Laboratory of Cell and Developmental Biology

Colorectal cancer, Hypermethylated in Cancer 1, intestinal stem cells, TCF/LEF transcription factors, Wnt signalling

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The single-layer epithelia of the small intestine and colon represent the most rapidly self-renewing adult tissue that completely regenerates approximately every five days. The long-lived stem cells located at the bottom positions of microscopic invaginations called crypts feed an upward compartment of transit-amplifying cells. On migrating up, cells terminally differentiate towards secretory goblet and enteroendocrine cells or absorptive enterocytes. Paneth cells of the small intestine are the only exception to this scheme. These cells produce antibacterial agents and stay at the crypt base, where they persist for three to six weeks.

The proper maintenance of epithelial architecture is controlled by various signalling pathways that regulate the balance between the opposing processes of proliferation and differentiation. Importantly, the majority of these pathways are deregulated in cancer.

The scientific goal of the laboratory is to characterize the molecular mechanisms driving the fate of healthy or diseased intestinal epithelial cells. Since the so-called Wnt pathway is the principal signalling network regulating behaviour of intestinal stem cells, our main focus is to identify genes activated by the Wnt pathway and/or encoding proteins directly involved in the intracellular signal transduction cascade. An important result in recent years was the identification of Troy as a novel modulator of Wnt signalling in the population of fast-cycling stem cells of the small intestine. Particular types of intestinal cancer, both sporadic and hereditary, can be recapitulated in genetically engineered mice. Therefore, the laboratory is using the gene-targeting technology in mouse embryonic stem cells to produce mouse strains that can bring new insights about the signalling mechanisms functioning in the gut tissue. Furthermore, we generated several "reporter" mice allowing lineage tracing experiments in mouse embryonic and adult tissues.

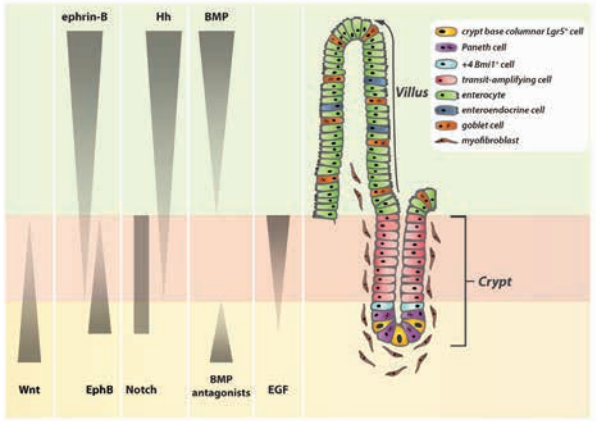

Fig. 1. Architecture of the small intestine epithelium and pathways governing its fate. The proper homeostasis of the intestinal epithelium is regulated by an interconnected network of principal signalling pathways that govern the balance between proliferation and lineage specification.

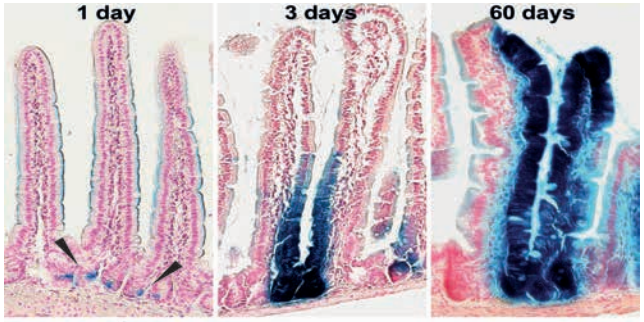

Fig. 2. Lineage tracing in the intestinal epithelium of the Troy-CreERT2 transgenic mice crossed with Rosa26-STOP-lacZ reporter mice. Histochemical detection of the LacZ activity in the duodenum 1 day, 3 days and 60 days after tamoxifen administration. One-day induction generates LacZ-positive cells located at the crypt base (black arrowheads). At later time points, "blue" cell clones were moving upwards from the crypt and reached the top of the villus.

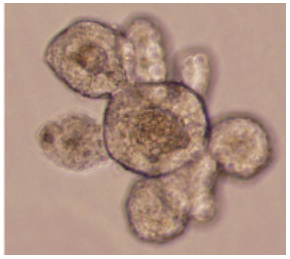

Fig. 3. Stereomicroscopic images of the organoid established from the intestinal crypt.

- Ministry of Education, Youth and Sports of the Czech Republic, 2B06077 - High throughput analysis of chromatin structure for development of novel diagnostic and therapeutic approaches in cancer, 2006-2011, V. Kořínek
- GA Charles University, Interaction of HIC1 and APC, two tumour suppressors involved in Wnt signalling, 2010-2011, V. Pospíchalová
- GA Charles University, Molecular mechanisms of the intestinal tumorigenesis upon loss of the APC tumour suppressor gene and aberrant activation of the Wnt signalling pathway, 2011, L. Tůmová
- GA CR, Intercellular signalling in development and disease; 2009-2012, V. Kořínek (Co-investigator)
- GA CR, GAP304/11/1252 - Bacteria in etiology, prevention ant therapy of experimentally induced intestinal inflammation and colon cancer, 2011-2014, V. Kořínek (Co-investigator)
- GA CR, GAP305/11/1780 - Wnt signalling in self-renewal and tumorigenesis of the intestinal epithelia, 2011-2014, V. Kořínek
- Ministry of Industry and Trade, FR-TI4/802 - Development of new chemical compounds with anti-tumour activities or use in regenerative medicine, 2012-2014, V. Kořínek (Co-investigator)
- GA CR, GAP305/12/2347 Molecular mechanisms of the tumour suppressor function of the HIC1 gene, 2012-2015, V. Kořínek
- Operational Programme 'Education for Competitiveness', Founding the Centre of Transgenic Technologies, 2012-2015, V. Kořínek (Guarantor)

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From the left:
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Not in the picture:
Lenka Doubravská, PhD / Postdoctoral Fellow (maternity leave) · Vendula Pospíchalová, MSc / PhD Student (until September, 2012) · Nikol Baloghová / Diploma Student (since 2012) · Dušan Hrčkulák / Diploma Student (since 2012)