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Review of the PhD thesis: Targeting mitochondria to overcome resistance of breast cancer to therapy

In her PhD thesis Katerina Rohlenova summarizes the experimental data on various aspects of mitochondrial targeting in tumor cells. Structure of the thesis is logical, well written and is easy to read. In the introduction, author focuses on the aspects relevant for the experimental part and yet it´s easy to follow the reasoning and hypothesis that drove and shaped the research activities. Second part of the thesis is composed of five original articles published in respected scientific journals. Katerina Rohlenova is the first author on two papers and a co-author of three additional studies.
An important and quite unique aspect of this thesis is a strong focus on the translational aspect of the experimental work. One of the compounds, MitoTam, developed and tested in this project passed the formal preclinical development stage and is planned to enter the clinical testing.

I have the following questions complementing the published reports:

- What other alternative strategies for targeting michondria in the tumor cells would you see as relevant and potentially specific and safe? Could targeting of mitochondrial RNA polymerase represent such an approach?

- Mitochondria are omnipresent. How would you explain that their targeting would preferentially affect the tumor cells while sparing the normal tissues?

- What is the explanation for differential toxicity of compounds such as rotenone vs metformin?

- Throughout the manuscript you state that cancer stem cells are dependent on OXPHOS. To what extent is this also true for „normal population" of tumor cells? Given the possibility of compensation mechanisms, such as glycolysis, do you see the use of mitochondrial targeting compounds as single agents or do you think they should be developed in combination with other treatments (chemotherapy)?

- Given the increased production of ROS, have you analyzed the presence of immunogenic cell death markers in cells treated by MitoTam?

Judging from the PhD thesis manuscript, I conclude that during her PhD studies K. Rohlenova showed a proficiency in the vast number of methods as documented by five original articles in the first tier scientific papers. The results of her scientific projects clearly show that she meets the requirements set by the Immunology board of PhD studies and she can be awarded the PhD degree.

Radek Špíšek