MIROSLAV BALAZ

Biomedical Research Center
Slovak Academy of Sciences

Project number
1148/01/02

Project duration
2/2022 - 1/2025

"I applied for the SASPRO2 fellowship to develop my research ideas and to es-tablish my own record of independent research. The ultimate goal of this fel-lowship is to create a productive research microenvironment, generating and publishing high-quality original research results, and opening new career possi-bilities for me, my students, and collabo-rators, which will in synergy advance our research careers and provide the oppor-tunity to work towards establishing an innovative research area in Slovakia."

S A S P R O 2

BIOGRAPHY

Miroslav Balaz is originally from Velky Krtis, Slovakia. Initially interested in biology, he studied at the Faculty of Natural Sciences of Comenius University in Bratislava, where he developed an enthusiasm in physiology. He pursued training in Jozef Ukropec's lab at the Institute of Experimental Endocrinol-ogy of the Slovak Academy of Sciences.
He holds a doctoral degree in Animal Physiology from Comenius University. In 2015, he moved to ETH Zurich for his postdoctoral training, where he worked with Christian Wolfrum to study adipose tissue biology. He contributed to identification of several molecular mechanisms driving thermogenic activ-ity of brown fat, which were published in renowned scientific journals. Miro is currently employed as a senior scientist at the Biomedical Research Center of the Slovak Academy of Sciences. His research activities are focused on fat metabolism and energetics.

PROJECT SUMMARY

Lactate, a metabolic signal and enery fuel driving alternative

Obesity is a major threat to human health, being the primary risk factor for type 2 diabetes, dyslipidaemia and cardiovascular disease. Since energy expenditure is increased as a conse-quence of thermogenesis, pharmacological induction of this process presents an interesting therapeutic approach. Both the classical and alternative thermogenic mechanisms require extensive fuel supply from either cellular reserves or systemic circulation. Tissues which pos-sess alternative thermogenic mechanisms will therefore need to have a high metabolic flux. Interestingly, the most obvious changes in plasma metabolome triggered by acute cold in-clude an increase in fatty acids, glycerol, and lactate.

The first two originate from lipolysis and fuel thermogenesis. However, it is not clear what is the source, fate, and function of cold-induced lactate. Based on my preliminary data I propose that white adipocytes are the main source of cold-induced lactate, which serves as a metabolic signal and energy fuel for alternative thermogenic mechanisms. Specific aims of this proposal are to 1) uncover the origin and fate of cold-induced lactate; 2) reveal the function and prove the physiological relevance of lactate during cold; 3) identify targets for pharmacological modulation of thermogenesis.

To meet these goals, I will utilize inducible adipocyte- and brown/beige adipocyte-specific Ldha knockout mice, gain- and loss-of-function studies on human brown and white adi-pocytes, primary skeletal muscle and liver cells, metabolic tracing and bioenergetic mea-surements. Comprehensive metabolomic and transcriptomic analyses of human and murine adipose tissue, skeletal muscle and plasma will serve as basis for identification of novel can-didates with therapeutic potential.

The proposed project will not only provide new models and datasets that will be an invalu-able resource for the metabolic community, but also identify and validate novel therapeutic targets with potential to improve metabolic control.

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PUBLICATIONS

Sun et al., snRNA-seq reveals a subpopulation of adipocytes that regulate thermogenesis. Nature, 2020; 587: 98-102. DOI: 10.1038/s41586-020-2856-x

Sun et al., Cold-induced epigenetic programming of the sperm enhances brown adipose tissue activity in the offspring. Nature Medicine, 2018; 24(9): 1372-1383. DOI: 10.1038/s41591-018-0102-y

Balaz et al., Inhibition of Mevalonate Pathway Prevents Adipocyte Browning in Mice and Men by Affecting Protein Prenylation. Cell Metabolism, 2019; 29(4): 901-916. DOI: 10.1016/j.cmet.2018.11.017

Ding et al., Peroxisomal beta-oxidation acts as a sensor for intracellular fatty acids and regulates lipolysis. Nature Metabolism, 2021; 3: 1648-1661. DOI: 10.1038/s42255-021-00489-2

Fischer et al., Lysosomal lipoprotein processing in endothelial cells stimulates adipose tissue thermogenic adaptation. Cell Metabolism, 2021; 33(3): 547-564. DOI: 10.1016/j.cmet.2020.12.001

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