NEW INSIGHTS INTO AMPK ACTIVITY CONTROL IN MALIGNANT MELANOMA

Vadovičová N.[1,2], Valčíková B. [1,2], Uldrijan S.[1,2]

[1]*Masaryk University, Faculty of Medicine, Brno, Czech Republic*
[2]*International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic*

AMP-dependent protein kinase (AMPK) is the primary cellular energy sensor, linking intracellular ATP levels to signaling pathways regulating crucial anabolic and catabolic processes, cell survival, growth, and proliferation. Malignant melanoma is aggressive skin cancer driven by oncogenic mutations of *BRAF* and *NRAS* genes constitutively activating the RAS/RAF/MEK/ERK mitogen-activated protein kinase (MAPK) signaling pathway. The high constitutive ERK pathway activity in *BRAF*-mutant melanoma was reported to be incompatible with AMPK activation in response to low ATP levels due to the inhibition by a canonical, LKB1 kinase-mediated activation mechanism. However, in a recent study, we reported that simultaneous ERK and AMPK activation can occur in melanoma cells with *BRAF* and *NRAS* mutations. Moreover, our new data show that a non-canonical LKB1-independent mechanism restricts AMPK activity in melanoma cells. We identified the essential negative AMPK regulator and showed that small molecule drugs targeting the new regulation can induce high AMPK activity in melanoma cells. Our findings could lead to new treatments for malignant melanoma.

This research 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).