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Introduction

Serine supports a number of anabolic processes, including protein, lipid, and nucleic acid synthesis. Cells can either import serine or synthesize it de novo. Recently, overexpression of 3-phosphoglycerate dehydrogenase (*PHGDH*), the gene encoding the first committed step of serine synthesis, via focal amplification and other mechanisms, has been identified in human cancers. Cancer cell lines that overexpress *PHGDH* are uniquely sensitive to PHGDH knockdown whereas lines that express little PHGDH are insensitive, suggesting that PHGDH may be a clinically interesting target. Here, authors report the discovery of a specific small molecule inhibitor of PHGDH, which enables preclinical evaluation of PHGDH as a target in cancer and provides a tool to study the biology of de novo serine synthesis.

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Identification of a small molecule inhibitor of 3-phosphoglycerate dehydrogenase to target serine biosynthesis in cancers

Mullarky E, Lucki NC, Beheshti Zavareh R, Anglin JL, Gomes AP, Nicolay BN, Wong JC, Christen S, Takahashi H, Singh PK, Blenis J, Warren JD, Fendt SM, Asara JM, DeNicola GM, Lyssiotis CA, Lairson LL, Cantley LC.

Abstract

Cancer cells reprogram their metabolism to promote growth and proliferation. The genetic evidence pointing to the importance of the amino acid serine in tumorigenesis is striking. The gene encoding the enzyme 3-phosphoglycerate dehydrogenase (PHGDH), which catalyzes the first committed step of serine biosynthesis, is overexpressed in tumors and cancer cell lines via focal amplification and nuclear factor erythroid-2-related factor 2 (NRF2)-mediated up-regulation. PHGDH-overexpressing cells are exquisitely sensitive to genetic ablation of the pathway. Here, we report the discovery of a selective small molecule inhibitor of PHGDH, CBR-5884, identified by screening a library of 800,000 drug-like compounds. CBR-5884 inhibited de novo serine synthesis in cancer cells and was selectively toxic to cancer cell lines with high serine biosynthetic activity. Biochemical characterization of the inhibitor revealed that it was a noncompetitive inhibitor that showed a time-dependent onset of inhibition and disrupted the oligomerization state of PHGDH. The identification of a small molecule inhibitor of PHGDH not only enables thorough preclinical evaluation of PHGDH as a target in cancers, but also provides a tool with which to study serine metabolism.