LABORATORY OF

# CELL AND DEVELOPMENTAL BIOLOGY

Stem cells, signalling pathways, gastrointestinal tract, cancer, haematological disorders

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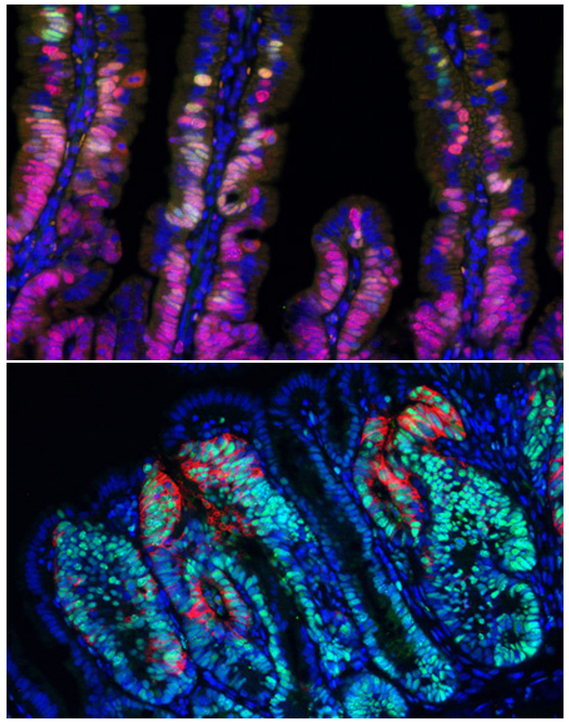
In the picture: 1. Kořínek Vladimír | 2. Kříž Vítězslav | 3. Danačíková Šárka | 4. Onhajzer Jakub | 5. Hrčkulák Dušan | 6. Šloncová Eva | 7. Galušková Kateřina | 8. Zimolová Veronika

The tissues of the adult organism contain a population of tissue-specific stem cells that form the cellular basis for the homeostatic maintenance of the adult tissue. Our aim is to elucidate the molecular mechanisms that influence the fate of normal and transformed adult stem cells in the intestine and the haematopoietic system.

Since the fate of intestinal stem cells is determined by the Wnt signalling pathway, one of our goals is to find and characterise genes that are regulated by this pathway. The first oncogenic mutation is thought to confer a selective advantage to future cancer cells that proliferate and form the first neoplastic lesion. Interestingly, our results suggest that the transformed cell activates a specific transcriptional programme depending on its position in the gut to ensure its long-term survival in the tissue. Importantly, only a cell that remains in the body for a long time can accumulate additional changes that drive tumour growth and progression. The identity of somatic stem cells is determined by a specific microenvironment called the stem cell niche, which allows tight control of tissue homeostasis. Recently, we discovered that subepithelial mesenchymal cells form the intestinal stem cell niche by secreting Wnt ligands that promote stem cell renewal. We further characterise specific features of niche cells.

Our research interests also include the molecular basis of haematological diseases, especially disorders related to red blood cell production and renewal. Myeloproliferative neoplasms (MPN) represent a group of diseases that arise from genetic defects in haematopoietic stem cells. Our aim is to identify the genetic predispositions for MPN and define their impact on different cellular backgrounds. We have shown that germline (or acquired) mutations in the gene encoding Janus kinase 2 (JAK2) amplify the oncogenic JAK2/STAT signalling pathway and cause a specific clinical course of the disease in MPN patients.

We use genetically modified (transgenic, gene knockout or knock-in) mice as the main experimental tool. Besides in vivo models, we also use intestinal organoid cultures obtained from healthy or tumour tissue. To investigate the genetic basis of haematological malignancies, we perform next-generation sequencing of genomic DNA isolated from human samples.



Top: Fluorescence microphotography documenting the heterogeneity of transformed cells in the early stages of tumour formation. Localization of Msx1 (green fluorescence signal) and PCNA (red fluorescence signal) proteins in a mouse model of small bowel cancer 4 days after the first oncogenic mutation. Samples were counterstained with DAPI (blue fluorescent nuclear signal). Actively proliferating cells are PCNA positive (note that the purple staining is the result of coalescence of blue and red fluorescent signal). These cells are mainly found in epithelial invaginations, the crypts. In contrast, Msx1 (mainly) labels transformed cells in the villi of the small intestine; some of these cells express Msx1 and PCNA together (yellow fluorescence). Bottom: Fluorescence micrograph of epithelial cells stained for the proliferation marker PCNA (green fluorescence signal) and cells positive for Trop2 protein (red fluorescence signal) in small intestinal tumors arising in an experimental mouse 6 weeks after inactivation of the tumor suppressor Apc; the sample was contrast stained with DAPI (blue fluorescence signal in the nucleus).

Selected publications: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