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Colorectal cancer, Wnt signalling, TCF/LEF transcription factors, Hypermethylated in Cancer 1, HIC1

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The majority of tissues in the adult organism contain a population of tissue-specific stem cells. These multipotent cells are involved in homeostatic self-renewal and tissue repair processes. The biology of the stem cells is driven by a limited set of signalling cascades. The deregulation of these cascades can ultimately lead to the cellular transformation and formation of tumours. This clearly indicates the connection between the stem cell physiology and cancer. The scientific goal of the laboratory is to elucidate molecular mechanisms influencing behaviour of normal and diseased intestinal epithelial cells. Since the fate of these cells is determined by the so-called Wnt signalling pathway, our main focus is to find genes regulated by the Wnt pathway and/or encoding proteins directly involved in the signalling process. The important result in the current years was the identification of the HIC1 (Hypermethylated In Cancer 1) tumour suppressor as a novel modulator of the Wnt signalling cascade. Moreover, using various molecular biology approaches we discovered several other proteins (e.g. Dazap2 and Troy) that participate in Wnt signalling or act in downstream molecular events triggered by active Wnt signalling. Currently, the laboratory used the gene targeting technology in mouse embryonic stem cells to produce a novel mouse strain containing a so-called conditional allele of the Hic1 gene. Furthermore, we generated several "reporter" mice allowing lineage tracing experiments in mouse embryonic and adult tissues.

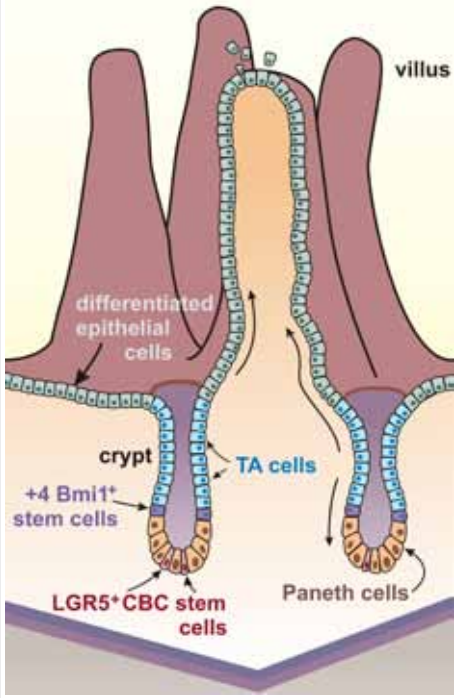

Fig. 1. Epithelium of adult small intestine. TA, rapidly dividing transit-amplifying cells (adopted from Reya and Clever, Nature, 2005).

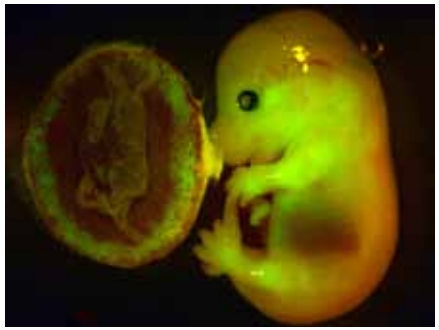

Fig. 2. Hic1 reporter mouse. The picture shows a mouse embryo at E 14.5 and its placenta. The animal was generated by a "knockin" of the enhanced yellow fluorescent protein (EYFP) into the Hic1 locus. These mice allow tracing Hic1 expression using EYFP-derived fluorescence as the surrogate marker. Notice the positive signal in the skeletal elements of the embryo and the junctional zone of the placenta.

Fig. 3. The lineage tracing experiment in the small intestine. The section of the gut tissue derived from the Troy-CreERT2 transgenic mice crossed with Rosa26-STOP-lacZ reporter mice 24 hour after tamoxifen injection. The blue stainings corresponding to the expression of the Troy gene is mainly found in the putative stem cells residing at the bottom of the crypts.

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- Ministry of Education, Youth and Sports of the Czech Republic, 1M0506 – Centre for Molecular and Cellular Immunology, 2005-2011, V. Kořínek
- GA CR, GA204/07/1567 – Tumour suppressors in the Wnt signalling pathway, 2007-2010, V. Kořínek
- GA CR, GD204/09/H058 – Intercellular signalling in development and disease; 2009-2012, V. Kořínek, J. Turečková
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