The combination of metformin and TMZ was superior to monotherapy using metformin or TMZ in terms of cell viability in vitro and survival in vivo. The combination of high-dose metformin and TMZ inhibited FASN expression in an orthotopic model. Inhibition of fatty acid synthase (FASN) might be a potential therapeutic target of GBM. [1].

Previous research has shown that metformin, an oral anti-diabetic drug, may decrease glioblastoma (GBM) cell proliferation and migration especially in brain tumor initiating cells (BTICs). As transforming growth factor β 2 (TGF-β2) has been reported to promote high grade glioma and is inhibited by metformin in other tumors, Seliger et al., explored whether metformin directly interferes with TGF-β2-signaling. Functional investigation of proliferation and migration of primary BTICs after treatment with metformin+/-TGF-β2 revealed that metformin doses as low as 0.01 mM metformin thrice a day were able to inhibit proliferation of susceptible cell lines, whereas migration was impacted only at higher doses. Known cellular mechanisms of metformin, such as increased lactate secretion, reduced oxygen consumption and activated AMPK-signaling, could be confirmed. However, TGF-β2 and metformin did not act as functional antagonists, but both rather inhibited proliferation and/or migration, if significant effects were present.

They did not observe a relevant influence of metformin on TGF-β2 mRNA expression (qRT-PCR), TGF-β2 protein expression (ELISA) or SMAD-signaling (Western blot). Therefore, it seems that metformin does not exert its inhibitory effects on GBM BTIC proliferation and migration by altering TGF-β2-signaling. Nonetheless, as low doses of metformin are able to reduce proliferation of certain GBM cells, further exploration of predictors of BTICs' susceptibility to metformin appears justified [2].

Evidence from other tumor models suggests that metformin inhibits STAT3, but there is no specific data on Brain tumor initiating cells (BTICs).

Leidgens et al., explored proliferation and migration of 7 BTICs and their differentiated counterparts (TCs) after treatment with Stattic, metformin or the combination thereof. Invasion was measured in situ on organotypic brain slice cultures. Protein expression of phosphorylated and total STAT3, as well as AMPK and mTOR signaling were explored using Western blot. To determine functional relevance of STAT3 inhibition by Stattic and metformin, they performed a stable knock-in of STAT3 in selected BTICs.Inhibition of STAT3 with Stattic reduced proliferation in all BTICs, but only in 4 out of 7 TCs. Migration and invasion were equally inhibited in BTICs and TCs. Treatment with metformin reduced STAT3-phosphorylation in all investigated BTICs and TCs. Combined treatment with Stattic and metformin led to significant additive effects on BTIC proliferation, but not migration or invasion. No additive effects on TCs could be detected. Stable STAT3 knock-in partly attenuated the effects of Stattic and metformin on BTICs.In conclusion, metformin was found to inhibit STAT3-phosphorylation in BTICs and TCs. Combined specific and unspecific inhibition of STAT3 might represent a promising new strategy in the treatment of glioblastoma [3].

1)
Lee JE, Lim JH, Hong YK, Yang SH. High-Dose Metformin Plus Temozolomide Shows Increased Anti-tumor Effects in Glioblastoma In Vitro and In Vivo Compared with Monotherapy. Cancer Res Treat. 2018 Jan 10. doi: 10.4143/crt.2017.466. [Epub ahead of print] PubMed PMID: 29334602.
2)
Seliger C, Meyer AL, Renner K, Leidgens V, Moeckel S, Jachnik B, Dettmer K, Tischler U, Gerthofer V, Rauer L, Uhl M, Proescholdt M, Bogdahn U, Riemenschneider MJ, Oefner PJ, Kreutz M, Vollmann-Zwerenz A, Hau P. Metformin inhibits proliferation and migration of glioblastoma cells independently

of TGF-β2. Cell Cycle. 2016 Jul 2;15(13):1755-66. doi: 10.1080/15384101.2016.1186316. PubMed PMID: 27163626; PubMed Central PMCID: PMC4957567.

3)

Leidgens V, Proske J, Rauer L, Moeckel S, Renner K, Bogdahn U, Riemenschneider MJ, Proescholdt M, Vollmann-Zwerenz A, Hau P, Seliger C. Stattic and metformin inhibit brain tumor initiating cells by reducing STAT3-phosphorylation. Oncotarget. 2016 Dec 24. doi: 10.18632/oncotarget.14159. [Epub ahead of print] PubMed PMID: 28030813.