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**TITLE:** Identification of thioridazine, an antipsychotic drug, as an antiglioblastoma and anticancer stem cell agent using big data analysis

**ABSTRACT:** Glioblastoma (GBM) is a common and malignant tumor with a poor prognosis. Glioblastoma stem cells (GSCs) have been reported to be involved in tumorigenesis, tumor maintenance and therapeutic resistance. Thus, to discover novel candidate therapeutic drugs for anti-GBM and anti-GSCs is an urgent need. We hypothesized that if treatment with a drug could reverse, at least in part, the gene expression signature of GBM and GSCs, this drug may have the potential to inhibit pathways essential in the formation of GBM and thereby treat GBM. Here, we collected 356 GBM gene signatures from public databases and queried the Connectivity Map. We systematically evaluated the in vitro antitumor effects of 79 drugs in GBM cell lines. Of the drugs screened, thioridazine was selected for further characterization because the gene expression signature of thioridazine can modulate the Signaling Pathways in Glioblastoma and thioridazine has potent anti-GBM and anti-GSCs properties. When investigating the mechanisms underlying the cytotoxic effects of thioridazine, we found that thioridazine induces autophagy in GBM cell lines, and upregulates AMPK activity. Moreover, LC3-II was upregulated in U87MG sphere cells treated with thioridazine. In addition, thioridazine suppressed GBM tumorigenesis and induced autophagy in vivo. We not only repurposed the antipsychotic drug thioridazine as a potent anti-GBM and anti-GSCs agent, but also provided a new strategy to search for drugs with anticancer and anticancer stem cell properties.