mgr **Marika Olga Ziętak**

tytuł pracy: **„The effect of ambient temperature and the gut microbiota on the development of diet-induced obesity”**

## SUMMARY

Reduced ambient temperature regulates energy metabolism through increasing thermogenic capacity of interscapular brown adipose tissue (iBAT) due to the presence of UCP1 (uncoupling protein 1), being a biomarker of adaptive thermogenesis. Gut microbiota has been considered to act on energy balance through the processing of food digested and processes related to fat mass accumulation in the body; however the causative relationships between ambient temperature and microbiome on the development of obesity have not yet been investigated. Therefore, we hypothesized that the increase in energy expenditure associated with a reduction in ambient temperature causes changes in the gut microbiota that affect energy balance and susceptibility to diet-induced obesity (DIO).

To determine energy balance phenotypes associated with temperature-dependent changes in the gut microbiota two experiments were performed. In the first experiment, adult C57BL6/J mice were housed at ambient temperatures of 29°C, 17°C and 12°C and fed a standard chow (STD) or high-fat diet (HFD) for 4 weeks. In the second experiment, caecum collected from C57BL6/J donor mice fed a HFD and reared at 12°C and 29°C was transplanted to germ-free (GF) hosts to determine whether cold-adapted gut microbiota is able to transfer and maintain metabolic phenotype associated with reduced ambient temperature.

After 4 weeks, C57BL6/J mice developed a highly variable obese phenotype that depended on the ambient temperature and/ or diet. We demonstrated that at reduced ambient temperatures (12°C or 17°C) DIO was suppressed in HFD-fed mice with significantly increased thermogenic energy expenditure. As ambient temperature was decreased, food intake was increased to fuel thermogenic energy expenditure. Metabolic efficiency, which defines the amount of energy preserved in the body`s fat stores in relationship to energy intake, was markedly diminished at 12°C and 17°C compared to 29°C, particularly on a HFD. We suggested that the changes in metabolic efficiency at cold environment were associated with increased *Ucp1*-dependent thermogenesis in iBAT rather than in white adipose tissue. Molecular analysis of markers of cold-induced thermogenic program showed a robust expression of *Adrb3*, *Pgc1a*, *Dio2* and *Fgf21* in brown adipocytes. Moreover, cold exposure

improved glucose and lipid metabolism in HFD-fed mice, as observed by higher levels of *Glut4* and *Irs1* expressed in iBAT and skeletal muscles and increased fatty acidy oxidation in liver, respectively. Gut microbiota, which diversity and composition at phylum and family levels were markedly changed due to diet and ambient temperature might constitute potential mechanism linking the reduction of DIO at reduced ambient temperature. HFD-fed mice reared at 29°C were characterized by increased abundance of bacteria belonging to *Erysipelotrichaceae*, whereas lean microbiome at 12°C were dominated by *Desulfovibrio*, *Adlercreutzia*, *Mogibacteriaceae* and *Ruminococcaceae*. Reduced ambient temperature altered gut microbiota metabolism that was efficiently stimulated to produce various bile acids (BAs) conjugated to taurine, as evident from elevated hepatic expression of genes related to BAs synthesis and conjugation with taurine. BAs are ligands for TGR5 receptors, which increased expression in iBAT could mediate enhanced thermogenesis. In our mouse model, the prevalence of taurine-conjugated BAs at cold resembled the pattern of BAs in GF mice that are protected against DIO. Noteworthy, our data indicated that cold-remodeled microbiota transferred lean phenotype to recipient mice that presented reduced adiposity associated with improved glucose tolerance, increased hepatic β-oxidation and altered BAs metabolism.

In conclusions, a link between the thermogenic capacity of the body and gut microbiota at cold might be associated with the induction of iBAT-dependent thermogenesis and BAs – metabolites that are regulated by the intestinal bacteria. Gut microbiota shaped by cold environment phenocopies GF state and reduces susceptibility to DIO. Therefore, the modulation of gut microbial pathways in response to cold-activated thermogenesis might constitute an alternative approach for the efficient utilization of energy and protection against DIO.