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Cancer Drug Resistance

Review

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PHGDH as a mechanism for resistance in metabolically-driven cancers

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Abstract

At the forefront of cancer research is the rapidly evolving understanding of metabolic reprogramming within cancer cells. The expeditious adaptation to metabolic inhibition allows cells to evolve and acquire resistance to targeted treatments, which makes therapeutic exploitation complex but achievable. 3-phosphoglycerate dehydrogenase (PHGDH) is the rate-limiting enzyme of de novo serine biosynthesis and is highly expressed in a variety of cancers, including breast cancer, melanoma, and Ewing's sarcoma. This review will investigate the role of PHGDH in normal biological processes, leading to the role of PHGDH in the progression of cancer. With an understanding of the molecular mechanisms by which PHGDH expression advances cancer growth, we will highlight the known mechanisms of resistance to cancer therapeutics facilitated by PHGDH biology and identify avenues for combatting PHGDH-driven resistance with inhibitors of PHGDH to allow for the development of effective metabolic therapies.

Keywords: PHGDH, cancer, metabolism, serine, one-carbon metabolism, folate cycle, drug resistance

INTRODUCTION

Recent advances in anti-cancer treatments have been based on the increased identification of biomarkers that allow for tumour-specific therapy. Biomarker-driven therapies allow for the differentiation between cancer and host cells, with the potential to decrease the side-effects often associated with chemotherapy