## Abstract

Metabolic syndrome is a prevalent disease characterized by concurrent manifestation of insulin resistance, obesity, dyslipidemia, hypertension and other hemodynamic and metabolic disorders. It has multifactorial type of inheritance and its resultant phenotype is determined by both environmental and genetic factors as well as their interactions. That is the main reason why comprehensive analysis of the genetic component of this syndrome is complicated in human population. Genetically designed experimental animal models are significant tools for analysis of genetic architecture of human complex conditions including the metabolic syndrome.

The aim of this Thesis is utilization of functional and comparative genomic tools to uncover pathogenesis of metabolic syndrome aspects and their genetic determinants. We also studied pharmacogenetic interactions of these genetic determinants with drugs affecting particular components of the metabolic syndrome. Establishing and utilizing several genetically designed congenic rat strains, we undertook four different research projects focusing on pharmacogenetic interaction of all-*trans* retinoic acid and ondansetron with differential segment of rat chromosome 8, pharmacogenetic interaction of differential segment of rat chromosome 4 and dexamethasone, determining *Plzf* as a candidate gene predisposing the spontaneously hypertensive rat to hypertension, left ventricular hypertrophy, and interstitial fibrosis. The main results of our projects included validating of congenic strain SHR-*Lx* PD5 as a model of RA-induced hyperlipidemia and glucose intolerance and pharmacogenomic characterization of this interaction. Further we established congenic strain SHR.(PD/BN)8 as a suitable experimental tool for pharmacogenetic and pharmacogenomic analysis of ondansetron effect on lipid and carbohydrate metabolism. We identified *Plzf* as a prominent candidate gene in the development of hypertension, LVH and interstitial fibrosis in SHR. Finally we described the contextually dependent effect of mutant *Cd36* gene on metabolic parameters including its pharmacogenetic interaction with glucocorticoid administration.

We demonstrated that functional comparative genomics provides significant insight into pharmacogenetic interactions of individual genetic determinants of metabolic syndrome.

**keywords:** metabolic syndrome, comparative genomics, pharmacogenomics, congenic strain, insulin resistance, cholesterol, triacylglycerol, all-*trans* retinoic acid, dexamethasone, systems biology, hypertension