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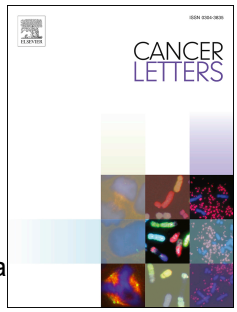

Aspartate beta-hydroxylase promotes cholangiocarcinoma progression by modulating RB1 phosphorylation

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Abstract

Cholangiocarcinoma (CCA) is a highly lethal and aggressive disease. Recently, IDH1/2 mutations have been identified in approximately 20% of CCAs which suggests an involvement of 2-oxoglutarate (2-OG) -dependent dioxygenases in oncogenesis. We investigated if the 2-OG dependent dioxygenase, aspartate beta-hydroxylase (ASPH) was important in tumor development and growth. Immunoassays were used to clarify how ASPH modulates CCA progression by promoting phosphorylation of the retinoblastoma protein (RB1). A xenograft model was employed to determine the role of ASPH on CCA growth. Knockdown of ASPH expression inhibited CCA development and growth by reducing RB1 phosphorylation. Expression of ASPH promoted direct protein interaction between RB1, cyclin-dependent kinases, and cyclins. Treatment with 2-OG-dependent dioxygenase and ASPH inhibitors suppressed the interaction between RB1 and CDK4 as well as RB1 phosphorylation. Knockdown of ASPH expression inhibited CCA progression and RB1 phosphorylation *in vivo* and they were found to be highly expressed in human CCAs. Knockdown of ASPH expression altered CCA development by modulating RB1 phosphorylation, as one of the major factors regulating the growth of these tumors.