Dopamine receptor in glioblastoma

see also trifluoperazine

Studies have reported important roles of dopamine receptors in the early development and progression of glioblastoma (GBM).

There are ongoing clinical trials exploring the efficacy of dopamine receptor D2 (DRD2) inhibition against glioblastomas. He et al. examined potential molecular determinants of this efficacy.

The Cancer Genome Atlas (TCGA) glioblastoma database and other published mRNA profiles were used to analyze the DRD2 and EGFR expression pattern. In vitro and in vivo responses to DRD2 inhibitors were determined using patient derived xenograft (PDX) glioblastoma models. Immunohistochemical studies were performed on clinically annotated glioblastoma samples derived from patients treated with ONC201.

Analysis of clinical glioblastoma specimens derived from independent patient cohorts revealed an inverse correlation between EGFR and DRD2 mRNA expression, with implication that signaling mediated by these proteins shares overlapping functions. In independent panels of PDX glioblastoma lines, high EGFR expression was associated with poor in vitro and in vivo response to DRD2 inhibitors, including haloperidol and ONC201. Moreover, ectopic expression of a constitutively active EGFR, EGFRvIII, suppressed glioblastoma sensitivity to ONC201. DRD2 expression positively correlated with expression of rate-limiting enzymes for dopamine synthesis as well as dopamine secretion, suggesting contribution of autocrine DRD2 signaling. Analysis of specimens from patients treated with ONC201 (n = 15) showed an inverse correlation between the intensity of EGFR staining and clinical response. The median overall survival for patients with high and low EGFR staining was 162 and 373 days, respectively (p = 0.037).

High EGFR expression is a determinant of poor glioblastoma response to DRD2. This finding should inform future clinical trial designs [1)].

Here, we tested the antitumor activity of a Dopamine receptor D1 (DRD1) agonist, either alone or in combination with temozolomide (TMZ) on GBM cells.

Methods: Immunofluorescence, immunohistochemistry and Western blotting were used to detect dopamine receptor expression in primary human GBM tissues. In addition, clinical data of GBM patients downloaded from The Cancer Genome Atlas (TCGA) were analyzed. Image-based tracking analysis of LC3 using a mCherry-eGFP-LC3 plasmid was utilized to monitor autophagic flux. Transmission electron microscopy (TEM) was used to visualize aggregation of autophagosomes/autolysosomes. Finally, DRD1 agonist (SKF83959)-induced inhibition of GBM growth was assessed in vitro and in vivo.

Results: Positive DRD1 expression was observed in human GBM tissues and found to be related with a good clinical outcome. DRD1 activation specifically inhibited GBM cell growth and significantly disrupted autophagic flux, which led to tumor cell death. Moreover, we found that DRD1 agonist treatment inhibited auto-lysosomal degradation in GBM cells and that this process was calcium

overload dependent and related to inhibition of mammalian target of rapamycin (mTOR). Finally, we found that DRD1 agonist and TMZ co-treatment yielded a synergistic therapeutic effect both in vivo and in vitro.

Conclusions: From our data we conclude that DRD1 activation inhibits GBM cell growth and may serve as an alternative avenue for the design of future GBM therapies [2].

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He Y, Li J, Koga T, et al. Epidermal Growth Factor Receptor (EGFR) as a molecular determinant of glioblastoma response to dopamine receptor 2 (DRD2) inhibitors [published online ahead of print, 2020 Aug 24]. Neuro Oncol. 2020;noaa188. doi:10.1093/neuonc/noaa188
2)
Yang K, Wei M, Yang Z, et al. Activation of dopamine receptor D1 inhibits glioblastoma tumorigenicity by regulating autophagic activity [published online ahead of print, 2020 Aug 6]. Cell Oncol (Dordr). 2020;10.1007/s13402-020-00550-4. doi:10.1007/s13402-020-00550-4