

University of Fribourg / Faculty of Science and Medicine / Department of
Endocrinology, Metabolism, and Cardiovascular System

Arginase-II drives tumour growth and malignancy by regulating
Sirt3-mtROS in melanoma cells

Yang Yang

Aberrant mitochondrial metabolism is a key source of massive mitochondrial reactive oxygen species (mtROS) in tumor cells. Arginase-II (Arg-II), a widely expressed mitochondrial metabolic enzyme, has recently been shown to be implicated in mtROS production as well as in the melanoma progression. However, whether it promotes cancer progression through mtROS remains unclear. Here, we show that overexpression of *arg-ii* in melanoma cells promotes colony formation and cell proliferation with concomitant enhancement in mtROS and suppression of mitochondrial tumor suppressor Sirtuin 3 (Sirt3), which is reversed by ablation of *arg-ii*. In supporting of these data, silencing Sirt3 promotes melanoma growth through enhancing mtROS. Moreover, overexpression of *arg-ii* induces nuclear deformation associated with enhanced migration and DNA damage also through suppressing Sirt3 and promoting mtROS; and overexpression of Sirt3 could protect the malignant phenotype of melanoma cells induced by *arg-ii* overexpression. Furthermore, we show that Arg-II mediates hypoxia-induced nuclear deformation and DNA damage which is mediated to Sirt3-mtROS axis. In addition, similar results are obtained in A549 human lung carcinoma cells. Altogether, our findings demonstrate a critical role of Arg-II-Sirt3-mtROS cascade in promoting melanoma growth, DNA damage and nuclear deformation linking to melanoma progression and malignancy, which could be therapeutic targets for cancers such as melanoma and lung carcinoma.

Jury:

Prof. Zhihong Yang, University of Fribourg (Thesis supervisor)

Prof. David Hoogewijs, University of Fribourg (Internal expert)

PD. Dr. Xiu-Fen Ming, University of Fribourg (Internal expert)

Prof. Christine Peinelt, University of Bern (External expert)

Prof. Stein Jens Volker, University of Fribourg (President of the jury)