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Fenofibrate suppresses oral tumorigenesis via reprogramming metabolic processes

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Objectives: In Taiwan, oral squamous cell carcinoma (OSCC) is the mostcommon head and neck cancerwith poor prognosis due to frequent lymph node metastasis and local invasion.Most cancer cells rely on a metabolic/cell signaling basis of Warburg effect to generate the energy needed for cellular processes. Metabolic and anti-inflammatory effects induced by peroxisome proliferator-activated receptors (PPARs) are reported to interfere with Warburg effect.Fenofibrate, an agonist of PPARα, is a potent and effective clinical lipid-lowering reagent. Our previous study demonstrated that fenofibrate reduced the tumor incidence rate, decreased the tumor size, and suppressed the tumor progression into squamous cell carcinoma in an oral-specific 4-nitroquinoline 1-oxide (4-NQO)/arecoline mouse model. We also found that fenofibrate inhibits the invasion and migration of CAL27oral cancer cells, which were correlated with adenosine 5'-monophosphate-activated protein kinase signaling. The aim of this study was to explore the antitumor effects and mechanisms of fenofibrate on metabolic reprogramming and molecular signaling.

Methods: We used SAS (high-grade malignant cells) and OECM1 (low-grade malignant cells)to explore the effect of fenofibrate on metabolic reprogramming. Primary cultured cells from mouse tongue cancer were used to examine the metabolites in glycolysis and tricarboxylic acid cycle. The preventive and therapeutic efficacy of fenofibrate was evaluatedin an oral-specific 4-NQO/arecoline mouse model.

Results: We found that fenofibrate induced metabolic reprogramming by changing the protein expressions of hexokinase II (HK II), pyruvate kinase, pyruvate dehydrogenase, and voltage-dependent anion channel (VDAC), which are associated with Warburg effect. In addition, fenofibrate inhibited the binding of HK II to VDAC and increased metabolites in tricarboxylic acid cycle.Inoral-specific mouse model, we found fenofibrate had both preventive and therapeutic efficacy on oral tumorigenesis.Fenofibrate treatment suppressed the incidence rate of tongue lesions, reduced the tumor multiplicity, decreased the tumor size, and decreased the immunoreactivity of mTOR.

Conclusions:*Fenofibrate demonstrated both preventive and therapeutic efficacy on oral tumorigenesis. The molecular mechanisms involved in inducing the dissociation of HK II from the mitochondria and promoting metabolic reprogramming. Our findings provide a molecular rationale, whereby fenofibrate exerts anticancer effects and additional beneficial effects for the treatment of cancer patients.*