Abstract

Mitochondrial isocitrate dehydrogenase 2 (IDH2) catalyzes reductive carboxylation (RC, reverse Krebs cycle pathway) and 2HG synthesis (2HG) – metabolite of which many scientists are interested. 2HG may be concurrently synthetized in cytosol by IDH1.

RC is involved in anabolic reactions necessary for cell proliferation - produces citrate, fatty acid precursor – especially in hypoxia.

IDH2 and IDH1 are not the only enzymes that are involved in 2HG synthesis. Recently, several enzymes, which participate in 2HG production, have been discovered.

2HG is useful in cancer diagnostics due to its overproduction by transformed cells. Moreover, 2HG may cause epigenetic changes via inhibition of 2-oxoglutarate dependent dioxygenase.

In this work, the importance of RC and 2HG synthesis in cancer and healthy cells was investigated by gas chromatography with mass spectrometry detection as well as IDH2 influence.

We found that IDH2 significantly participates in reverse RC and 2HG synthesis in breast cancer cell lines and uses glutaminolysis as a supplementary anaplerotic pathway. RC is increased by hypoxia, inhibition of respiration, and decreased by activation of respiration or hypocapnia.

We confirmed 2HG synthesis and RC in healthy cells (fibroblasts, breast epithelial cells etc.) as well as in cancer cells. Interestingly, we observed changes of physiological 2HG levels in healthy cells which correlated with proliferation (This effect was not so obvious in cancer cells.).

It seems that IDH2 could be suitable target of anticancer therapy.