Regulation of the Wnt signaling pathway

Summary

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Supervisor:	Prof. Dr. Tobias Madl
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between July 15, 2019 00:00 and September 15, 2019 23:59 (Europe/Zurich)

Description

Background:

The canonical Wnt signaling pathway plays a pivotal role in a wide range of developmental and physiological processes. Wnt signaling controls essential cellular decisions on growth and differentiation during embryonic development and in adult tissue homeostasis (1,2). Inappropriate activation of the Wnt pathway due to mis-regulation - caused for example by mutations - is frequently linked to a plethora of human diseases such as cancer (1-5).

A key event of the Wnt pathway is the regulated degradation of the transcription co-activator β-catenin by the *β-catenin destruction complex*, consisting of Glycogen synthase kinase 3β (GSK3β), Casein Kinase 1 (CK1), Adenomatous Polyposis Coli (APC), the scaffold protein Axin-1 and the transcription co-factor β-catenin (6; Fig. 1). In the absence of Wnt ligand, free cytoplasmic β-catenin is trapped in the destruction complex, phosphorylated by GSK3β (Ser33/Ser37/Thr41) (7-11) following priming phosphorylation by CK17,11 (Ser45), ubiquitinated, and degraded via the proteosomal pathway (12,13). The Wnt pathway gets activated upon binding of a Wnt ligand to the cell-surface receptor Frizzled (Fz) and low-density lipoprotein receptor-related protein (LRP) 5/6, resulting in the deactivation of the β-catenin phosphorylation/degradation cascade (2,14-17). The resulting increase in the cytoplasmic and subsequently also the nuclear levels of free β-catenin leads to transcription activation of Wnt target genes by binding of β-catenin to the Tcf (T-cell factor)/Lef (lymphoid enhancing factor) family of transcription factors (12,13,17).

Hypothesis and objective:

Based on our recent studies and supported by our preliminary data, we propose to study key elements of the Wnt pathway and their regulation by post-translational modifications. We propose to reveal the structural and functional mechanisms of Wnt pathway and to develop drugs targeting newly discovered key interactions by:

Aim 1) studying interaction, structure and function of the novel protein complexes

Aim 2) studying regulation of the novel protein complexes by post-translational modifications, disease mutations, and co-factors

This will set the base for the development discovery of early-stage drugs for the treatment of a plethora of diseases, such as human cancers related to distortions in Wnt signaling.

Methodology:

The PhD candidate will make use of our recent methodological achievements for studying structure of large protein complexes by combining solution Nuclear Magnetic Resonance (NMR) spectroscopy, and molecular modeling (18-23), and extend it with complementary approaches such as Mass Spectrometry (MS) and cell biology.

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