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A comprehensive study of epigenetic alterations in hepatocellular carcinoma identifies potential therapeutic targets

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Abstract

Background & aims: A causal link has recently been established between epigenetic alterations and hepatocarcinogenesis, indicating that epigenetic inhibition may have therapeutic potential. We aimed to identify and target epigenetic modifiers that show molecular alterations in hepatocellular carcinoma (HCC).

Methods: We studied the molecular-clinical correlations of epigenetic modifiers including bromodomains, histone acetyltransferases, lysine methyltransferases and lysine demethylases in HCC using The Cancer Genome Atlas (TCGA) data of 365 patients with HCC. The therapeutic potential of epigenetic inhibitors was evaluated in vitro and in vivo. RNA sequencing analysis and its correlation with expression and clinical data in the TCGA dataset were used to identify expression programs normalized by Jumonji lysine demethylase (JmjC) inhibitors.

Results: Genetic alterations, aberrant expression, and correlation between tumor expression and poor patient prognosis of epigenetic enzymes are common events in HCC. Epigenetic inhibitors that target bromodomain (JQ-1), lysine methyltransferases (BIX-1294 and LLY-507) and JmjC lysine demethylases (JIB-04, GSK-J4 and SD-70) reduce HCC aggressiveness. The pan-JmjC inhibitor JIB-04 had a potent antitumor effect in tumor bearing mice. HCC cells treated with JmjC inhibitors showed overlapping changes in expression programs related with inhibition of cell proliferation and induction of cell death. JmjC inhibition reverses an aggressive HCC gene expression program that is also altered in patients with HCC. Several genes downregulated by JmjC inhibitors are highly expressed in tumor vs. non-tumor parenchyma, and their high expression correlates with a poor prognosis. We identified and validated a 4-gene expression prognostic signature consisting of CENPA, KIF20A, PLK1, and NCAPG.

Conclusions: The epigenetic alterations identified in HCC can be used to predict prognosis and to define a subgroup of high-risk patients that would potentially benefit from JmjC inhibitor therapy.

Lay summary: In this study, we found that mutations and changes in expression of epigenetic modifiers are common events in human hepatocellular carcinoma, leading to an aggressive gene expression program and poor clinical prognosis. The transcriptional program can be reversed by pharmacological inhibition of Jumonji enzymes. This inhibition blocks hepatocellular carcinoma progression, providing a novel potential therapeutic strategy.

Keywords: Bromodomains; Epigenetic; Epigenetic inhibitors; Gene expression signature; Histone acetyltransferases; Histone demethylases; Histone methyltransferases; Human hepatocellular carcinoma; Jumonji C demethylases; Lysine demethylases; Patient survival.

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