Insulin resistance, i.e. decreased biological response to insulin, is closely associated with obesity and predisposes to type 2 diabetes, hypertension, atherogenic dyslipidemia, atherosclerosis, coronary heart disease, neurodegenerative diseases and many other disorders. Skeletal muscle is the most important site of insulin action, disturbances of glucose metabolism in muscle in insulin resistant states are observed. Despite many studies, molecular mechanisms of insulin resistance remain unclear. There is an ongoing research on the novel factors regulating insulin action.

Skeletal muscle tissue has a great regenerative potential, due to muscle stem cells, termed satellite cells. It was demonstrated that in insulin resistance skeletal muscle had a lower potential for myogenesis, i.e. the formation of muscle tissue. In our previous studies, conducted in the Program Innovative Economy, in mRNA microarray analysis of skeletal muscle collected from young healthy volunteers, we identified genes, which differentiated subjects with high and low insulin sensitivity most significantly. The most important group among these genes are the novel genes associated with myogenesis.

The aim of the project is to assess the role of the novel transcription factors and the nuclear import receptors regulating the process of myogenesis in the pathogenesis of insulin resistance in subjects at risk of type 2 diabetes.

The study groups will consist of 45 subjects, 15 healthy normal-weight individuals (body mass index, BMI between 19 and 25 $kg/m^2$, control group) with normal glucose tolerance; 15 obese subjects with normal glucose tolerance and 15 obese subjects with impaired glucose tolerance and/or impaired fasting glucose. The groups will be matched for sex and age. Only subjects who will give written informed consent will enter the study. Insulin sensitivity will be evaluated with the euglycemic hyperinsulinemic clamp technique. Before the clamp, the biopsy of vastus lateralis muscle will be performed. The part of the obtained material will be preserved for mRNA and protein isolation. The remaining part of the material will be designated for muscle cell cultures.

The first part of the study will be L6 myoblasts cell culture, where the silencing of the examined genes will be performed at the stage of myoblasts and (separately) at the stage of myoutbes to discover their mechanism of action on insulin sensitivity. Culture growth and glucose metabolism will be assessed. Subsequently, in the material from the biopsies analysis of the gene expression will be performed. The culture of muscle satellite cells from the part of the material collected during the biopsies will be developed to confirm the results from L6 myoblasts.

The project may provide an evidence about the role of the novel factors in the pathogenesis of insulin resistance and may contribute to our understanding of their mechanism of action. The results of the project may contribute to the discovery of novel therapeutic options for the prevention and treatment of insulin resistance-related diseases.