Laboratory of Cell and Developmental Biology

Colorectal cancer, liver, stem cells, TCF/LEF transcription factors, Wnt signalling

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The proper maintenance of adult tissues 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 elucidate the molecular mechanisms influencing the behaviour of normal and transformed intestinal and liver cells. Since the fate of these cells is determined by the so-called Wnt signalling pathway, our main focus is to identify genes activated by the Wnt pathway and/or encoding proteins directly involved in the intracellular signal transduction cascade.

The activity of the Wnt pathway undergoes complex regulation that ensures its proper functioning. The regulation may occur at several levels and includes both positive and negative feedback regulators. Recently, we characterized a negative feedback regulator of the Wnt signalling pathway, naked cuticle homologue 1 (Nkd1), in the intestine and liver and in tumours originating from these organs. We generated transgenic mice to trace Nkd1 expression in the gut and liver. Furthermore, we employed two mouse models of intestinal cancer to localize Nkd1 in tumour tissues. We also utilized an experimental collection of human sporadic tumours of the colon and liver to show that NKD1 can serve (along with three other genes involved in Wnt signalling) as a robust marker of neoplasia linked to aberrant Wnt signalling. Another important result in the current years was the identification of Troy as a novel modulator of Wnt signalling in stem cells of the intestinal epithelium. In addition, we identified monensin, a carboxylic polyether antibiotic, as a potent and specific inhibitor of the Wnt signalling pathway. The inhibitory effect of monensin on Wnt signalling was observed not only in various cell lines (including cells derived from human colonic carcinomas), but also in several in vivo tests such as the tail fin regeneration assay in zebrafish and body axis duplication assay in Xenopus. Importantly, monensin treatment significantly reduced the tumour burden in mice carrying multiple intestinal neoplasia. Since these mice represent an animal model of the human hereditary familial adenomatous polyposis (FAP) syndrome, our data imply that the antibiotic might be used as a chemopreventive agent for reduction of neoplastic growth in individuals suffering from the FAP syndrome.

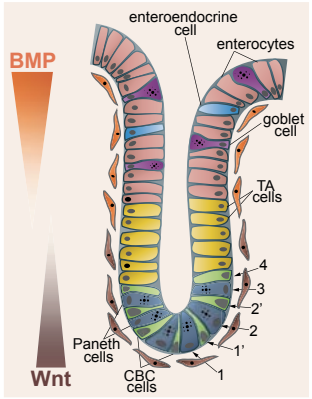

Fig. 1. Cellular architecture in the crypt of the small intestine
Intestinal homeostasis is sustained by crypt base columnar (CBC) stem cells that occupy the crypt floor in positions alternating with post-mitotic Paneth cells. The stem cells stochastically self-renew or give rise to committed daughter transit amplifying (TA) cells. As the progenitors further ascend the crypt, mesenchyme-derived BMP signalling promotes their differentiation towards predominant absorptive enterocytes, or secretory goblet and enteroendocrine cells that produce mucus and release peptide hormones, respectively. The pluripotency and proliferation of stem cells is maintained by Wnt cues, redundantly supplied by the stem-neighbouring Paneth cells and subepithelial myofibroblasts. Numbers assigned to individual cell positions in the crypt are indicated.

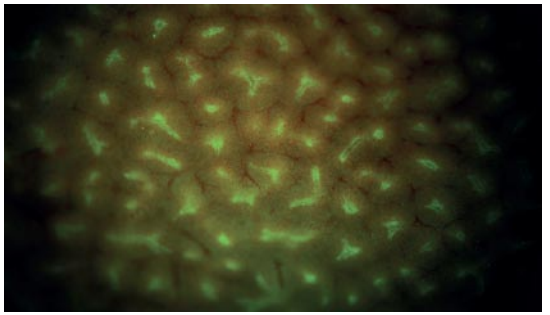

Fig. 2. Zonation of the liver visualized in Nkd1-CreERT2 transgenic mouse
Whole-mount fluorescent image of the Nkd1-CreERT2+/Rosa26R-EYFP liver taken four days upon tamoxifen administration. The perivenous hepatocytes are labelled by green fluorescence. Scale bar: 0.4 mm.

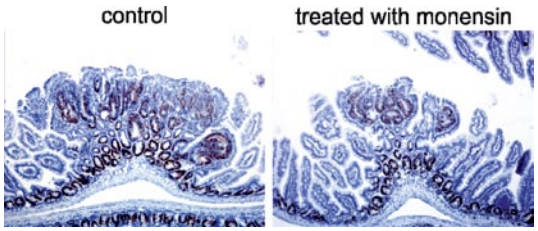

Fig. 3. Monensin treatment decreases the size of adenomas in mice
Haematoxylin- and anti-Ki67-stained sections of the jejunum of APC+/Min mice treated with monensin or vehicle alone (control).

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From the left: Eva Šloncová, MSc / Research Assistant, Kateřina Galušková, MSc / Research Assistant, Dušan Hrčkulák MSc / PhD Student, Oľga Babošová, MSc / PhD Student (since 2014), Vítězslav Kříž, PhD / Postdoc, Bohumil Fafílek, PhD / Postdoc, Vladimír Kořínek, PhD / Head of Laboratory, Martina Vojtěchová, PhD/ Research Fellow, Lucie Láníková, PhD / Postdoc, Nikol Baloghová/ Diploma Student, Lucie Janečková, PhD / Postdoc (since 2014), Monika Horázná, MSc / PhD Student

Not in the picture: Michaela Krausová, PhD/ Postdoc, Jiří Švec, MD, PhD / Postdoc, Jitka Stančíková, MSc / PhD Student (until 2014)