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Small molecule inhibitor screening identifified HSP90 inhibitor 17-AAG as potential therapeutic agent for gallbladder cancer.

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Abstract

Gallbladder cancer (GBC) is a lethal cancer with poor prognosis associated with high invasiveness and poor response to chemotherapy and radiotherapy. New therapeutic approaches are urgently needed in order to improve survival and response rates of GBC patients. We screened 130 small molecule inhibitors on a panel of seven GBC cell lines and identified the HSP90 inhibitor 17-AAG as one of the most potent inhibitory drugs across the different lines. We tested the antitumor efficacy of 17-AAG and geldanamycin (GA) in vitro and in a subcutaneous preclinical tumor model NOD-SCID mice. We also evaluated the expression of HSP90 by immunohistochemistry in human GBC tumors.In vitro assays showed that 17-AAG and GA significantly reduced the expression of HSP90 target proteins, including EGFR, AKT, phospho-AKT, Cyclin B1, phospho-ERK and Cyclin D1. These molecular changes were consistent with reduced cell viability and cell migration and promotion of G2/M cell cycle arrest and apoptosis observed in our in vitro studies.In vivo, 17-AAG showed efficacy in reducing subcutaneous tumors size, exhibiting a 69.6% reduction in tumor size in the treatment group compared to control mice ($p < 0.05$).The HSP90 immunohistochemical staining was seen in 182/209 cases of GBC (87%) and it was strongly expressed in 70 cases (33%), moderately in 58 cases (28%), and weakly in 54 cases (26%).Our pre-clinical observations strongly suggest that the inhibition of HSP90 function by HSP90 inhibitors is a promising therapeutic strategy for gallbladder cancer that may benefit from new HSP90 inhibitors currently in development.