Structure-based analysis of a natural GOT1-inhibitor Aspulvinone H arrests pancreatic ductal adenocarcinoma cells growth

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) cells are Gln-metabolism dependence, which can preferentially utilize glutamic oxaloacetate transaminase 1 (GOT1) to maintain the redox homeostasis of cancer cells. Therefore, small molecule inhibitors targeting GOT1 can be used as a new strategy for developing cancer therapies. Here, we identified a cyclobutyrolactone lignan, Aspulvinone H (AH), showing significant GOT1 inhibitory activity in vitro. The complex crystal structure of GOT1-AH elucidated the molecular mechanism, which AH and the cofactor pyrido-aldehyde 5-phosphate (PLP) competitively bound to the active sites of GOT1. Structure-activity relationship (SAR) analysis exhibited that the π-π stacking and isopentenyl side chain of aspulvinone were related to the inhibition of GOT1 activity. Further biological study indicated that AH could suppress glutamine metabolism, which made PDAC cells sensitive to oxidative stress and inhibited cell proliferation. Besides, AH exhibited potent in vivo antitumor activity in the SW1990 cell-induced xenograft model. These findings suggest that AH could be considered as a promising lead molecule for the development of PDAC anticancer agents.

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