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The inhibition effects of fenofibrate on gastric cancer cells via inducing mitochondrial dysfunctions and reversing cancer cell metabolic reprogramming dependent on PPARα pathway

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Statement of the Problem: The purpose was to explore the mitochondrial functions, energy substrates metabolism regulation roles and antitumor effects of PPARα agonist fenofibrate in gastric cancer cells, to verify PPARα's roles in fenofibrate's effects and to further observe its safety and effectiveness *in vivo*.

Methodology & Theoretical Orientation: In gastric cell lines MGC803 and SGC7901 cells with or without fenofibrate treatment, CCK8 assay was used to detect the proliferation; western blot and mitochondrial stress test were performed. The mitochondrial glycolysis levels, glucose metabolism and free fatty acids quantity were detected by corresponding kits. Flow cytometry (FCM) was used to detect the apoptosis and the western blot was conducted to detect Bcl-2, Bid, Bax, Caspase3, PARP and AMPK and PI3K/Akt signal pathway. The Kaplan-Meier was used to analyze the relationship between PPARα gene expression and prognosis in gastric cancer patients and PPARα gene function was further conformed by siRNA technology. The subcutaneous tumor-bearing animal model of gastric cancer was established in immunodeficient mice to further observe its safety and effectiveness *in vivo*.

Findings: The results showed that fenofibrate could inhibit the proliferation and promote the apoptosis of gastric cancer cells by damaging mitochondrial structures, mediating mitochondrial dysfunctions, inhibiting glycolysis and fatty acid anabolism, promoting triglyceride and fatty acid catabolism. Meantime, fenofibrate activated the AMPK pathway and inhibited the PI3K/Akt pathway. The expression of PPARα in gastric cancer is higher than that in normal gastric tissues and the prognosis of patients with high PPARα expression is worse. The effects of fenofibrate on cell growth inhibition, mitochondrial functions and metabolic reprogramming of gastric cancer cells depends on the PPARα pathway. Fenofibrate also inhibited gastric cancer cell growth in vivo with no obvious side effects.

Conclusion & Significance: Fenofibrate reversed metabolic reprogramming of gastric cancer cells via inducing mitochondrial dysfunctions through PPARα pathway.

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