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Metabolism as a target for drug development

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Already at an early stage of cancer drug development it was recognized that metabolism in cancer cells is different from normal cells. The Warburg effect postulates that in (hypoxic) tumor cells energy supply switches from the mitochondrion to the cytoplasmic glycolysis. Nobel laureates Georges Hitchings and Gertrude Elion developed a number of drugs targeting metabolism, which appeared to be life-saving such as antifolates and thiopurines. These drugs are not only the mainstay in curative treatment of pediatric leukemia, but are also standard medication for various inflammatory diseases. Their rational design of antimetabolite based combinations formed the basis for the curative treatment of various viral diseases (e.g. AIDS-HIV) and cancer. All these approaches have in common that various pathways in cellular metabolism are being targeted.

Targeting metabolism benefits from methodologies such as genomics, proteomics and most importantly metabolomics. Genomics enables to characterize potential targets in tumors, while metabolomics (using e.g. imaging mass spectrometry) enables to determine hundreds of metabolites demonstrating major metabolic changes in cancer cells. With molecular modeling effective drugs were designed (with suitable ADME properties) that target key enzymes in metabolism. We have demonstrated that some of these enzymes, such as lactate dehydrogenase A (LDH-A) and transporters such as GLUT1, are increased in tumors, including non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC) and malignant pleural mesothelioma (MPM). Specific inhibitors of LDH-A (NHI-1, NHI-2) were more effective against hypoxic tumor cells, and increased the efficacy of standard chemotherapeutics such as gemcitabine and pemetrexed in PDAC and MPM, respectively. A combination of LDHA and GLUT1 inhibitors was synergistic in MPM cells, and associated with specific depletion of adenine nucleotides and NAD+/NADH. In order to increase the cellular uptake of NHI-2, a glycosylated derivative was synthesized (NHI-GLC-2), which showed a marked antitumor effect against MPM cells. Targeting of pyruvate dehydrogenase kinase (PDK1) in NSCLC cells with compound 64 in combination with LDH-A inhibitors was highly synergistic leading to increased apoptosis and inhibition of the AKT-mTOR pathway, as well as normalization of mitochondrial respiration, The combination of LDH-A and PDK1 inhibition was also very effective in an in vivo model of NSCLC.

In conclusion, novel inhibitors of the glycolytic pathways have marked anticancer activity in notably resistant tumors, such as PDAC, MPM and NSCLC. Synergism (both in vitro and in vivo) was observed for combinations with standard anticancer drugs, as well as for combined inhibition of e.g. LDH-A and GLUT-1 or LDH-A and PDK1.