LABORATORY OF

CELL AND DEVELOPMENTAL BIOLOGY

Stem cells, signalling pathways, intestinal epithelium, cancer, haematological disorders

Vladimír Kořínek

more information

e-mail

Tissues in the adult organism contain a population of tissue-specific stem cells that provide the cellular basis for homeostatic maintenance of adult tissues. The stem cell behaviour is controlled by multiple signalling pathways that regulate stem cell renewal and the balance between cell proliferation and differentiation. Genetic alterations in tumour suppressors and proto-oncogenes lead to deregulation of these cascades, resulting in cellular transformation and tumour formation. Our research is focused on three scientific themes:

Research theme 1 – Tumour-initiating programme in the intestine

Since the fate of intestinal stem cells is determined by the Wnt signalling pathway, our aim is to find genes that are regulated by Wnt signalling. Advanced colorectal tumours display high heterogeneity; however, tumour-initiating mutation in the Apc tumour suppressor underlies the origin of the vast majority of them. Our recent results indicate that depending on the position in the intestine, the transformed cell activates a specific transcriptional programme to ensure its long-term survival in the tissue.

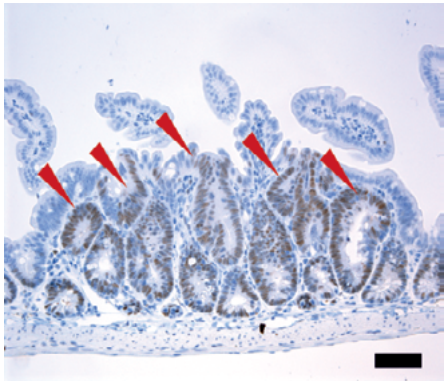

Figure 1. Microadenomas (red arrowheads) arising in the Apc-deficient small intestine. Immunohistochemical localization of proliferating cell nuclear antigen (PCNA; brown cell nuclei) in the small intestine of ApccKO/cKO Lgr5-EGFP-IRES-CreERT2 mice 21 days after tamoxifen administration. Sections were counterstained with haematoxylin (blue nuclear signal); scale bar: 0.3 mm.

Research theme 2 – Adult somatic stem cell niche

The identity of somatic stem cells is determined by a specific microenvironment, so-called stem cell niche, which promotes a strict control over tissue homeostasis. Our aim is to depict the complex interactions between the stem cell niche and stem cells during epithelial renewal and in colon cancer. Recently, we have discovered that sub-epithelial mesenchymal cells constitute the intestinal stem cell niche by secreting Wnt ligands that promote the stem cell renewal.

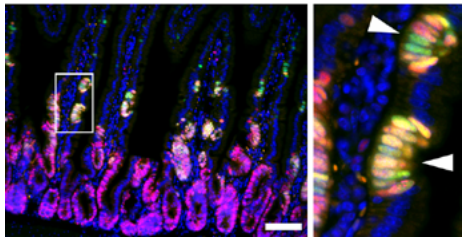

Figure 2. Msx1 marks ectopic crypts formed on the small intestinal villi upon Apc loss. Fluorescent microscopy images of Msx1 (green fluorescent signal) and PCNA (red florescent signal) protein localization in ApccKO/cKO Villin-CreERT2 small intestine 4 days after tamoxifen administration. Ectopic crypts containing Msx1- and PCNA-positive cells are formed on the villi (white arrowheads in inset). Some of these cells co-express Msx1 and PCNA (yellow fluorescence). Specimens were counterstained with DAPI (nuclear blue florescent signal). Notice that the purple colour results from the coalescence of the blue and red fluorescent signal. Scale bar: 0.15 mm.

Research theme 3 – Genetic basis of haematological malignancies

Myeloproliferative neoplasms (MPN) represent a group of disorders arising due to the genetic defect(s) in haematopoietic stem cells. While the concept of somatic driver mutations in MPNs is well established, the contribution of other factors, such as germ-line variants that modulate the risk of MPN development by promoting acquisition of additional somatic mutations, is less understood. Our aim is to identify the new genetic predispositions to MPN and characterize them. We have demonstrated that a germ-line (or acquired) mutation in the gene encoding kinase JAK2 enhances oncogenic JAK2/STAT signalling and causes a specific clinical course of the disease in MPN patients.

Selected publications:

1. Babosova O, Kapralova K, Raskova Kafkova L, Korinek V, Divoky V, Prchal JT, Lanikova L* (2019) Iron chelation and 2-oxoglutarate-dependent dioxygenase inhibition suppress mantle cell lymphoma's cyclin D1. *J Cell Mol Med*, **23**:7785-7795.
2. Horazna M, Janeckova L, Svec J, Babosova O, Hrckulak D, Vojtechova M, Galuskova K, Sloncova E, Kolar M, Strnad H, Korinek V* (2019) Msx1 loss suppresses formation of the ectopic crypts developed in the Apc-deficient small intestinal epithelium. *Sci Rep*, **9**:1629.
3. Degirmenci B, Valenta T*, Dimitrieva S, Hausmann G, Basler K* (2018) GLI1-expressing mesenchymal cells form the essential Wnt-secreting niche for colon stem cells. *Nature*, **558**:449-453.
4. Mambet C, Babosova O, Defour JP, Leroy E, Necula L, Stanca O, Tatic A, Berbec N, Coriu D, Belickova M, Kralova B, Lanikova L, Vesela J, Pecquet C, Saussoy P, Havelange V, Diaconu CC, Divoky V*, Constantinescu SN* (2018) Cooccurring V617F and R1063H mutations increase JAK2 signaling and neutrophilia in myeloproliferative neoplasms. *Blood*, **132**:2695-2699.
5. Hrckulak D, Janeckova L, Lanikova L, Kriz V, Horazna M, Babosova O, Vojtechova M, Galuskova K, Sloncova E, Korinek V* (2018) Wnt effector TCF4 is dispensable for Wnt signaling in human cancer cells. *Genes* **9**(9).

In the picture: 1. Hrčkulák Dušan | 2. Švec Jiří | 3. Vojtěchová Martina | 4. Berková Linda | 5. Danačíková Šárka | 6. Kořínek Vladimír | 7. Janečková (Tůmová) Lucie | 8. Šloncová Eva | 9. Galušková Kateřina | 10. Láníková Lucie | 11. Šťastná Monika | 12. Kříž Vítězslav