THE INTERPLAY OF GUT MICROBIOTA AND PERIPHERAL IMMUNE RESPONSE IN OBESITY-RELATED NON-ALCOHOLIC FATTY LIVER DISEASE AND PRIMARY HYPERTENSION IN CHILDREN

The increasing childhood obesity epidemic calls for appropriate measures and effective policies to be applied for medical practice. The major complications of obesity are primary hypertension (PH) and non-alcoholic fatty liver disease (NAFLD), and the both may progress with time to severe organ damage, which are the main health problems in adults. Currently available therapies fail in treatment of obesity and its complications in children. Better understanding the mechanism of PH and NAFLD development is required for planning future therapies and defining obese children at high risk of PH and NAFLD development. Because PH and NAFLD affect 30% to 40% of adult population worldwide and about 10% of 18 years old adolescents, these issues are of utmost importance for public health.

PH and NAFLD are characterized **by chronic, systemic low-grade inflammatory response**. While adult obesity is usually associated with combined fatty liver disease, PH and insulin resistance or diabetes, NAFLD children rarely develop PH, and PH children usually do not suffer from NAFLD. Composition of gut microbiome plays an important role in development of obesity and obesity-related morbidities by enhancement of inflammation and immune system dysregulation. It leads to the changes in the gut permeability and its inflammatory status along with dysbiosis and enhancement of bone marrow activities (by bacterial metabolites) towards production of pro-inflammatory immune cells that participate in target organs damage. Therefore analysis of gut microbiome composition and bacterial metabolome profiles in relation to immune cells responsiveness pattern to activation by bacterial metabolites (fecal extracts) in children with PH and NAFLD may allow better understanding the role of major mechanism claimed to be involved in development of these complications in the obese subjects.

The aims of the project are: a) to characterize the microbiota and metabolome patterns in the PH and NAFLD children stool samples, b) to evaluate their associations with fecal extracts (FEs)-induced peripheral blood mononuclear cells (PBMCs) activation status and transcriptomic profiles.

Methods: Obese children with NAFLD and PH will be studied and compared to obese children with normal liver function and normal blood pressure and healthy lean children. Several microbial and immune parameters will be analyzed: 1/ clinical and laboratory characteristics of project participants (anthropometric, metabolic, vascular and liver tests; 2/ characterization of microbiome and metabolome composition in stool samples; 3/ PBMCs responsiveness to fecal extracts (FEs) assessed by cytokines production pattern, lymphocyte phenotype characteristics and lymphocyte transcriptome network evaluation.

Expected impact of the research project on the development of science. We expect to uncover the differences and similarities concerning immune mechanisms engaged in NAFLD and PH development in relation to microbiome composition changes and to gut bacteria metabolic characteristics. The model system should allow to assess which of the gut metabolome-induced immune response profiles are NAFLD- and/or PH-specific and whether they associate with gut dysbiosis. The results of the project should also impact on development of methods of assessment of hepatic and cardiovascular disease risk and therapy choices.