Fenofibrate

Fenofibrate, a fibric acid derivative, is a lipid-lowering drug and an agonist of the peroxisome proliferator-activated receptor alpha (PPARα). Han et al. found that FF inhibited glycolysis in a PPARα-dependent manner in glioblastoma cells. Fenofibrate inhibited the transcriptional activity of NF-κB/RelA and also disrupted its association with hypoxia inducible factor1 alpha (HIF1α), which is required for the binding of NF-κB/RelA to the PKM promoter and PKM2 expression. High ratios of PKM2/PKM1 promote glycolysis and inhibit oxidative phosphorylation, thus favoring aerobic glycolysis. Fenofibrate decreased the PKM2/PKM1 ratio and caused mitochondrial damage. Given that fenofibrate is a widely used non-toxic drug, Han et al. suggest its use in patients with glioblastoma multiforme (GBM) [1].

Fenofibrate exhibited dose-dependent tp53-independent anti-proliferative effects on high grade glioma (HGG] starting at 25 µM and pro-apoptotic effects starting at 50 µM, suggesting that the anti-proliferative actions are present only at 25 µM. PPARα was expressed in all HGG cell lines. Inhibition of PPARα with specific inhibitor GW6471 did not affect either proliferation or apoptosis suggesting that these are PPARα-independent effects. Fenofibrate treatment of HGG cells robustly diminished the expression of key signaling pathways, including NF-κB and cyclin D1. Phosphorylation of Akt was also diminished, with no change in total Akt. Effects on apoptotic signaling molecules, Bax and Bcl-xL, had a trend towards pro-apoptotic effects. With respect to GSC, fenofibrate treatment at 25 µM significantly decreased invasion in association with a decrease in CD133 and OCT4 expression. Overall, results support consideration of fenofibrate as an anti-glioma agent and establish its potential as an adjunct treatment strategy for HGG. Translation to the clinical setting could be rapid given its current use as a clinical agent and its low toxicity profile [2].

Although fenofibrate-induced peroxisome proliferator-activated receptor alpha (PPARα) transcriptional activity has been reported to exhibit anticancer effects, the underlying mechanisms are poorly understood. In a study, Han et al. investigated the mechanisms behind the antiproliferative effects of fenofibrate in U87MG cells (human glioma cell line) using the WST-8 Cell Proliferation Assay Kit. Furthermore, Han et al. examined genome-wide gene expression profiles and molecular networks using the DAVID online software. Fenofibrate reduced the expression of 405 genes and increased the expression of 2280 genes. DAVID analysis suggested that fenofibrate significantly affected cell cycle progression and pathways involved in cancer, including the mTOR signaling pathway and insulin signaling pathway. Results of flow cytometry analysis indicated that fenofibrate induced cell cycle G0/G1 arrest in U87MG cells. Furthermore, we identified the FoxO1-p27kip signaling axis to be involved in fenofibrate-induced cell cycle arrest. These findings suggest that in addition to its known lipid-lowering effects, fenofibrate may be used as an antitumor agent in glioma therapy [3].

1)
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