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Human hepatocellular carcinoma in a mouse model: assessment of tumor response to percutaneous ablation by using glyceraldehyde-3-phosphate dehydrogenase antagonists.

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Abstract

PURPOSE: To characterize tumor response to percutaneous injection of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) antagonists in a mouse model of human hepatocellular carcinoma (HCC).

MATERIALS AND METHODS: Animal experiments were approved by the Johns Hopkins University Animal Care and Use Committee. Luciferase (luc) gene-expressing Hep3B tumor-bearing athymic nude mice were randomly divided into four groups of six mice each. Tumor-specific GAPDH inhibition was achieved by using percutaneous injection of GAPDH antagonists-3-bromopyruvate (3-BrPA) or GAPDH-specific short hairpin RNA (shRNA). Tumor response to treatment was assessed by using bioluminescence imaging and analysis of GAPDH function and apoptotic markers (caspase-3, caspase-9, and positive staining for terminal deoxynucleotidyl transferase-mediated deoxyuridine 5-triphospate nick end labeling). HCC samples from 34 patients were obtained from the Johns Hopkins tumor bank, as approved by the Institutional Review Board, for GAPDH expression analysis. Statistical analysis was performed by using a two-sample t test or Spearman rank correlation coefficient.

RESULTS: In vitro, 3-BrPA affected Hep3B cell viability (half maximal inhibitory concentration = 0.15 mmol/L), and GAPDH shRNA suppressed (45.5%) colony formation. In vivo, percutaneous injection of GAPDH antagonists into luc-Hep3B tumors decreased bioluminescence imaging signal and viability (3-BrPA, P < .0001; GAPDH shRNA, P = .03). The 3-BrPA treatment primarily inhibited GAPDH activity (74.5%) compared with its expression (34.3%), whereas GAPDH shRNA inhibited both activity (60.6%) and expression (44.4%). Targeted inhibition of GAPDH by using 3-BrPA or shRNA induced apoptosis. HCC samples from patients demonstrated a strong correlation between GAPDH upregulation and the proto-oncogene c-jun expression (r = 0.543, P = .003).

CONCLUSION: Percutaneous injection of GAPDH antagonists induces apoptosis and blocks Hep3B tumor progression, which demonstrates the therapeutic potential of targeting GAPDH in human HCC.

Comment in

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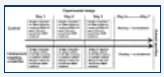
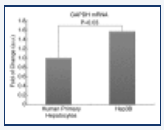
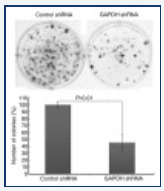
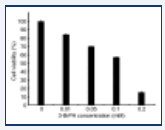

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