Abstract

Metabolic syndrome (MetS) is a worldwide highly prevalent disease defined as a clustering of at least three of the following conditions: central obesity, hypertension, diabetes, high level of low-density lipoproteins, low level of high-density lipoprotein or high level cholesterol. MetS is a multifactorial disease which is caused by both environmental factors and a heritable component. Unfortunately, because of its ever rising worldwide incidence MetS emerges as a worldwide epidemic and a heavy socioeconomic burden. In order to effectively fight the MetS pandemic, it is vital to dissect the genetic background and mechanisms that underlie MetS and its individual components, a goal that is profoundly benefitted by physiological and genetic studies in animal models of MetS.

The aim of this thesis was to dissect the genetic background of metabolic syndrome by using comparative transcriptomic analysis in relevant organs obtained from genetically defined rodent models. Each of our genetically defined rat strains is phenotypically distinct in terms of manifesting individual components of MetS. We present three separate transcriptomic experiments in order to unravel the genetic background of MetS. First, we performed the global comparative transcriptomic analysis of left ventricular tissue from SHR and SHR-derived minimal congenic strain PD5 with attenuated cardiac fibrosis. An overexpression of nuclear orphan receptor *Nur77/Nr4a1* in PD5 and dysregulation of *Nr4a3, Per1* and *Kcna5* were revealed. In the second experiment, we observed phenotypic changes in PD, SHR and BN rat strains, respectively, after high fat diet administration, with subsequent transcriptomic analysis so as to find the pathophysiologic and genetic background of higher susceptibility of PD strain to MetS. A promising candidate gene contributing to higher susceptibility of PD rats to MetS is *Acsm3* (coding for acyl-CoA-synthetase for medium-chain member 3), which belongs to a family of enzymes activating medium chain fatty acids (C4-C14) to beta-oxidation, and which was absent in liver of PD on both mRNA and protein levels. In the third experiment we tried to unravel mechanisms underlying differential liability of SHR and PD5 to glucocorticoid induced metabolic syndrome. We performed comparative transcriptomic analysis of PD5 and SHR liver tissue after dexamethasone treatment unraveling potential genetic determinants; furthermore, we performed a proteomic analysis unraveling potential targets of *Plzf* as a possible candidate gene responsible for this aspect of metabolic syndrome.

Using defined rodent models and transcriptomic approach we mapped several key pathophysiological pathways accountable for development of MetS features and unraveled several candidate genes in the context of these pathways.

Key words: metabolic syndrome, hypertension, congenic strain, SHR, PD, PD5, candidate genes, *Nur77, Acsm3, Plzf*