# Genetic and pharmacological inhibition of pyruvate dehydrogenase kinases (PDKs) enhance chemotoxicity in gastric cancer cells

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**Background**: Pyruvate dehydrogenase kinases (PDKs) play a pivotal role in maintaining aerobic glycolysis, a hallmark of cancer known as the Warburg Effect. The metabolic alteration associated with the Warburg Effect confers survival advantages to cancer cells, including enhanced proliferation during hypoxic conditions and reduced oxidative cell stress. Consequently, targeting PDKs has emerged as a promising strategy in anticancer therapy. We investigated the impact of genetic and pharmacological PDK inhibition on cell metabolism and chemotherapy resistance in gastric cancer cells.

**Methods**: Two gastric cancer cell lines (MKN-45 and AGS) were cultured and subjected to chemotherapy treatment (CTx; oxaliplatin, docetaxel, or 5-fluorouracil). PDK activity was inhibited by sodium dichloroacetate (DCA), a pharmacological inhibitor, or small interfering RNAs (siRNAs) to individually downregulate PDK1-4. Cellular viability was assessed performing WST-1 assay. Metabolic assays were performed to quantify intracellular levels of lactate and reactive oxygen species (ROS). Gene expression levels were detected by RT-qPCR.

**Results**: CTx induced PDK mRNA levels in both gastric cancer cell lines. Upon CTx, inhibition of PDKs utilizing DCA further enhanced the anti-proliferative effects of CTx and reduced cell viability and intracellular lactate levels, suggesting metabolic reprogramming in these cells. In contrast, ROS levels were increased by DCA treatment upon CTx. Knockdown of PDK1, PDK2 and PDK3 showed comparable effects in the gastric cancer cell lines.

**Conclusion**: Pharmacological PDK inhibition increased the susceptibility of gastric cancer cells to CTx most likely by mitigating PDK activity. Moreover, our findings suggest metabolic reprogramming of gastric cancer cells by targeting PDK, which could thus present a promising therapeutic target in gastric cancer treatment.