First person – Jiří Funda

First Person is a series of interviews with the first authors of a selection of papers published in Disease Models & Mechanisms, helping early-career researchers promote themselves alongside their papers. Jiří Funda is first author on 'Adipose tissue-specific ablation of PGC-1β impairs thermogenesis in brown fat', published in DMM. Jiří is a PhD student in the lab of Martin Rossmeisl at The Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic, investigating adipose tissue energy metabolism and its modulation by pathological conditions such as obesity.

How would you explain the main findings of your paper to non-scientific family and friends?

PGC-1β is a protein that controls transcription of various genes, meaning that it regulates how much of a certain gene product is made. Genes regulated by PGC-1β are mostly involved in the control of mitochondrial functions. In addition, PGC-1α, a protein closely related to PGC-1β, is the main regulator of the adaptive thermogenic program in brown adipose tissue (BAT), which is a specialized type of fat that uses fatty acids for heat production. Relatively little is known about the function of PGC-1β in adipose tissue; therefore, we examined mice with adipose tissue-specific deletion of the PGC-1β gene. We exposed these mice to a cold environment and observed that the absence of PGC-1β results in defective heat production in cold-exposed mice injected with the stress hormone norepinephrine. Norepinephrine injection stimulates BAT thermogenic mechanisms as BAT thermogenesis is activated when the organism experiences cold stress. Moreover, BAT of PGC-1β-deficient mice maintained at 30°C, where no thermogenesis is needed (thermoneutral environment), displayed impaired connections between mitochondria and lipid droplets, which are organelles that serve as fatty acid deposits in adipose tissue. OPA1 is a protein that contributes to the mediation of the mitochondria-lipid droplet interaction. PGC-1β-deficient mice at 30°C had a lower protein content of the long OPA1 form, suggesting that PGC-1β could regulate OPA1 expression in BAT. Our study demonstrated irreplaceable function of PGC-1β in the control of norepinephrine-stimulated BAT thermogenesis and in the mediation of mitochondria-lipid droplet interactions in BAT.

What are the potential implications of these results for your field of research?

Our findings show that PGC-1β is necessary for the maintenance of the key thermogenic and metabolic functions of BAT. PGC-1β seems to have an irreplaceable role in BAT adaptive thermogenesis, which is believed to be controlled mostly by PGC-1α. In addition, our results propose a previously unknown function of PGC-1β in regulating the mitochondria-lipid droplet interactions through OPA1 protein. The BAT thermogenic pathway, which is activated by hormones in response to a cold stress and results in heat production from fatty acid combustion, could potentially be used as a therapeutic treatment for obese patients. However, this pathway is not yet fully characterized.

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Jiří Funda

The findings obtained in our study contributed to the characterization of another protein that has a critical role in BAT thermogenesis.
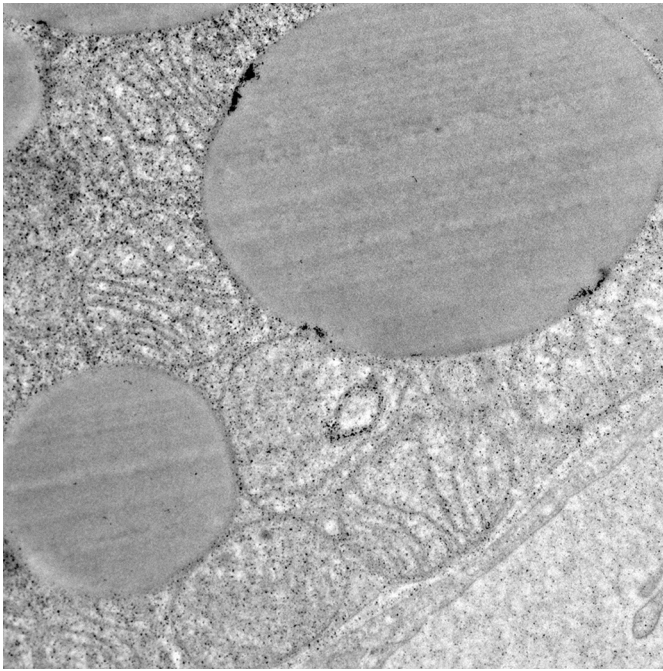
What are the main advantages and drawbacks of the model system you have used as it relates to the disease you are investigating?

The main advantage of our model is that it allowed us to examine the role of PGC-1β exclusively in adipose tissue, while all other organs maintained normal PGC-1β expression. This was accomplished by silencing the PGC-1β gene by Cre recombinase expressed under the adiponectin promoter, which means that the PGC-1β gene was only deleted in adipocytes. Our aim was to characterize the effects of PGC-1β deletion specifically in adipose tissue and the absence of PGC-1β in other organs could cover these effects. The drawback of our model was the relatively low amount of material for analyses dissected from a single mouse. We were primarily interested in BAT and the average weight of the biggest BAT depot in our mice was only around 100 mg. Therefore, the experiments were repeated many times in order to perform a comprehensive and statistically sufficient characterization of BAT functions by various analyses.

What has surprised you the most while conducting your research?

The biggest surprise in the study was that the absence of PGC-1β only manifested in BAT, while no differences between PGC-1β-deficient mice and their wild-type littermates were

Lipid droplets surrounded by mitochondria in brown fat of a mouse.

detected in white adipose tissue (WAT). As PGC-1β is mostly involved in the regulation of mitochondrial function, we believe that this effect was due to a low mitochondrial content in WAT. By contrast, BAT has a lot of mitochondria; therefore, PGC-1β deletion had a great impact in this tissue.

Describe what you think is the most significant challenge impacting your research at this time and how will this be addressed over the next 10 years?

I believe that currently the biggest challenge for obesity research is the lack of funding. Perhaps this partially applies to all life sciences. Generally, if society considers a certain disease highly threatening, it becomes less complicated to get funding for research focused on that disease. The recent COVID-19 pandemic allowed for a lot of funding to be dedicated to the development of vaccines and other treatments against viruses. Global obesity prevalence exceeds its all-time maximum every year and diseases associated with obesity are leading causes of death worldwide. It is expected that the number of obese individuals is going to increase further; therefore, more resources might be allocated to obesity research in 10 years from now. It would indeed be beneficial if the best brains in the field could spend most of their time conducting their research instead of trying to get funding for it.

What changes do you think could improve the professional lives of early-career scientists?

Early-career scientists too often spend their time performing simple and monotonous tasks that should ideally be assigned to technicians and other assistant staff. Early-career scientists would benefit from spending more of their time gaining new knowledge and developing and mastering new skills. I believe that the ability to share research outcomes with the rest of the scientific community by writing articles or by presenting at conferences is particularly important. After all, even groundbreaking results must be well presented, otherwise they do not have much value. Senior investigators should make sure that their less-experienced colleagues get a lot of opportunities to practice these soft skills. Early-career scientists should therefore be encouraged to attend training workshops and conferences, and they should also participate in writing manuscripts. Events such as summer schools and congresses for young scientists are especially useful as they help early-career scientists to network and learn from each other.

What's next for you?

In the following weeks, I want to defend my PhD thesis. After that, I am still going to stay in basic preclinical research. I am going to start a research fellowship in Preclinical Imaging Laboratory at Turku PET Centre in Finland, where I am supposed to start working on a project that combines my current field, which is adipose tissue biology, with cancer research. The project is focused on translocator protein (TSPO), which is a protein abundantly expressed in adipose tissue. The expression of TSPO is increased in various types of cancer and very little is currently known about its role in adipose tissue biology, so the project is indeed very intriguing.

Reference

Funda, J., Villena, J. A., Bardova, K., Adamcova, K., Irodenko, I., Flachs, P., Jedlickova, I., Haasova, E., Rossmeisl, M., Kopecky, J. et al. (2022). Adipose tissue-specific ablation of PGC-1β impairs thermogenesis in brown fat. *Dis. Model. Mech.* **15**, dmm049223. doi:10.1242/dmm.049223