Rapidly proliferating cells, including many tumors, face the need to produce both ATP by catabolic processes as well as many compounds serving as building blocks for anabolic reactions. These opposing requirements lead to specific adaptations of cellular metabolism, including high rates of glucose utilization. In order to sustain high glycolytic rate, many cancer types depend on functional mitochondrial respiration (aerobic glycolysis) for reoxidation of cytosolic NAD(P)H pool. An important component of this pathway is glycerophosphate (GP)-shuttle, which connects mitochondrial and cytosolic processes (glycolysis, lipogenesis) and plays an important role in cell bioenergetics, both under physiological and pathological conditions. One component of GP-shuttle, namely mitochondrial glycerol-3-phosphate dehydrogenase (mGPDH), has highly variable expression across mammalian tissues and effectively acts as rate limiting component of the whole shuttle. In our research, we focus on the utility of mGPDH as potential druggable target in cancer cells lines.

Recently, several compounds were identified as mGPDH inhibitors: α-tocopheryl succinate (α-TOS), biguanides (metformin and phenformin) and a novel specific compound i-GP1. At first, we focused on direct inhibitory mechanisms of the inhibitors on brown adipose tissue (BAT) mitochondria, an established model of high mGPDH content. We found that physiologically relevant inhibitors are α-TOS and i-GP1 (IC50~10 uM). Unlike biguanides, these inhibitors did not increase oxidative stress.

In parallel, we decided to test whether the proliferation of selected cancer cells is affected by mGPDH inhibitors in order to verify mGPDH as a druggable target. Given that metastasis is one of the cancer hallmarks, we identified prostate cancer cell lines of metastatic origin with high mGPDH content and activity. Regardless of the profound inhibitory effect of α-TOS and i-GP1 on the enzyme activity, cell proliferation was modulated solely by suprapharmacological levels of metformin. However, epidemiological studies have clearly indicated that the type II diabetes patients treated with metformin have lower risk of cancer. Therefore we propose an indirect modulatory mechanism of pharmacological concentrations of metformin as a cause of antitumorigenic activity.

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