

Dihydroorotate dehydrogenase

Dihydroorotate dehydrogenase (DHODH) is an enzyme that in humans is encoded by the DHODH gene on chromosome 16. The protein encoded by this gene catalyzes the fourth enzymatic step, the ubiquinone-mediated oxidation of dihydroorotate to orotate, in de novo pyrimidine biosynthesis. This protein is a mitochondrial protein located on the outer surface of the inner mitochondrial membrane (IMM).

Inhibitors of this enzyme are used to treat autoimmune diseases such as rheumatoid arthritis.

Glioblastoma-initiating cells (GICs) comprise a **tumorigenic subpopulation** of **cells** that are resistant to **radiotherapy** and **chemotherapy** and are responsible for **recurrent glioblastoma**. The aim of a study of Echizenya et al. was to identify novel compounds that specifically eradicate GICs using a high throughput drug screening approach.

They performed a **cell proliferation**/death-based drug screening using 10,560 independent compounds. They identified **DHODH** as a target protein of hit compound 10580 using ligand-fishing and mass spectrometry analysis. The medical efficacy of 10580 was investigated by in vitro cell proliferation/death and differentiation and in vivo tumorigenic assays.

Among the effective compounds, they identified 10580, which induced **cell cycle arrest**, decreased the expression of **stem cell** factors in GICs and prevented tumorigenesis upon oral administration without any visible side effects. Mechanistic studies revealed that 10580 decreased **pyrimidine nucleotide** levels and enhanced **SOX2** nuclear export by antagonizing the enzyme activity of DHODH, an essential enzyme for de novo pyrimidine synthesis.

In this study, Echizenya et al. identified 10580 as a promising new drug against GICs. Given that normal tissue cells, in particular brain cells, tend to use the alternative salvage pathway for pyrimidine synthesis, this findings suggest that 10580 can be used for **glioblastoma treatment** without side effects ¹⁾.

¹⁾

Echizenya S, Ishii Y, Kitazawa S, Tanaka T, Matsuda S, Watanabe E, Umekawa M, Terasaka S, Houkin K, Hatta T, Natsume T, Maeda Y, Watanabe SI, Hagiwara S, Kondo T. Discovery of a new pyrimidine synthesis inhibitor eradicating glioblastoma-initiating cells. Neuro Oncol. 2019 Sep 10. pii: noz170. doi: 10.1093/neuonc/noz170. [Epub ahead of print] PubMed PMID: 31499527.

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