

Centre Méditerranéen de Médecine Moléculaire U1065

Directeur : Dr. Patrick Auberger

Equipe 7 : Jean-François Tanti et Mireille Cormont
« Physiopathologie cellulaire et moléculaire de l'obésité et du diabète »

Review Report on PhD Thesis of Veronika Sramkova

Entitled

“Regulation of lipogenesis in human adipose tissue: Effect of metabolic stress, dietary intervention and aging “

submitted to University Toulouse 3 Paul Sabatier, Doctoral School of Molecular Genetic, France in the frame of cotutelle with the Charles University, Third Faculty of Medicine, Prague

Veronika Sramkova submitted the doctoral thesis dealing with the investigation of change in lipogenesis in adipose tissue in the context of endoplasmic reticulum stress, calorie restriction and aging in obese patients.

Veronika Sramkova introduces four objectives in her doctoral thesis dealing with the modification in lipogenesis in adipocytes 1) To assess the impact of ER stress on differentiation and lipogenic capacity of human adipocytes; 2) To evaluate the effect of aging on lipogenic potential of human subcutaneous adipose tissue and adipocytes in relation to senescence and ER stress markers; 3) To compare the effects of 2 days and 28 days very low calorie diet on metabolic inflammation and related indices in subcutaneous adipose tissue and their possible relationship with systemic inflammatory and metabolic status in moderately obese women; 4) To investigate and compare the effects of moderate calorie restriction on preadipocytes and adipocytes from young and elderly obese women.

Adipose tissue dysfunction is known to play an important role in the metabolic complication of obesity including insulin resistance and type 2 diabetes. Hence, there is a need for a better understanding of the effect of adipose stress such as ER stress on the dysfunction of the adipocytes and for the investigation of nutritional intervention such as calorie restriction on the physiology of adipose tissue in order to improve the management of obesity and its metabolic complications. Moreover, the management of obesity in elderly represent a new challenge and therefore there is a need to study the impact of calorie restriction on the function of adipose tissue in this population. Therefore, the novelty as well as scientific level of the thesis is very good, considering the importance of the research subject and the medical impact.

This PhD thesis is well structured, the text is well written in clear and concise manner and very well documented. Its consists of 7 main chapters including the bibliography, covers 122 pages and enriched by adequate number of figures. In addition, Summary, List of Abbreviations and two Appendices with the two published articles are presented.

The first chapter is the literature background, introducing the reader to the dissertation topic. This chapter is divided in four sections. In the first section, Veronika Sramkova presents the different type of adipose tissue and shortly described the cellular composition of adipose tissue. The second section described the physiology of adipocytes and adipose tissue focusing mainly on lipogenesis that is the main topic of the thesis. Very useful piece of information is given to the reader in this section even if the lipolysis part could be improved (see my suggestions at the end of the review). The third section described the pathophysiology of adipocyte and adipose tissue. This section is well written and up to date but I have some suggestion to slightly improve the senescence part by describing the impact of p53 inhibition on adipose tissue function and on insulin sensitivity (suggestion at the end

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of this review). The fourth section described the different approaches to manage obesity focusing on the lifestyle modifications and introduce the specific problem of the weight loss in the obese elderly. The section is well written and give to the reader sufficient piece of information to understand the experimental work.

To summarize, the theoretical part of this thesis is very good. Veronika Sramkova has studied carefully research subject with critical view, and used appropriate number of bibliography sources. It is evident that Veronika Sramkova deeply understood the theoretical knowledge and the discussed problems.

Chapter 2 clearly presents the different aims of the experimental work and **Chapter 3** is dedicated to the description of the used of the material and methods. **The next parts** of the dissertation is focused on results and discussion of the results and on the perspectives open by her work. The hypothesis and arguments are well formulated.

In the first project, Veronika Sramkova demonstrated that acute ER stress in adipocytes inhibits the expression of lipogenic genes and the *de novo* lipogenesis whereas chronic low ER stress that could mimic what happens in obese adipocyte did not modify lipogenesis in mature adipocytes but impaired adipogenesis. Her work suggests that the ER-stress induced alteration in lipogenic capacity of adipose tissue in obese patients could be due to an effect on preadipocytes rather than on mature adipocytes. This work was published in BBRC-2016.

In the second project, she compared the lipogenic capacity of adipose tissue from young and elderly obese women. She found that the lipogenic capacity of adipose tissue was reduced in elderly together with an increase of marker of senescence in the tissue, a reduced expression of chaperone proteins in the ER and an increase in markers of mitochondrial dysfunction. However, correlation analysis suggests that the decrease in lipogenic capacity is not related to the increase in senescent cells or ER but to mitochondrial dysfunction.

In the third project, she found that a 2 days or 28 days of a very low calorie diet (VLCD) differ with respect to metabolic and inflammatory response of subcutaneous adipose tissue. An important finding of the study, maybe quite unexpected, is that the beneficial effect of the 2 days VLCD on the insulin sensitivity seems unrelated to change in gene expression in subcutaneous adipose tissue but an interplay between liver and adipose tissue through FGF21 could explain the improvement in the insulin sensitivity. This work was published in 2016 in J Clin Endocrinol Metab.

In the fourth project, she demonstrated that a moderate calorie restriction combined with exercise in seniors can have beneficial effects on metabolism in adipocytes by increasing the oxidative capacity of the adipocytes. This is an original study with a great medical importance since the management of obesity and the consequences of weight loss in elderly required intensive investigation to avoid harmful effects such as sarcopenia. The results she has obtained need to be completed by other investigations but I have no doubt that this work could be published soon.

To summarize, the experimental part of the thesis is very good and Veronika Sramkova performed an impressive work. All experiments are well arranged and measurements techniques and methods are correctly applied, combining cellular studies and investigation on adipose tissue and adipocytes from obese patients. The results she has obtained are original and of great scientific value opening new hypothesis and research avenues mainly about mechanisms involved in change of adipose tissue biology during nutritional intervention that could be now experimentally tested. The quality of the work of Veronika Sramkova is reflected in its being published in two

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international peer-reviewed journals, *The Journal of Clinical Endocrinology* (2016) as first author and *Biochemical and Biophysical Research Communications* (2015) as second author. Moreover, results presented in the thesis manuscript should lead to at least one other article soon. The discussion of the results obtained for the different aims is of great quality.

To sum up, the dissertation thesis represents high level scientific work. However, I have some suggestions to improve the theoretical part of the dissertation:

- The section about lipolysis (p 30) is short and more detail description of the regulation of the lipase especially ATGL by CG158 and G0S2 is needed.
- For the adipokines (p 31) it should be nice to mention apelin and to describe the effect of apelin on the metabolism.
- In the senescence part, the different articles of Minamino group on the invalidation of p53 in adipocytes should be described and added to the bibliographic reference list.
- In the inflammation part, it should be stated that change in microbiota could also be involved in the inflammation of adipose tissue and to add at least one reference on this topic.
- In addition to adipose macrophages, should be added a more detailed description of the role of the change in adipose T cells such as Treg.

In my opinion, the reviewed thesis of Mrs. Veronika Sramkova fulfills all requirements for obtaining PhD degree including scientific novelty, an extensive range of research, excellent presentation of the literature background and excellent quality of the discussion of the obtained results, very good scientific activity confirmed by published papers. Therefore, I highly recommend Mrs. Veronika Sramkova for the title of PhD degree of the Toulouse University.

Nice, July 20th 2017

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