An ID1-EGF-EGFR Axis is Critical for Tumorigenesis and Regulates Chemoresistance in Glioblastoma

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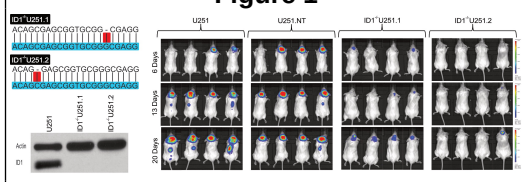
Introduction

Glioblastoma is the most common primary brain tumor in adults. While the introduction of temozolomide chemotherapy has increased long-term survivorship, treatment failure and rapid tumor recurrence remains universal. In colon cancer, knockdown of ID1 and ID3 have been shown to impair self-renewal of colon cancer tumor initiating cells, reduce tumor growth and enhance sensitivity to chemotherapy. In this study, we investigated the role of ID1 in tumor initiation, treatment resistance, and disease recurrence in glioblastoma.

Methods

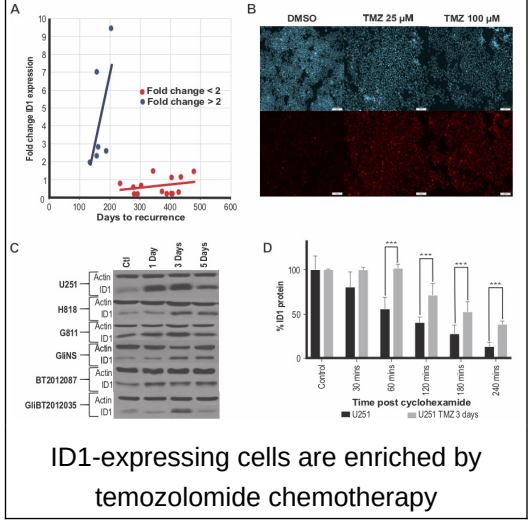
To elucidate the oncogenic properties of ID1, we used the CRISPR-Cas9 mediated lentiviral system to knockout ID1 in glioblastoma (U251), breast adenocarcinoma (MDA-MB-231), and melanoma (A375) cells. In vtiro proliferation assays were performed, as were assays to determine temozolomide sensitivity. Xeongraft studies utilizing luciferase-expressing glioma cells and bioluminescence were performed to study tumorigenic potential and tumor progression in vivo. The neuroleptic drug pimozide was identified as a potent chemical inhibitor of ID1.

Figure 1



ID1 is necessary for tumor initiation and growth in glioblastoma

Figure 2

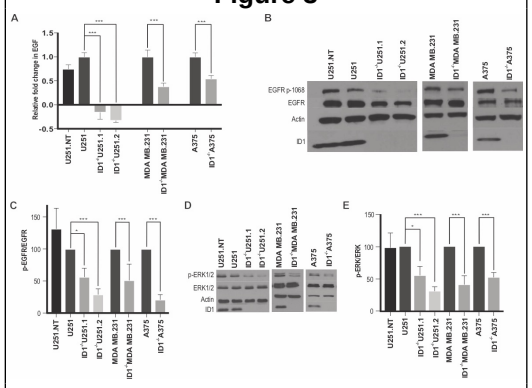


ID1-expressing cells are enriched by temozolomide chemotherapy

Results

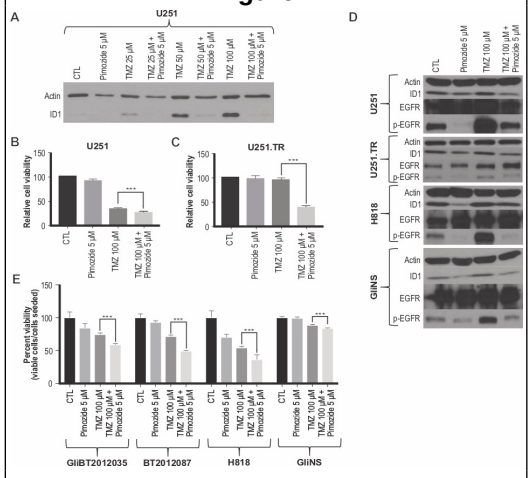
We show that ID1 is necessary for tumor initiation and tumor growth in multiple solid cancers, including glioblastoma, breast adenocarcinoma and melanoma (Fig. 1). Treatment of glioblastoma cells with temozolomide results in enrichement of ID1-expressing cells (Fig. 2). Through induction of EGF, ID1 maintains EGFR in a continuously activated state (Fig. 3). Inhibition of ID1 by genetic knockout or with the antipsychotic agent, pimozide, enhances the cytotoxic effect of the alkylating agent, temozolomide (Fig. 4). Concurrent pimozimde therpay delays tumor recurrence and prolongs survival in a mouse model of glioblastoma (Fig. 5).

Figure 3



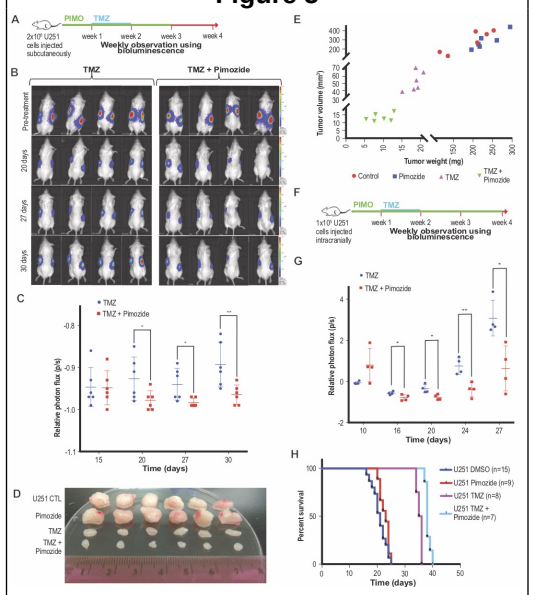
ID1 maintains EGFR in a continuously activated state

Figure 4



Inhibition of ID1 by genetic knockout or with the antipsychotic agent, pimozide, enhances the cytotoxic effect of the alkylating agent, temozolomide

Figure 5



Concurrent pimozimde therpay delays tumor recurrence and prolongs survival in a mouse model of glioblastoma

Conclusions

Taken together, our data suggests that ID1 regulates multiple tumor-promoting pathways in cancer by positively regulating EGF expression and thereby EGFR activity. Targeting ID1 and thereby the EGFR pathway with drugs such as pimozide may represent a novel and promising strategy for therapy in patients with glioblastoma.