Epigenetic modifications of insulin pathway genes and their role in obesity-induced insulin resistance

Insulin resistance (IR) along with consequently developed type 2 diabetes (T2D) are nowadays leading problems of modern civilization. In the IR and T2D pathogenesis a key role is played by obesity. Obesity is characterized by hyperglycemia, dyslipidemia and chronic low-grade inflammatory state and is considered as a risk factor for numerous metabolic disorders. Insulin resistance is define as a state, when the proper response of peripheral tissues for physiological insulin level is impaired. Numerous data implicate obesity with DNA hypermethylation at both global and site-specific level, including genes regulating insulin sensitivity. A body of literature documented also the role of histones modifications in obesity-induced insulin resistance development, however, most obtained so far results concerns animals models.

Our previous reports demonstrated that the strongest risk factor of insulin resistance development is BMI (OR 5,21). Based on our preliminary results increased in global DNA methylation increases the risk of insulin resistance development with OR 2,09. Furthermore, our preliminary results suggest that obesity-induced insulin resistance development might be mediated via epigenetic modifications of insulin pathway genes. Present project aims to assess the role of obesity in induction of epigenome changes (DNA methylation, histone modifications) within promoter of insulin pathway genes and subsequent insulin resistance development.

In the development of IR, and consequently T2D, a special role is attributed to visceral adipose tissue. However, excess of subcutaneous fat also carries the risk of developing insulin resistance. For this reason, the presented project aims to examine the metabolic and molecular differences in the two types of fat depots of importance in the induction of insulin resistance. A number of planned analyzes related to DNA methylation and histone modifications will determine metabolic differences between these two types of tissues and their involvement in the insulin resistance pathogenesis. Above all, the project aims to identify epigenetic changes that occur in both types of fatty tissue in obese individuals and their relationship with the induction of insulin resistance.

A number of planned experiments carried out *in vitro* with the use of human preadipocytes will confirm the participation of epigenetic modifications in the induction of insulin resistance. Moreover, the mechanisms and the factors that cause changes in epigenome leading to induction of insulin resistance will be revealed.

The results created after the implementation of the project will undoubtedly contribute to better knowledge of the insulin resistance development in obesity. At present the effective manner of insulin resistance treatment remains unknown and still the most common treatment is insulin therapy. From clinical point of view postponing or even discontinuation of insulin therapy for some patients is beneficial and postpone pathogenesis of numerous, mainly cardiovascular, complications. Author believes that obtained results in the future will help establish new methods to overcome insulin resistance using epigenome modulating drugs.