Lysophosphatidic Acid in Pathogenesis of HNF1B-MODY Syndrome

DESCRIPTION FOR THE GENERAL PUBLIC

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic disorder in human population and the most common form of kidney cystic disease in general. It is caused by gene mutation in *PKD1* and *PKD2* genes. Over the time ADPKD leads to renal failure, dialysis and if avaiable kidney transplant. Molecular studies in this disease revealed that specific intracellular pathways (mTOR signaling and Wnt/beta-catenin pathway) are dysregulated in this disease and then they were connected with cyst growth. Further, animal studies showed that inhibition of mTOR pathway may slow down disease progression what gave basis for drug tests with mTOR inhibitors trials on people. Also, trials with Wnt/beta-catenin inhibitors are currently tested.

Other genetic disease which leads to cyst formation in kidney is *HNF1B*-MODY syndrome caused by mutations in *HNF1B* gene. It is a very rare disease and to be confirmed genetic tests has to be performed. In *HNF1B*-MODY despite renal symptoms other organs are also affect what presents with young onset diabetes, abnormal liver function or neurological features. However, among them it is the kidney failure that is the most dangerous threat to patients' health and life. Unfortunately, up to this date we do not know the molecular basis of cyst formation and insulin resitance (one of the diabetes cause) in *HNF1B*-MODY so no drug which could slow down disease progression was tested so far. Few years ago, our research group conducted a nationwide genetic screening of monogenic forms of diabetes in children. Thus, we were able to identify and molecularly diagnose 9 families with this disease in polish population – first such group in Poland. We also collected biological material for further tests. After preliminary test, we identified highly bioactive compound – lysophosphatidic acid (LPA) - to be elevated in blood (serum) of those families. In literature, we found clues that LPA may be associated with two impornat intracellular signaling pathwats - mTOR pathway and with Wnt/beta-catenin. Prevoiusly those pathways were associated with cyst formation and insulin resistance. Thus, we want to conduct the experiment on human liver cells culture with dysregulation of *HNF1B* gene to check the effect of LPA stimulation on mTOR and Wnt/beta-catenin activation. As the liver is actively up-taking LPA from the bloodstream the disturbances casued by LPA should be most prominent in those cells. Additionally, we want to use the biological materials from the experiment to performed all genes profile expression in order to evaluate if the activation of the suspected pathways is observed also on genetic level (mRNA). What is more, gene profiling will secure data to search for other pathways that may be up-regulated by LPA stimulation in *HNF1B*-MODY sydrome if our hypothesis about mTOR and Wnt/beta-catenin deregulatios fail to be confirmed.

However, if our *in vitro* experiments show that those pathways are activated thus, the similar therapeutic strategies may be further tested in *HNF1B*-MODY syndrome as their were used in ADPKD.