ABSTRACT

Wnt signalling represents an important mechanism participating in control of cellular and developmental processes, including establishment of cell polarity, cell fate specification, stem cell self-renewal, tissue patterning and organogenesis, homeostasis maintenance and regeneration. Misregulation of the Wnt signalling during embryogenesis leads to developmental defects while aberrant activation later in development is associated with degenerative diseases and a number of cancers.

The presented PhD thesis is based on four original publications that deal with the post-translational modifications of Wnt ligands and molecular mechanisms contributing to the regulation of a transcriptional profile of the so-called canonical Wnt pathway.

Wnt signalling pathway is used repetitively both in time and different cellular contexts throughout development of multicellular organisms. Inevitably, in each single situation β-catenin/TCF complexes, the downstream effectors, induce only subsets of all potential target genes. How this differential tissue- and stage-specific control over various subsets of target genes is achieved with such a limited number of nuclear effectors is not fully understood. Along with the expression of specific LEF/TCF family members or their variants containing different functional domains and the abundance of post-translational modifications, apparently, binding to various partners in distinct transcriptional complexes can render LEF/TCFs abilities required for launching context-dependent expression profiles.

The first publication reports on the identification of C-terminal binding protein (CtBP) that represses the TCF4-mediated transcription of the known Wnt target gene *Axin2* in human embryonic kidney cells. The second study investigates the consequence of TCF4 association with the tumour suppressor Hypermethylated in cancer (HIC1). The suppressive effect of HIC1 is likely based on the recruitment of β-catenin/TCF4 complexes to the specific subnuclear structures that are spatially and functionally separated from the transcription of the Wnt target genes. The third article presents the identification of an evolutionarily conserved protein DAZap2 (Deleted in azoospermia-associated protein 2) as a context-dependent modulator of a subset of Wnt target genes. Finally, the fourth report examines roles of post-translational modifications in secretion, extracellular movement and signalling activity of mammalian Wnt1 and Wnt3a ligands.

Our findings have broadened the knowledge of molecular mechanisms that affect the Wnt signalling.