DESCRIPTION FOR THE GENERAL PUBLIC

Cilia are hair-like structures present on the surface of cells. Although two major types of cilia exist (primary and motile cilia), which differ in number and localization in the human body, both primary and motile cilia have a similar, highly conserved ultrastructure, and share a lot of their proteins. Both primary and motile cilia are important for proper functioning of the organisms, as evidenced by a large group of multi-systemic genetic disorders, known as ciliopathies. Genetic defects of motile cilia cause primary ciliary dyskinesia (PCD), manifesting with recurrent upper and lower airway infections, male infertility and reversed symmetry of body organs. Genetic defects of primary cilia can have different clinical manifestations, including e.g. obesity, brain, skeletal dysmorphism, intellectual delay, polycystic kidney disease or *retinitis pigmentosa*.

Our laboratory performs long-term genetic and molecular studies on the basis of PCD, the only genetic disease associated with defects of motile cilia. Our recent research in that field has identified several PCD patients with mutations shortening a cilia-related protein, *OFD1.* OFD1 is a protein associated with the formation of primary cilia, and its mutations are usually associated with serious neurological symptoms. Surprisingly, mutations which we have discovered in our patients, have manifested only with symptoms typical for defect of motile cilia, without severe neurological symptoms typical for other OFD1 mutations. Analysis of motile cilia in respiratory of the airways showed impaired structure of the motile cilia, which is consistent with earlier suggestions on the role of OFD1 protein in the formation of motile cilia.

The mutations we have discovered, resulted in shortening of the very end of the OFD1 protein (C-terminus), thus, we would like to characterize the influence of the mutations in this region of OFD1 protein on the process of cilia generation and other OFD1-related aspects of cell biology. Because the observed symptoms may be due to the lack of OFD1 interaction with relevant protein partners, we would also like to study how these OFD1 mutations affect protein interaction networks in primary and motile cilia. We will study epithelial cell lines containing OFD1 mutations, which are known to lead to motile cilia defect. We will also use a fish model, *Danio rerio,* to observe the influence of identified OFD1 interactors specific to motile cilia on the embryo development and formation of motile cilia.

Despite a broad list of OFD1 interactors, which has been generated by recent high-throughput proteomic studies, we still don't have enough knowledge about OFD1 interactions during ciliogenesis, and which OFD1 interactors bind to different parts of OFD1. Thus, it is still impossible to verify, lack of which OFD1-protein interaction(s) is causing defects in functioning of motile cilia observed in patients identified by our laboratory. It is also not known, how various OFD1 mutations affect the binding of OFD1 protein interactors associated with particular cellular processes. Knowledge about the effects of OFD1 shortening on particular protein interactions could allow to identify the OFD1 regions associated with increased risk of specific syndromic symptoms. For patients with OFD1 mutations in these regions, this could lead to more frequent, targeted examinations of particular tissues/organs at risk. This would allow an earlier detection of the decrease in the function of particular organs. Moreover, disease-relevant OFD1 interactions identified in the truncation mutants may potentially become therapy targets for patients with PCD, leading to improved symptoms in these patients. These would lead to reduced disease burden, improved healthcare and increased quality of life of patients with OFD1 mutations.