ECOLE DOCTORALE BIOLOGIE-SANTE-BIOTECHNOLOGIES

DOCTORAT DE L'UNIVERSITE PAUL SABATIER
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RAPPORT ETABLI PAR: ***RNDr. Monika Cahová, Ph.D.***

SUR L'AUTORISATION DE SOUTENANCE A ACCORDER A: ***à Toulouse le 26 Juin 2017***

Titre de la thèse : ***Regulation of lipogenesis in human adipose tissue : Effect of metabolic stress, dietary intervention and aging. (par Veronika Mayerová-Šrámková)***

1°) EVALUATION GENERALE

Par comparaison avec des thèses de doctorat récentes soutenues dans la discipline ou dont le rapporteur a eu connaissance personnellement, cette thèse est à son avis :

Digne d'être soutenue en vue du doctorat

☐ **NON** **X OUI (sans modification)** ☐ **OUI (avec modifications de forme)**
☐ **OUI (avec modifications notables)**

Dans l'affirmative cette thèse est-elle:

d'un niveau scientifique

☐ **EXCEPTIONNEL** **X EXCELLENT**
☐ **TRES BON**
☐ **BON** ☐ **SATISFAISANT**

d'une présentation matérielle

X EXCEPTIONNELLE ☐ **EXCELLENTE** ☐ **TRES BONNE**

☐ **BONNE** ☐ **SATISFAISANTE** ☐ **A REVOIR**

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2°) ANALYSE CRITIQUE ET REMARQUES

(Un rapport détaillé doit être fourni en pièces annexe. Il devra être accompagné de la présente fiche d'évaluation)

The thesis is written in good English on the 160 pages. Text is accompanied with numerous figures and tables that well document and illustrate the substantiality of the thesis. The structure of thesis conforms to principles and requests to the structure of scientific thesis. The whole text is divided into six main chapters including Introduction, Aims, Matherial and methods, Results, Discussion and Conclusions. The rich bibliography consisting of 363 references is the evidence that the applicant has the deep theoretical knowledge and is well oriented in the problem discussed in the thesis. The thesis fulfils the formal requests on excellent level.

The topic of the presented doctoral thesis is very up-to-date especially in the view of increasing incidence of obesity and related metabolic disorders in developed countries. The main topic of this thesis is lipogenesis discussed in the context of endoplasmic reticulum stress, chronic caloric restriction and aging. With respect to the ongoing demographic changes in the society, the focus on the relationship between aging and the biology of adipose tissue is of particular importance. The thesis consists of four relevant specific projects. The aims of each of them are precisely formulated, the results are clearly described and well documented. The conclusions are discussed in the wide context of the current knowledge in the field. The results, obtained in these studies, were published as two papers in respected scientific journals with IF, the applicant was the first author in one case.

PROJECT A: Assessment of the impact of ER stress on differentiation and lipogenic activity of human adipocytes. The main and novel finding of this study is the difference between the effects of acute vs chronic stress when only acute ER stress weakens the lipogenic capacity of human adipocytes. In preadipocytes, chronic low ER stress impairs both differentiation and lipogenesis. This finding contributes to the understanding of mechanisms underlying the worsening of adipose tissue function in obesity.

PROJECT B: Evaluation of the effect of aging on lipogenic potential of human subcutaneous adipose tissue in relation to aging. Comparing two cohorts of young and elderly women the author demonstrated that the decreased capacity of elderly adipocytes to accumulate lipids could be linked to diminished expression of lipogenic enzymes and suggested the mitochondrial dysfunction as probable mechanism underlying this phenomenon.

PROJECT C: Comparison of short (2 days) and long (28 days) very low caloric diet on metabolic and inflammation-related indices in subcutunaeous adipose tissue in moderately obese women. Results presented in this thesis show that early and later phases of VLCD differ with respect to metabolic and inflammatory responses in subcutaneous fat depots.

PROJECT D: The investigation of the effect of moderate caloric restriction on preadipocytes and adipocytes from young and elderly obese men. This elegant study

challenged the previously published data and showed that the age does not negatively affect the preadipocyte differentiation in response to appropriate stimuli (caloric restriction and exercise). The author also showed that in some aspects only senior group responded to the intervention (glucose uptake by adipocytes, expression of genes involved in fatty acid oxidation, lipolysis and browning of adipose tissue). Taken together, these results helps to understand metabolic response of the older organism and may even have practical impact in the preventive health care of the elderly.

The author proved mastering of wide scale of methods including isolation and culture of stromal-vascular cells; methods used for analysis of senescence, proliferation activity and sensitivity to insulin in (pre)adipocytes *in vitro;* gene expression analysis; analysis of metabolites (i.e. fatty acids, neutral lipids etc.) and a spectrum of biochemical analytic methods. The employed methods are adequate to the task and are clearly described. The results are precisely and comprehensively presented with a lot of intelligible plots and tables. The results are critically interpreted and properly discussed and the interpretation reflects sufficient relevant knowledge within the field.

The questions for a discussion:

1. From obvious reasons (accessibility of the tissue), your studies were performed on subcutaneous fat. According to your opinion, are different fat depots (i.e. subcutaneous vs visceral) comparable with regard to the progression of aging?
2. You identified mitochondrial dysfunction as the probable mechanism of the diminished lipogenic capacity of elderly sc adipocytes. Could you suggest some therapeutic intervention in order to increase mitochondrial metabolism?
3. In "project C" you found elevated plasma levels of pro-inflammatory cytokines after 2 days of VLCD but the expression of relevant genes in sc fat depot was not increased. Could you speculate about the source of these cytokines?
4. "Project D": Subjects in both young and aged cohort have relatively high BMI but their serum Tg and cholesterol levels are quite low. Do you have any explanation? Did they have any medication affecting Tg and cholesterol metabolism?

In my opinion, mgr. Veronika Šrámková clearly demonstrated her ability for scientific work. This thesis fulfills all required criteria and it can be judged as a doctoral (PhD.) dissertation. I suggest to accept this thesis and I recommend award mgr. Šrámková a PhD. title.

Prague, August 9th, 2017