ABSTRACT

The Wnt signalling pathway is one of the major signal transduction cascades in all multicellular organisms ensuring successful embryogenesis, regeneration and tissue homeostasis. Accordingly, mutations in the pathway lead to birth defects and to various diseases, most notably cancer.

β-catenin is a central mediator of canonical Wnt signalling (also called Wnt/β-catenin signalling). In unstimulated cells β-catenin is being constantly destabilized by a multiprotein complex and degraded in the proteasome. Unlike in the presence of Wnt ligands when they engage their receptors, degradation complex disassembles, β-catenin is stabilized and translocates to the nucleus to serve as a co-activator of Lef/Tcf transcription factors and to drive the transcription of Wnt target genes. Wnt/β-catenin signalling is tightly regulated at various levels by as many as hundred proteins.

This thesis is based on four original articles and unpublished data that aim to increase the knowledge of the regulation of the Wnt signalling pathway. The first publication focuses on sequential posttranslational processing of the Wnt ligands. The next article discusses the positive role of nuclear protein Dazap2 in determination of the Wnt/β-catenin signalling outcome. The third study reports TROY as a novel negative modulator of the Wnt pathway which reduces the levels of Wnt signalling in LGR5-positive stem cells of intestinal epithelium. Finally, the last issue depicts generation of two gene-targeted mouse strains that enable studying the role of Hic1 *in vivo*. The last chapter of the thesis describes unpublished data on the nature of HIC1 bodies, HIC1 physical interaction with members of the Wnt pathway, novel target genes and consequences of conditional *Hic1* deletion in the intestinal epithelium which results in mis-regulation of secretory cell types and enhanced tumourigenesis.

In conclusion, our findings contributed to the field of regulation of a fundamental signalling pathway in development and disease.