The aim of the project is to detect the changes in liver and intestine, which contribute to the predisposition of newborns with intrauterine growth retardation (IUGR) to obesity and type 2 diabetes in adulthood. Tasks, which are planned to be implemented within the project, were designed on the basis of our pilot study results, describing the previously unknown changes in newborns, which affect those predispositions.

Current project will be a model study conducted on piglets due to numerous similarities in anatomy (especially the digestive tract), features of nutrient absorption and digestion, which could be explained with the fact that both humans and pigs are omnivore . Body size and metabolic rate are very similar as well. Moreover, the possibility of newborns to possess IUGR syndrome is almost the same – 6-8%. Considering the abovementioned similarities, pig appears to be an ideal model organism for conducting studies on IUGR's pathological profile of gastrointestinal tract; obtained results might be of high value when applied to human newborns.

The project suggests holistic approach in indicating the differences within the neonatal period, the consequences of which manifest themselves predisposed to obesity and type 2 diabetes So far, despite the fragmentary reports on this topic, mechanism of this dependence is still poorly understood.

The first part of the project assumes probing of liver tissue response with insulin using standard markers (insulin sensitivity of tissues will be determined), in other words we will examine expression levels of insulin receptor, glucose transporter, which is intestinal- and liver-specyfic :GLUT2 and intracellular signal transducers for serine threonine kinase Akt.

The first identified change is the increased in Kupffer cells (liver macrophages) to hepatocytes (the basic structural building blocks of liver) ratio. It led us to an assumption that chronic inflammation may develop in liver of newborns with IUGR syndrome, which is caused by the massive secretion of pro inflammatory cytokines by Kupffer cells. This, in turn, can directly contribute to an increased insulin resistance in liver and to be the direct cause of type 2 diabetes To test this hypothesis we will examine the levels of three pro inflammatory cytokines secreted by Kupffer cells: TNF-alpha, IL-6, and IL-1B.

Our preliminary experiments demonstrated the two-fold increase in FTO protein expression level in IUGR newborn liver, compared to piglets with average body weight. This result is exceptionally interesting due to the fact that particular FTO gene alleles are the strongest factors, contributing to predisposition to obesity. The role of the FTO protein (FTO gene product) is not clear. Recent discoveries, however, revealed that the increased FTO expression level can affect proteins, participating in the development of insulin resistance, namely hormone leptin and its receptor (LepRb). On the other hand, it is possible that FTO affects the pathway, where leptin is engaged as a signal transducer – STAT3. Therefore the hypothesis, whether the significant rise of FTO level in IUGR newborn piglets affects the leptin-LepRB-STAT3 pathway will be tested.

Another issue that emerged from our preliminary results analysis is to determine the magnitude of pathological alterations in glucose metabolism (glycolisis): significant reduction in the activity of one of the enzymes within this pathway in the mucosa of the small intestine of IUGR piglets was postulated. Since glycolysis is the pathway where chain reactions take place, it is concluded that this entire pathway in IUGR newborns could be impaired. In order to verify this result we are planning to measure the level of this enzyme (hexokinase 1) in bigger number of animals using different molecular techniques. Also we are planning to measure level of key enzyme fin gluconeogenesis pathway-PEPCK.

Current project suggests the determination of overall changes, which could contribute to the predisposition of obesity and type 2 diabetes development. For these purposes we will use the cutting-edge mass spectrometry techniques, which will identify the complete protein profile. The results of these experiments will allow us not only to describe the changes within the liver and intestine in IUGR newborns, but also measure their magnitude and find the ones, responsible for predisposition to obesity and type-2 diabetes.

Current research topic is of significant economic and social importance due to its strong impact on the development of science considering the fact that 6-8% of human newborns possess the IUGR syndrome; many other animals have the same problem, i.e. farm ones such as pigs. IUGR is an important issue in livestock production, because it is linked to high mortality in the first period of life, high susceptibility to diseases in the neonatal period and poor meat quality of fattening pigs. Studies on pig model are also a valuable source of data for unraveling the mechanisms involved in human IUGR newborns. Since obesity with comorbidities is included in the metabolic syndrome (Syndrome X), it is now recognized as the epidemic of the XXI century. The mechanisms, underlying this pathology, are still not fully understood, therefore the research activities towards identifying the factors, which predispose the newborns to IUGR syndrome are of crucial importance.