Abstract

The plot of this PhD thesis is dedicated to investigation of the molecular pathways and events and their disruptions in the gastrointestinal tract (further abbreviated as GIT). The major role in this part plays the Wnt signaling pathway. This marvelous multipurpose machinery is responsible for epithelia renewal from stem cells (SCs) in the stomach and intestine, and for correct zonation and function of hepatic units. Of note, the Wnt pathway directs also development of embryo as well as homeostasis of many tissues apart from GIT in all metazoans, thus its flawless function is indispensable from one´s origin to death. The main part of the thesis follows canonical Wnt signaling in its physiological condition and, in contrast, with pathological disturbances. This issue can be taken by variety of means as it is described in attached publications.

The first publication deals with searching for new participants of Wnt signaling and their functions and describing unique markers of SCs in the intestine. *Troy*, the member of tumor necrosis factor receptor (TNFR) superfamily, was identified as a novel marker of intestinal SCs by probing microarray data from chromatin immunoprecipitation obtained in cultured colorectal cancer cell lines. Moreover, we found that *Troy* is a Wnt target gene inhibiting the signaling pathway in the feedback loop. From the same microarray data we also chose a gene encoding *naked cuticle homolog 1* (*Nkd1*) for further analysis. This gene was already determined as a Wnt-regulated inhibitor of the pathway, but a little was known about its role in intestinal homeostasis and tumorigenesis. Our published results depict *Nkd1* expression in Wnt-responsive cells of the small intestine and liver. Additionally, we found *Nkd1* highly expressed in intestinal lesions of mice. In human patient samples NKD1 was described as a potential marker of intestinal and liver tumors. The next publication describes identification of the unique marker of SCs in the stomach corpus: muscle, intestine and stomach expression 1 (Mist1). This particular protein was previously described as a marker of short-living gastric epithelial progenitors. Our recent study uncovered its novel expression site – quiescent stem cells in the corpus isthmus. The last publication from this group relates to *hypermethylated in cancer (Hic1)*, a tumor suppressor inactivated in many types of tumors. We used a genetically modified mouse strain to identify genes influenced by Hic1 loss. As the most interesting we described Hic1-mediated regulation of *toll-like receptor 2 (Tlr2*) expression. Tlr2 upregulation upon Hic1 depletion leads to switching on proinflammatory pathways [e. g. nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)], that have the potential to initiate tumor growth.

Another approach to investigate molecular relations in the gut is to search for therapeutics, which affect the Wnt signaling pathway leading to tumor growth reduction. We published that monensin, a small compound already used in dairy industry, is able to reduce size of intestinal lesions in mice via decreased Wnt signaling. The particular effect of monensin has not been disclosed yet.

The final publication encompasses the microarray data gained from germ-free (GF) mice compared to conventionally reared (CR) and monoassociated animals populated with a particular bacterial strain. Results confirmed previous data that in GF mice the immune system development is the most impaired. Additionally, we presumed that monoassociation did not rescue immunity development. We described various genes with different expression in GF mice, which are linked to inflammation, intestinal development and cancer.