Abstract

Motile cilia are evolutionary conserved organelles that form protrusions on the surface of many eukaryotic cells. Pathogenic variants in genes encoding structural proteins or proteins involved in the biogenesis of cilia lead to a range of genetic disorders collectively called ciliopathies. A key example of ciliopathy caused by dysfunction of motile cilia is primary ciliary dyskinesia (PCD; OMIM244400). PCD is a rare disease inherited mainly in an autosomal recessive manner and is characterized by a great genetic and clinical heterogeneity. Symptoms of PCD include recurrent respiratory, ear and sinus infections and reduced fertility or infertility; in addition, in about 50% of PCD patients, *situs inversus* is observed.

Although more than 50 genes are known to be involved in the pathogenesis of PCD, in about 30% of patients the genetic basis of PCD remains unknown. Therefore, the search for new pathogenic variants and genes responsible for the occurrence of this disease, combined with confirmation of their role in the functioning of motile cilia, is still a current research challenge. The aim of this doctoral dissertation was to optimize and practically apply *Schmidtea mediterranea* as a model organism to confirm the role of genes associated with dysfunction of motile cilia and the PCD pathogenesis. *S. mediterranea'* movement depends on multiciliated cells covering the ventral site of the planarian body; knockdown of cilia-related genes is manifested by changes in worm locomotion. Although planarians are described as an animal model for studying motile cilia, there is insufficient information in the literature on the use *S. mediterranea* as an *in vivo* model to confirm the role of studied genes in the pathogenesis of PCD.

This dissertation is a collection of four publications that verify the possibility of using *S. mediterranea* to study genes involved in the pathogenesis of PCD. The first publication (a review article) describes the current state of knowledge on the possibility of using planarians to study motile cilia and ciliopathies associated with dysfunction of these organelles. The remaining publications are original papers, the aim of which was to confirm the role of identified pathogenic variants in the *CFAP221* and *CFAP300* genes, and the *POLR2K* gene (a part of which is deleted, together with part of the known PCD gene, *SPAG1*). In order to confirm the role of selected genes in the functioning of motile cilia and the PCD pathogenesis, their silencing was carried out using the RNA interference (RNAi) method in the planarian model. The obtained results allowed to confirm the role of *CFAP221* and *CFAP300* in the pathogenesis of studied disorder and indicated the lack on involvement

of *POLR2K* in PCD. Studies using *S. mediterranea* have demonstrated the evolutionary conserved role of *CFAP221*, *CFAP300* and *SPAG1* in the functioning of motile cilia. *S. mediterranea* after *SPAG1* and *CFAP300* silencing moved several times slower than controls, which was accompanied by a change in the movement pattern; the effect of silencing was similar to the significant impact of the presence of pathogenic variants on the function of respiratory epithelial cells of the PCD patients. The influence of *CFAP221* silencing on the function of motile cilia in worms was more subtle, consistent with mild phenotype observed in patient. The obtained results confirmed that *Schmidtea mediterranea* is a simple, cheap and easily accessible model for studying genes potentially involved in the pathogenesis of PCD.