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Review Report on PhD Thesis of Paweł Nowialis entitled „*Identification of mechanisms remodeling mitochondria during adaptation of adipose tissue to changing ambient temperature*”.

Supervisor: Professor Leslie P. Kozak PhD

Paweł Nowialis submitted the doctoral thesis dealing with the testing the effects of changes of ambient temperatures on adipose tissue remodeling with special focus on mitochondria dynamics and a role of A-kinase anchoring protein 1 (AKAP1). In my opinion this is very interesting subject considering the fact that adipose tissue plays an important role in thermogenesis and is also a main source of several hormones and growth factors. Moreover, cryotherapy is widely used in treatment of several morbidities in Poland and many other countries. Better understanding of the molecular mechanism of adipose tissue remodeling induced by changes in ambient temperature may have the implication in many areas of science and medical practice.

This PhD thesis is well structured and correctly presented. It consists of 8 main chapters. At the beginning of the dissertation list of abbreviations and symbols are introduced. The thesis is written on 52 pages altogether, and enriched by 18 figures. The theoretical principles as well as the research part were validated with 76 valuable references.

To summarize, the theoretical part of the thesis is worth to note that the Author has studied research subject carefully and with critical view, and used appropriate number of bibliography sources. It is evident that Paweł Nowialis deeply understand the theoretical knowledge and discussed problems.

He demonstrated that AxB mice, when exposed to cold, developed brown adipocytes in the inguinal white adipose tissue. Mice that after cold exposure were re-exposed to neutral temperature reorganized their mitochondrial network with visible mitofission. In experiments performed on AKAP1-KO mice Mr Nowialis was able to demonstrate that anchoring of PKA by AKAP1 to mitochondrial membranes was not essential for induction of adaptive changes in the white adipose tissue to changing in ambient temperature. Moreover, he observed that AKAP1-KO mice were characterized with the higher level of caspase 3 after returning to

normal temperature what suggests that this protein somehow regulates apoptosis however, the exact mechanism is not known.

Specific comments:

1. The thesis research generates significant new knowledge in area of adaptive changes to surrounding temperature and signaling pathways involved in regulation of mitochondria dynamics.
2. The methodology used is appropriate. Author applied different technics and methods, like Western Blotting, electron microscopy, PCR and some others, and description of these methods are sufficient to reproduce the experiments. There is only objection, which I expect to be discussed during the procedure, is animals handling. Mice, rats and some other rodents are natural runners, thus experiments performed on mice kept in the cage without possibility to do exercise (wheel in the cage) is unnecessary more artificial than it could be.
3. In most of the cases the results are presented clearly, with the appropriate controls and statistical analysis. In some cases, figures are too small and thus, difficult to evaluate. For example, fig. 14 demonstrates picture from transmission electron microscope, however, it is impossible to see mitochondria and the differences in their structure and size. The same applies to some data from Western Blots.
4. The results are discussed properly in relation to the research of others, and it can be seen that Mr Nowialis shows a good understanding of the implications of his work in a broader scientific context.
5. Analysis of the thesis convince me that the candidate's contribution to each aspect of this work is significant and he appropriately acknowledges contribution by others (TEM ultrastructure studies by prof. Bogdan Lewczuk)

This thesis is lucidly written and very well documented. There are almost no typing errors and the text is well written in clear and concise manner. The figures, schemes, and tables are shown properly in most of the cases as well. The hypothesis and arguments are well formulated with meritorious conclusions based on valuable and actual literature. The conclusions confirm that the research objectives of the work have been successfully met.

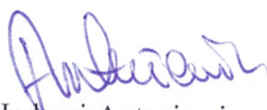
However, there are some remarks that need to be explained in details:

page 1: Author states sometimes as 'we...', and I do not think this is the case for Ph.D. thesis (should be written in first person). The same occurs on **page 2** in polish language.

2. There is some inconsistency in references list, for example comparing ref. 17 and 21 one can notice at least two different styles.

To sum up, the dissertation thesis represents high level of scientific work. It is an interesting topic for scientists working on mitochondria dynamics, physiologist and many others.

In my opinion, the reviewed dissertation of Mr Nowialis fulfills all requirements posed on theses aimed for obtaining PhD degree. This thesis is ready to be defended orally, in front of the respective committee.



Jędrzej Antosiewicz

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