

Title: Search for alternative signaling pathway associated with pathogenesis of tuberous sclerosis complex.

The aim of the proposal project is to find alternative signaling pathway associated with pathogenesis of tuberous sclerosis complex (TSC) throughout the selection of specific microRNA (miRNAs) and corresponding metabolites.

TSC is a genetic disorder caused by mutations of genes encoding one of two proteins (hamartin or tuberin), that form a complex, mammalian target of rapamycin (mTOR). It leads to hyperactive mTOR signaling and consequent abnormalities in many cellular processes, including cellular growth, proliferation, protein synthesis and metabolic control. In patients with TSC multiple benign tumors (hamartoma) in various organs developed. Inhibitors of mTOR signaling (rapamycin and its analogue everolimus) are effective drugs in TSC patients. Emerging evidence suggested that hamartin and tuberin act not only as a complex, but in some way independently from mTOR pathway. At the same time there is evidence of miRNAs connections with mTOR pathway in various diseases including cancers. Our preliminary results let us to selection of miRNAs (miR-199a, miR-130a, miR-192 and miR-215), which persist dysregulated after mTOR inhibitor therapy. It leads us to hypothesis that those “mTOR independent” miRNAs are involved in alternative signaling pathway connected to additional symptoms of TSC besides the mTOR pathway.

The first step of our project will be miRNA profiling before and after mTOR inhibitor treatment on the larger group of patients with TSC, to find “mTOR independent” miRNAs.

On the other hand, mTOR signaling is connected with a large amount of metabolic processes of the cell. Hyperactive mTOR might cause dysregulation of metabolites in the body, dysregulation of metabolomics. Metabolomics profiling is a global analysis of tissue and biofluids metabolites and their changes, in order to discover new potential biomarkers and reveal information about the general metabolic condition of an organism.

The second step of our project will be metabolomics profiling in the same groups of individuals – to find TSC specific metabolites, which dysregulation will persist after mTOR inhibition. Those finding will allow us to select them as metabolites “mTOR independent”.

The third step of our project will be bioinformatics analysis to find links between selected miRNAs with genes and signaling pathways as well as particular metabolites.

The fourth step of our project will be validation of obtained results on cellular model of TSC. During cell culture experiment we will perform mRNA gene expression profiling connected to selected signaling pathways.

The results of planning project could extend our understanding of the role of alternative to mTOR signaling pathways in pathogenesis of TSC and help to clarify the mechanisms of its actions. It might be the basis for novel target therapy based on selected miRNAs inactivation.