Glioblastoma is the most aggressive type of brain tumor and is characterized by rapid and infiltrative growth. Current therapeutic approaches involving surgical resection, radiation and chemotherapy are largely ineffective, rendering glioblastoma essentially untreatable. MicroRNAs are small, non-coding RNAs of single-stranded RNA that regulate gene expression by incomplete base pairing with messenger RNA. They bind to the 3’ untranslated region of mRNAs and inhibit translation. We previously found that mir-3189-3p inhibits proliferation and migration of glioblastoma cells. Interestingly, expression of this microRNA is low in clinical samples of astrocytomas, suggesting that a forced expression of mir-3189-3p in these tumors may be an effective strategy for glioblastoma treatment.

Methods

Fenofibrate is a peroxisome-proliferator activated receptor alpha (PPAR-α) agonist, a lipid-lowering drug commonly used for the treatment of cardiovascular disease (CV disease). We previously showed that fenofibrate-mediated expression of GDF15 and miR-3189-3p is PPAR-α independent. Furthermore, we have demonstrated that miR-3189-3p expression is involved in the transcriptional control of proliferation, cell cycle progression and immune evasion. Since fenofibrate-mediated expression of GDF15 and miR-3189-3p is PPAR-α independent, we investigated whether fenofibrate treatment affects STAT3 phosphorylation in our experimental conditions.

To test this hypothesis, we first tested the efficacy of two different JAK2 inhibitors (AG490, JAK2 specific inhibitor, and Tofacitamib, a pan-JAK inhibitor) in our experimental conditions. To this end, we found that fenofibrate treatment is PPAR-α independent.

Results

1) Fenofibrate-mediated expression of GDF15 and mir-3189-3p is PPAR-α independent. Quantitative RT-PCR analysis, as expected, revealed increased expression of both GDF15 and mir-3189-3p in all samples treated with fenofibrate and the addition of the PPAR-α inhibitor (Fig. 3A). The silencing of the receptor through siRNA (Fig. 3A) did not significantly change the levels of expression of these two molecules. The effectiveness of siPPAR-α in downregulating PPAR-α mRNA was also evaluated by quantitative RT-PCR in all the samples and results in Figure 3B show this downregulation.

Conclusion

In the current study, we found that increased expression of GDF15 and mir-3189-3p by fenofibrate treatment is PPAR-α independent. We also found that fenofibrate-treated cells expressed levels of phosphorylated STAT3 that were lower than control cells, suggesting that fenofibrate treatment decreases STAT3 phosphorylation.