Abstract

The Wnt pathway is one of the major signaling cascades contributing to multiple cellular processes during embryogenesis, and adult tissue homeostasis and regeneration. Moreover, aberrant activation of the Wnt signaling pathway is connected with development of neoplasia, notably colorectal cancer.

The aim of the thesis was to identify new ways of the Wnt pathway regulation to understand better physiological as well as non-physiological mechanisms of Wnt signaling. The results are summarized in four publications.

The first article deals with TROY, a member of tumor necrosis factor receptor family. We identified *TROY* as a Wnt target gene during our search for Wnt responsive genes in colorectal cancer cell lines. Additionally, we detected expression of *Troy* in tumors of two mouse models of intestinal cancer. In the healthy gut, Troy is produced in fast cycling intestinal stem cells where negatively regulates the Wnt pathway.

The second study focuses on processing and posttranslational modification of murine Wnt1 and Wnt3a. Wnts are glycosylated and double acetylated by lipid adducts and our results revealed that O-linked acylation of serine is required for the subsequent S-palmitoylation of cysteine. Moreover, acylation of Wnts is connected with their signaling activity which is related to Wnt1 and Wnt3a ability to associate with the extracellular matrix.

The third report describes the generation of conditional knock-out and citrine-reporter alleles of the gene *Hic1*, a tumor suppressor gene which was previously described in our laboratory as a negative regulator of the Wnt signaling pathway.

Finally, protein Dazap2 a small, evolutionary conserved, ubiquitously expressed gene was identified as an interacting partner of the TCF proteins. We detected Dazap2 modulates the affinity of TCF4 for its DNA recognition motif and thus enhance the expression of the Wnt signaling target genes.