The essential role of LAMTOR1 in the control of AMPK activity in *BRAF*-mutated melanoma cells

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Targeted therapy of malignant melanoma often aims at the components of the overactivated ERK pathway, especially BRAF and MEK kinases. However, patients treated with ERK pathway inhibitors usually develop resistance within several months. Our team recently identified new molecular mechanisms involving the metabolic sensor AMPK that could significantly affect ERK signaling pathway activity in melanoma despite the presence of *NRAS* and *BRAF* oncogenic mutations, leading to the suppression of melanoma cell growth.

In the current project, we focused on the LAMTOR1/p18 subunit of the Ragulator complex, a known AMPK and ERK regulator, and its role in AMPK signaling activation in the cellular context of melanoma. We identified a partial disruption of the Ragulator complex in response to compounds promoting the LAMTOR1/p18 subunit accumulation on the interfaces of enlarged endolysosomes in melanoma. Crucially, the AMPK activation by metabolic stress was disrupted under these circumstances in *BRAF*-mutated melanoma cells. The essential role of LAMTOR1/p18 for AMPK activation in *BRAF*-mutated melanoma was verified using RNA interference targeting LAMTOR1 gene expression. Finally, we observed increased interactions between LAMTOR1/p18 and AMPK proteins after metabolic stress using proximity ligation assays and immunoprecipitations in *BRAF*-mutated melanoma.

Our results indicate the importance of the LAMTOR1/p18 subunit of the lysosomal Ragulator complex for AMPK kinase activation in response to metabolic stress in *BRAF*-mutated melanoma cells.

This work was funded by the Czech Science Foundation (GA22-30397S), the European Regional Development Fund - Project ENOCH (No. CZ.02.1.01/0.0/0.0/16_019/0000868), the European Union – Next Generation EU - the project National Institute for Cancer Research (Programme EXCELES, Project No. LX22NPO5102), and Masaryk University (MUNI/A/1393/2022).