Running projects supported by grants

1. The role of Adipose tissue and muscle crosstalk in regulation of METabolic flexibility: exploration of novel predictors of the lifestyle Intervention Success in obese (AMETIS)

Czech Health Research Council project NU23-01-00509

Our position: PI

The incidence of obesity and related diseases such as type 2 diabetes, cardiovascular disease, liver steatosis and cancer is increasing worldwide. The need for innovative early intervention approaches for patients with obesity is therefore pressing. One of the core yet understudied pathophysiological mechanisms underlying metabolic dysregulation in obesity is metabolic inflexibility, characterized by the inability to efficiently adapt metabolism to substrate demand or availability. However, an accurate yet simple analysis of metabolic flexibility is lacking, and clinically relevant marker of metabolic flexibility which could readily identify at risk patients with high specificity and sensitivity is needed. Therefore, the main aim of this study is to identify surrogate markers of metabolic flexibility, with the capacity to predict the success of complex lifestyle intervention in patients with obesity. We hypothesize that these markers will be factors responsible for paracrine and endocrine communication between skeletal muscle and adipose tissue in the context of metabolic flexibility. Therefore, samples of (i) vastus lateralis muscle, (ii) adjacent intramuscular adipose tissue, and (iii) subcutaneous adipose tissue will be collected from individuals with well-characterized metabolic flexibility (glucose ingestion/feeding: Oral glucose tolerance test, euglycemic hyperinsulinemic clamp; exercise test: VO2max, low intensity cycling) and characterized by state-of-the-art transcriptomic, proteomic and metabolomic methods. The mechanism of action of regulated molecular markers of metabolic flexibility derived from these studies will be tested using the primary cultures of human muscle cells and adipocytes. Clinical relevance of the identified markers of metabolic flexibility will be validated in the large and complex dataset generated in previous cross-sectional and intervention (exercise and/or dietary) studies.

Colaborators: biomedical Research Center of the Slovak Academy of Sciences, Faculty Hospital Kralovske Vinohrady

2. Relation of de novo lipogenesis and peroxisomal metabolism in obesity (PEROXI)

GAUK 254923

Our position: PI

Adipose tissue (AT) dysfunction in obese patients is associated with a decrease in de novo lipogenesis (DNL) in adipocytes. These changes likely result in alterations in the membrane lipidome and insulin sensitivity. According to recent data, it appears that ether-phosphatidylcholines, which are mainly formed in peroxisomes, probably play an important role in the development of dysfunctional AT. These membrane phospholipids are induced when DNL decreases and may contribute to the development of oxidative stress and subsequently insulin rezistance. Thus, we focus in this study on the association of reduced DNL with peroxisome metabolism and ether-phospholipid production. We will also investigate the association of DNL inhibition with oxidative stress and insulin sensitivity using ex-vivo AT samples from clinical studies and in vitro primary adipocyte cell cultures. Unraveling the relationship between DNL-peroxisome-insulin sensitivity pathways should help to establish new strategies for the treatment of obesity, insulin resistance and diabetes.

3. Novel approaches to enhance insulin-sensitizing effects of exercise: targeting PAHSA metabolism (ETAPA)

Czech Health Research Council project NU21-01-00469

Our position: co-PI

Exercise is an important tool in the prevention and treatment of metabolic disorders associated with obesity and aging, such as type 2 diabetes and cardiovascular disease. In addition to skeletal muscle and its myokines metabolic effects of exercise also depend on inducing beneficial changes in function adipose tissue. Adipose tissue, for example, is a source of lipokines of the ester family palmitic acid with hydroxy fatty acids (PAHSA), which have anti-inflammatory and insulin-sensitising properties. We have recently shown that 4 months of exercise increases PAHSA levels in adipose tissue and circulation.

However, the mechanisms involved in the induction of PAHSA levels in response to exercise are unknown. Therefore, the aim of the ETAPA project is to investigate the regulation of of PAHSA metabolism in response to acute and chronic exercise, and at the same time investigate strategies that could enhance the effect of exercise on PAHSA levels, thereby increasing insulin sensitivity and maximising therapeutic benefits.

Colaborators: Institute of Physiology ASCR, Faculty Hospital Kralovske Vinohrady

4. Gene Therapy to restore lymphatic flow lymphedema (TheraLymph)

H2020 SC1-BHC-07-2019, Project # 874708

Our position: partner, WP3

Lymphedema is a disabling condition induced by the accumulation of fluid and fat in the arm or in the leg. It is an untreatable disease that affects 4 millions people in Europe and more than 120 millions people worldwide. It is handicapping, painful and impacts substantially the quality of life. In western countries, lymphedema is generally a consequence of cancer treatments i.e. ten to fifteen percent of women will develop lymphedema after breast cancer. The main objective of Theralymph will be to establish a non-integrative gene therapy for this unmet medical need. The theralymph translational research program brings together bench scientists from 5 European countries and physicians from the hosted Rangueil hospital in which the PI institute is located to perform a Phase I/II trial focusing on women who developed lymphedema after breast cancer. Our team (partner # 8) will participate in the project by analysing the functional interrelationships between adipocytes and lymphatic endothelial cells in in vitro models.

https://theralymph-europe.eu/

Collaborators:
1. (Coordinator) Institut national de la santé et de la recherche médicale (Inserm) France
2. University of Helsinki (UnivHel) Finland
3. University of Lausanne (UnivLau) Switzerland
4. Uppsala University (UnivUps) Sweden
5. University of Louvain (UniLou) Belgium
6. University of Liege (UniLiege) Belgium
7. Centre National de la Recherche Scientifique (CNRS) France
8. Centre Hospitalier Universitaire, Toulouse hospital (CHUT) France
9. Flash Therapeutics (FTX) France
10. Inserm Transfert (IT) France

5. Ketogenic diet as a modulator of de novo lipogenesis in liver and amount of visceral adipose tissue (KETOLIVA)

Czech Health Research Council project NU20J-01-00005

Our position: co-PI

The hypocaloric ketogenic diet (KD), a diet with very low carbohydrate energy, has become a very popular dietary option for weight loss. However, it remains less clear whether the beneficial metabolic effects can be attributed to an isocaloric KD containing predominantly lipids. Recent research suggests that isocaloric KD may worsen the lipid profile and insulin sensitivity of the liver. This suggests that switching to an isocaloric KD or carbohydrate diet, which usually follows a hypocaloric KD, may induce adverse metabolic changes in liver metabolism. Therefore, this project aims to investigate the effects of isocaloric KD followed by a carbohydrate diet on ectopic fat accumulation and de novo lipogenesis in the liver in relation to metabolic status in obese women and to describe the communication between liver and adipose tissue in response to this type of dietary load through miRNA and cytokine analysis in plasma and extracellular vesicles. The project combines state-of-the-art imaging technologies and molecular biology techniques.

Collaborator: The Institute for Clinical and Experimental Medicine

6. The Role of De Novo Lipogenesis in Regulation of Insulin Sensitivity in adipose tissue in obese (DELISA)

Czech Health Research Council project NV19-01-00263

Our position: PI

One of the manifestations of adipose tissue (TT) dysfunction in the obese is impaired de novo lipogenesis (DNL). DNL impairment in TT plays a role in the metabolic complications of obesity. The aim of this project is to study novel factors regulating DNL in TT. DNL will be monitored during nutritional interventions in healthy and obese subjects: exposure to a 2-day high carbohydrate diet, which will be a) a 2-day fasting period b) a multi-week ketogenic diet. The chosen nutritional protocol creates conditions to study the change of DNL in TT: suppression of DNL during fasting or ketogenic diet and stimulation during the subsequent high carbohydrate phase. Relevant systemic phenotypic traits will be monitored in these protocols and the spectrum of molecular markers of DNL regulation will be investigated in subcutaneous TT samples, with specific attention to the newly described factors hormone-sensitive lipase and the transcription factor ChREBP.

Collaborators: Faculty Hospital Kralovske Vinohrady

7. Pancreatic cancer: metabolic derangements assiocated with insulin resistance (PAMIR)

Czech Health Research Council project NV19-01-00101

Our position: co-PI

Pancreatic cancer (PC), whose incidence is increasing in the Western countries, ranks among tumours with the worst prognosis. PC is associated with early development of cancer cachexia, a systemic condition leading to the depletion of host substrate reserves. The project aims to identify key metabolic pathways of the tumour and adipose tissue related to cancer cachexia. Patients with PC will be characterized (anthropometry, insulin sensitivity and secretion, substrate utilization, inflammatory parameters) to describe complex metabolic phenotype. Primary cultures of the tumour will be subjected to metabolomics analyses, specifically related to glutamine and branched chain amino acid metabolism and interference of their degradation pathways. Peripancreatic fat will be analysed for its lipolytic and secretory activity. In differentiated adipocytes, the ability of insulin sensitizing drugs to ameliorate lipolysis induced by tumour medium will be assessed. Results will enable to describe host-tumour substrate cross-talk and to identify potential treatment targets of PC induced cachexia.

Collaborators: Faculty Hospital Kralovske Vinohrady, Institute of Physiology ASCR