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Mitochondrial enzyme FAHD1 regulates complex II activity in breast cancer cells, and is indispensable for BT-20 cells in vitro

FAH domain containing protein 1 (FAHD1) is a mammalian oxaloacetate decarboxylase (ODx) involved in the regulation of the TCA cycle flux1. Oxaloacetate is not only required for the central citrate synthase reaction in the TCA cycle but also acts as a competitive inhibitor of succinate dehydrogenase (SDH, complex II) and as a cataplerotic metabolite. Our working model refers to a mitochondrial dysfunction associated senescence-like phenotype, where the mitochondrial oxaloacetate levels are tightly regulated by FAHD1 activity. In particular, we investigate the role of FAHD1 in human cell metabolism, focusing on metabolic shifts in human cell lines upon FAHD1 knockdown, and we assess the dependence of these cells on FAHD1 for proliferation and survival. FAHD1 was identified to be up-regulated in breast cancer tissues. The consequences of a lentiviral FAHD1 knockdown were investigated in two breast cancer cell lines representative for the luminal and the basal subtype, namely MCF-7 and BT 20. Cellular proliferation was assessed in different media compositions and metabolic alterations were analyzed by high resolution respirometry and protein expression patterns. Depletion of FAHD1 in MCF-7 and BT-20 breast cancer cells results in lower succinate dehydrogenase activity. This leads to reduced proliferation of luminal MCF-7 when cultured in medium containing only glutamine as carbon source. Of note, both cell lines show attenuated protein levels of the enzyme glutaminase (GLS). Basal BT-20 cells activate programmed cell death due to FAHD1 withdrawal2. We currently assess the dependence of breast cancer cells in particular on FAHD1 for proliferation and survival, and we develop competitive inhibitors of FAHD13. We anticipate that a successful elucidation of the role of FAHD1 as a therapeutic target in cancer will stimulate translational research and may contribute to new therapeutic strategies for human malignancies.

Biography:

Dr. Alexander Weiss after his studies of chemistry at the University of Innsbruck, he obtained his magister and doctor degrees in Theoretical Chemistry, working on numerical models and statistics in terms of computer aided simulations and quantum mechanics.

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