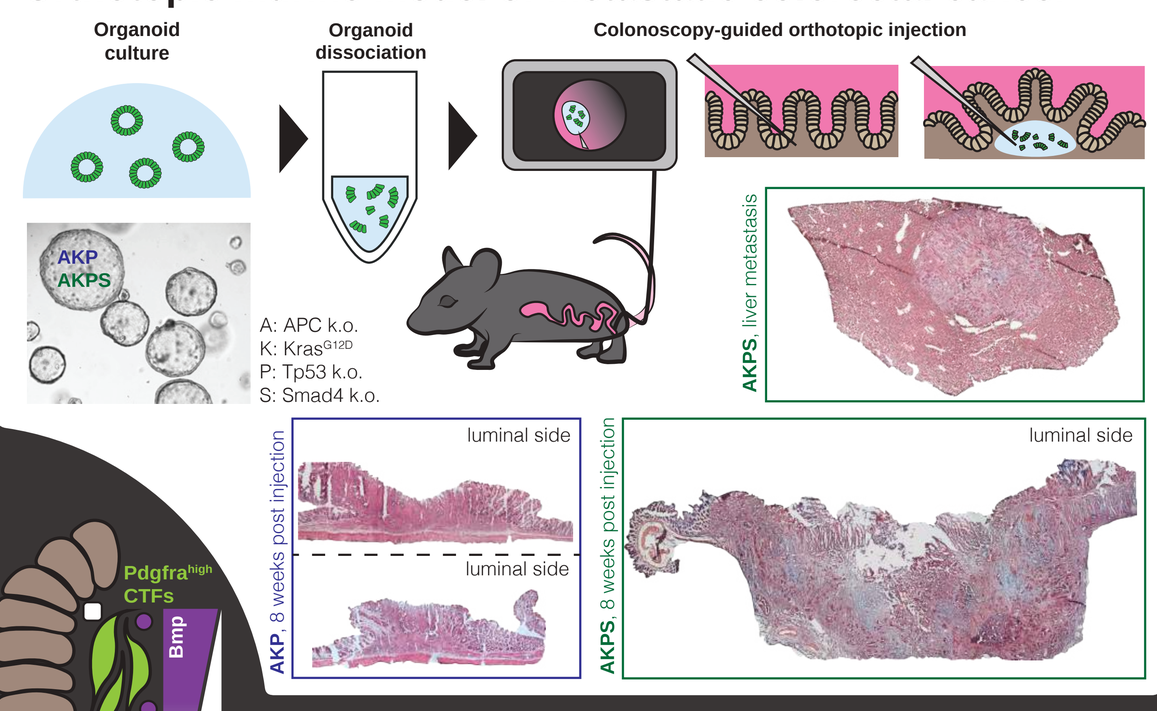
Murine CTFs and CBFs populations are conserved in healthy human colon

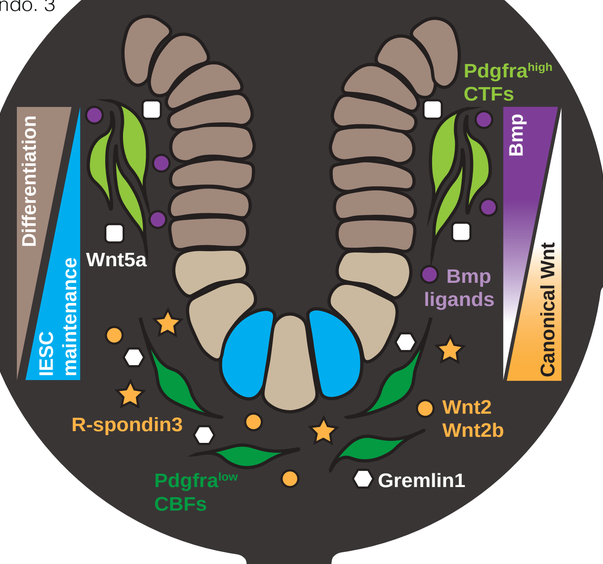


Unbiased scRNAseq analysis of the murine colon

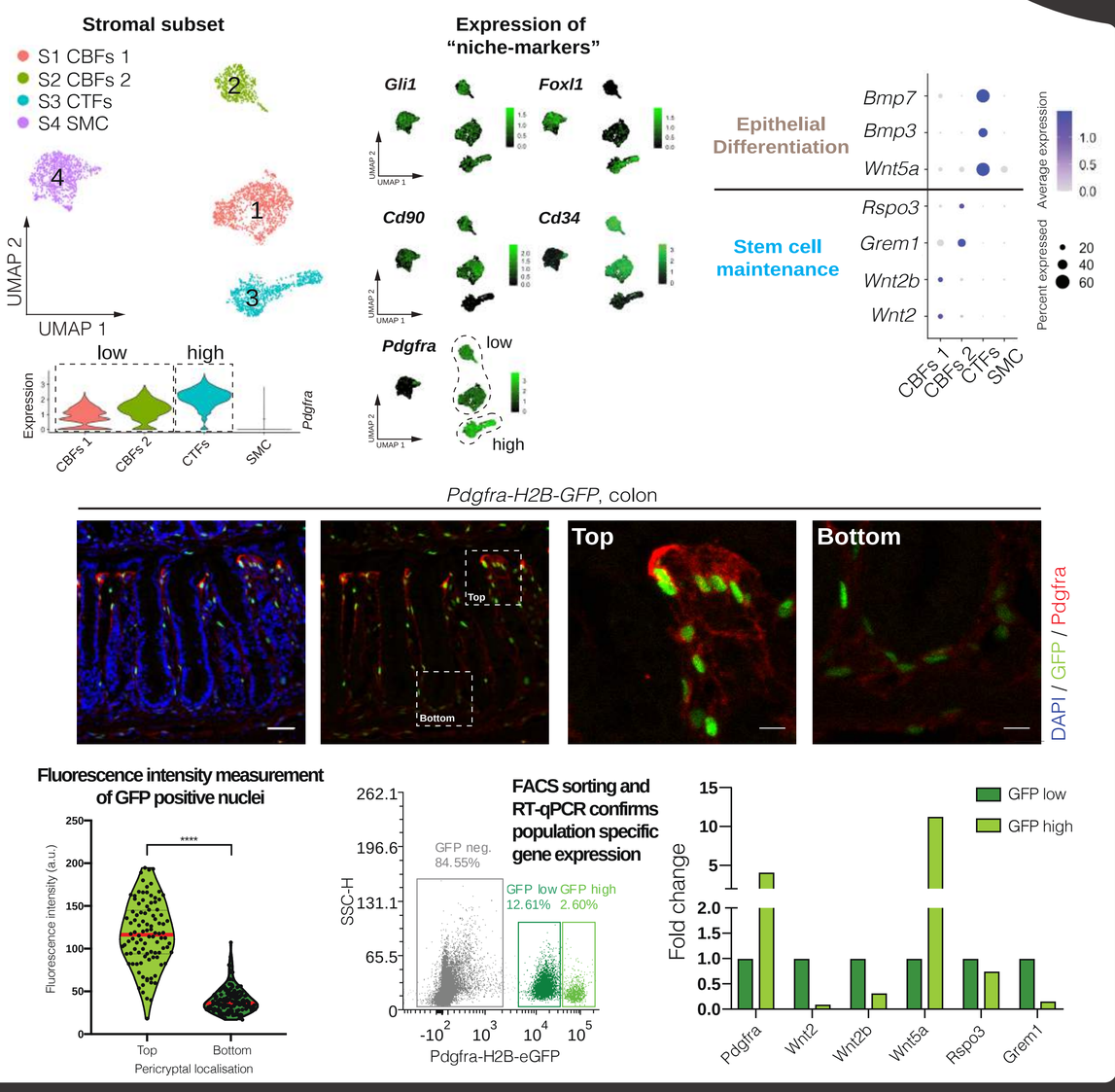


Orthotopic murine model of metastatic colorectal cancer

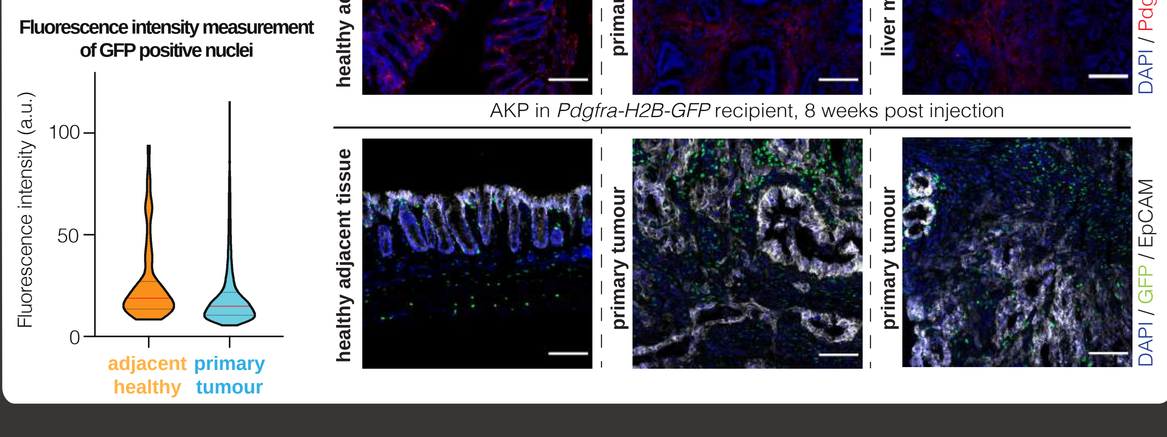




CTFs (*Pdgfra*^{high}) and CBFs (*Pdgfra*^{low}) mark distinct signalling hubs along the crypt axis that control stem cell proliferation and epithelial differentiation in the murine colon



Tissue-resident CTFs (*Pdgfra*^{high}) and CBFs (*Pdgfra*^{low}) are constituents of the murine colonic tumour microenvironment



Conclusion

- Unbiased analysis of murine colon landscape reveals complexity and heterogeneity of epithelial and mesenchymal cells.
- Crypt-bottom fibroblasts (CBFs), close to the intestinal stem cells express low levels of Pdgfra and secrete canonical Wnt ligands, Wnt potentiators, and bone morphogenic protein (Bmp) inhibitors, thereby maintaining the intestinal epithelial stem cells.
- Crypt-top fibroblasts (CTFs) exhibit high Pdgfra levels and secrete noncanonical Wnts and Bmp ligands, inducing differentiation in the neighbouring epithelial cells.
- CBFs and CTFs identity is conserved in the human colon, making them compelling cell populations to study both in health and disease.
- Colonoscopy-guided, orthotopic injection of colonic cancer organoids presents a versatile platform to study the biology of primary and metastatic tumours
- CBFs and CTFs are constituents of the murine colonic tumour microenvironment

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