MITOCHONDRIAL BCAA METABOLISM IN PANCREATIC CANCER FACILITATES MITOCHONDRIAL IMPORT OF FATTY ACIDS

Gotvaldová K.[1], Špačková J.[1], Smolková K.[1]

[1]*Laboratory of Mitochondrial Physiology, Institute of Physiology of the Czech Academy of Sciences, Prague, Czech Republic*

Catabolism of branched-chain amino acids (BCAA) takes place in mitochondria but the main directions of BCAA-derived carbons are not clear in many cell types and tissues. We asked what is the cellular fate of BCAA in pancreatic carcinoma (PDAC) cells and what the metabolic consequences of BCAA utilization are. In general, PDAC-derived cells grown in media without BCAA have lower respiration, lower levels of TCA metabolites (citrate and 2OG), decreased viability and growth rate. Subsequent profiling of the cellular lipid pool uncovered upregulation of triglycerides (TG) in BCAA-depleted conditions and buildup of lipid droplets (LD). TG and LD deposition was prevented by inhibition of DGAT1 and the treatment with branched-chain keto acid (BCKA). We have focused on downstream metabolites of the BCAA catabolic pathway that could possibly mediate TG upregulation and we found a negative correlation between TG species and short-chain carnitines (SC-CAR), which rise from downstream BCAA metabolites SC-CoAs by mitochondrial enzyme carnitine-acetyltransferase (CRAT). We have subsequently confirmed the downregulation of SC-CAR species in BCAA-depleted conditions and also in BCKDHA and CRAT knockout cells, which demonstrate that several specific species of SC-CAR are direct products of the BCAA catabolic pathway. We hypothesized that SC-CARs interfere with the import of long-chain carnitines (LC-CAR) into mitochondria and cause the deposition of cytosolic fatty acids into triglycerides and lipid droplets. Indeed, we observed a decreased import of the green fluorescent fatty acid, BODIPY-FL-C16, into mitochondria in BCAA-depleted conditions. We presume that the mitochondrial FA import might be regulated by malonyl-CoA levels via AMPK-ACC-CPT1 axis. So, our findings extend our knowledge of BCAA biochemistry beyond oxidative metabolism toward cellular FA handling between anabolic and catabolic pathways. Our data imply the functional consequences of BCAA metabolism in non-cancerous as well as cancerous tissues and possibly also in the development of PDAC-related cachexia.

Supported by the grant NV19-01–00101 of the Czech Health Research Council.