Dual targeting of polyamine synthesis and uptake in diffuse intrinsic pontine gliomas

Aaminah Khan[1], Laura D Gamble[1], Dannielle H Upton[1], Caitlin Ung[1], Denise M T Yu[1], Anahid Ehteda[1], Ruby Pandher[1], Chelsea Mayoh[1], Steven Hébert[2], Nada Jabado[3], Claudia L Kleinman[2], Mark R Burns[4], Murray D Norris[1,5], Michelle Haber[1,5], Maria Tsoli[#1], David S Ziegler[#6,7]
Affiliations Expand

- PMID: 33579942
- PMCID: PMC7881014
- DOI: 10.1038/s41467-021-20896-z

Abstract

Diffuse intrinsic pontine glioma (DIPG) is an incurable malignant childhood brain tumor, with no active systemic therapies and a 5-year survival of less than 1%. Polyamines are small organic polycations that are essential for DNA replication, translation and cell proliferation. Ornithine decarboxylase 1 (ODC1), the rate-limiting enzyme in polyamine synthesis, is irreversibly inhibited by difluoromethylornithine (DFMO). Herein we show that polyamine synthesis is upregulated in DIPG, leading to sensitivity to DFMO. DIPG cells compensate for ODC1 inhibition by upregulation of the polyamine transporter SLC3A2. Treatment with the polyamine transporter inhibitor AMXT 1501 reduces uptake of polyamines in DIPG cells, and co-administration of AMXT 1501 and DFMO leads to potent in vitro activity, and significant extension of survival in three aggressive DIPG orthotopic animal models. Collectively, these results demonstrate the potential of dual targeting of polyamine synthesis and uptake as a therapeutic strategy for incurable DIPG.

https://pubmed.ncbi.nlm.nih.gov/33579942/