Molecular studies of the mammalian basic helix-loop-helix transcription factor TCF4 and its Drosophila homologue Daughterless in the nervous system

Summary

Taltech School of Science, Department of Chemistry and Biotechnology offers a four-year PhD student position in molecular neuroscience

Research field:	Chemistry and biotechnology
Supervisors:	Prof. Dr. Tõnis Timmusk Mari Palgi
Availability:	This position is available.
Offered by:	School of Science Department of Chemistry and Biotechnology
Application deadline:	Applications are accepted between June 01, 2020 00:00 and July 03, 2020 23:59 (Europe/Zurich)

Description

TCF4 is a broadly expressed basic helix-loop-helix transcription factor that binds to E-box DNA sequences as a homo- or heterodimer. TCF4 gene is implicated in susceptibility to schizophrenia, and mutations in TCF4 cause mild-to-moderate intellectual disability (MMID) and Pitt-Hopkins syndrome (PTHS), a rare developmental disorder characterized by severe motor and mental retardation. We have previously demonstrated that human TCF4 gene is transcribed using numerous 5' exons yielding in TCF4 protein isoforms with different N-termini that vary in their ability to regulate transcription (Sepp et al., PLoS ONE, 2011). Additionally, we have found that PTHS-associated mutations impair the functions of TCF4 by diverse mechanisms (Sepp et al., Hum Mol Genet. 2012). Our screen for signalling pathways and compounds that upregulate the activity of TCF4 in neurons has identified, among others, cAMP and resveratrol (Sepp et al., J Neurosci. 2017). Drosophila has a single homologue of TCF4, Daughterless (Da), providing an excellent model system to study the function of Da. We have shown that human TCF4 can rescue Da deficiency during fruit fly embryonic nervous system development. All studied PTHS-associated mutations that we introduced into Da led to similar either dominant negative or hypomorphic effects in vivo as were known for these mutations in TCF4 in vitro (Tamberg et al., Biol Open, 2015). The aim of the PhD project is to further study the expression and molecular mechanism of action of TCF4 and its Drosophila homologue Daughterless. Novel disease-associated protein variants will be also functionally characterized to decipher critical pathogenic mechanisms of a disorder and to discover functionally important sites in the protein.

Responsibilities and tasks
The responsibilities of the PhD student will be planning and carrying out experiments and analyzing obtained results, writing and publishing manuscripts based on obtained results.

Qualifications: MSc degree

The applicants should fulfill the following requirements:

- The candidates are expected to have strong expertise in cell and molecular biology techniques

- Additional expertise with rodent and Drosophila model organisms, primary neuron cultures and live cell imaging will also be assets to the project

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