Dysregulation of the epigenetic regulator SETDB1 in liver carcinogenesis—more than one way to skin a cat

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Provenance: This is a Guest Editorial commissioned by Guest Editor Haitao Zhao, MD, PhD (Associate Professor, Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China).

Comment on: Wong CM, Wei L, Law CT, *et al.* Up-regulation of histone methyltransferase SETDB1 by multiple mechanisms in hepatocellular carcinoma promotes cancer metastasis. Hepatology 2016;63:474-87.

Abstract: Hepatocellular carcinoma (HCC) is one of the most prevalent human cancers worldwide. Its development is considered a step-wise process in which genetic and epigenetic alterations lead to the activation of oncogenes and the inactivation of tumor suppressor genes. In contrast to genetic alterations, epigenetic changes that include aberrant methylation, histone modification and RNA interference do not alter the genetic code, but affect the level of mRNA transcripts. In addition, these epigenetic alterations may influence each other. In their elegant study, Wong *et al.* analyzed the expression of 591 known epigenetic regulators in human HBV-induced HCC by transcriptome sequencing. They identified SETDB1 as the most significantly up-regulated epigenetic regulator in human HCC. In their cohort SETDB1 overexpression was associated with metastasis formation and poorer prognosis of HCC patients. Interestingly, the authors observed several complementary mechanisms contributing to the upregulation of SETDB1 in HCC cells. Besides copy number gains at the SETDB1 gene locus at chromosome 1q21 enhanced SETDB1 transcription mediated by the transcription factor SP1 could be detected. Finally, Wong and colleagues showed that SETDB1 is a target of miR-29, which is frequently downregulated in human HCCs. Taken together, SETDB1 overexpression is mediated by several complementary acting mechanisms suggesting that upregulation of SETDB1 may be a hallmark of HCC progression. This study warrants for independent validation, analyses of a larger series of non-HBV-associated human HCCs, and for further testing of methyltransferase inhibitors as well as molecules targeting SETDB1 in (pre-)clinical studies.

Keywords: Hepatocellular carcinoma (HCC); RNA sequencing; microRNA (miRNA); histone; methylation

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Hepatocellular carcinoma (HCC) is one of the most prevalent human cancers worldwide (1). The most prevalent etiological factors are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, chronic alcohol consumption and, in certain geographical areas, aflatoxin B1 exposure (2).

Human hepatocarcinogenesis is considered a step-wise process in which genetic and epigenetic alterations lead to the activation of oncogenes and the inactivation of tumor suppressor genes. In contrast to genetic alterations, epigenetic changes that include aberrant methylation, histone modification and RNA interference do not alter the genetic information, but affect the level of mRNA transcripts. Importantly, epigenetic alterations may influence each other. For instance, methylation of microRNA (*miRNA*) genes may affect their expression level (3), while genes affecting the chromatin structure (e.g., DNMT1, DNMT3a/b, HDAC4 etc.) may be targeted by

miRNAs (4).

Covalent modification of specific residues within amino terminal tails of histones alters chromatin structure and function. The unique combination of certain modifications has been described as the histone code. In principal two groups of multiprotein complexes that affect this code can be differentiated: the Polycomb (PcG) and the Thritorax group (TrxG). PcG proteins establish histone modifications that repress transcription, whereas TrxG proteins establish histone modifications that activate transcription (5).

The SET domain, bifurcated 1 (*SETDB1*) gene is located at chromosome 1q21 and encodes a 143-kDa protein with multiple functional domains. The C-terminal SET domain is responsible for H3K9-specific lysine methylation (6). SETDB1 was linked to transcriptional repression of euchromatin (7) and has been shown to be important for the maintenance of ES cell state by repressing lineage specific gene expression (8,9). A body of evidence indicates that 'miswriting', 'misreading', or 'mis-erasing' of histone modifications contributes to the initiation and development of human cancer (10).

In their study, Wong *et al.* analyzed the expression of 591 known epigenetic regulators in HBV-induced human HCCs by transcriptome sequencing (11). They observed that upregulation of epigenetic modulators (341/351 deregulated modulators) is a common event in human HCC and identified SETDB1 as the most significantly up-regulated epigenetic regulator in this type of liver cancer. SETDB1 overexpression was significantly associated with HCC progression, cancer aggressiveness (e.g., formation of tumor microsatellites and metastasis), and poorer prognosis of HCC patients. In particular, SETDB1 was upregulated in all metastatic lesions analyzed and inactivation of SETDB1 reduced the proliferative and migratory capacity of HCC cells, suppressed orthotopic tumorigenicity, and abolished the formation of lung metastasis, suggesting that SETDB1 is a bona fide oncogene that is important for HCC growth and metastasis. Depletion of SETDB1 reduced global H3K9 trimethylation level leading to transcriptional reactivation of 828 genes, while the levels of H3K27 trimethylation and H3K4 trimethylation remained unaffected. Consistently, the expression level of these SETDB1 target genes was downregulated in human HCC and negatively correlated with the SETDB1 expression levels.

The second important finding of Wong *et al.* is the identification, that several complementary mechanisms contribute to the SETDB1 upregulation in HCC cells (11).

Besides copy number gains at the *SETDB1* gene locus at chromosome 1q21 enhanced SETDB1 transcription mediated by the transcription factor SP1 could be detected. Finally, Wong and colleagues showed that SETDB1 is a target of miR-29, which is frequently downregulated in human HCCs (11). Taken together, SETDB1 overexpression is mediated by several complementary acting mechanisms suggesting that upregulation of SETDB1 may be a hallmark of HCC progression.

We recently reported a similar multi-layer dysregulation of the Mouse double minute homolog 4 (MDM4) in human HCC, which leads to functional inactivation of p53 signalling, another hallmark of cancer (12). Thus, the present study by Wong *et al.* underscores that hallmarks of HCC development and progression are dysregulated by several different, but co-acting mechanisms. Furthermore, the miR-29 supported reactivation of SETDB1 expression leads to epigenetic silencing of numerous target genes suggesting the potential presence of an epigenetic boost mechanism that may constitute a switch for the development of HCC metastases.

In summary, this elegant study by Wong *et al.* warrants for independent validation, analyses of a larger series of non-HBV-associated human HCCs, and further testing of methyltransferase inhibitors as well as molecules directly targeting SETDB1 in (pre-)clinical studies. Considering that SETDB1 is reported as commonly upregulated in human cancers, the findings by Wong *et al.* may have importance beyond liver cancer.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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