Hepatocellular carcinoma (HCC), a major form of adult primary liver cancer, is the third cause of cancer-related deaths worldwide. The development of this tumor has been associated with various risk factors, mostly chronic viral hepatitis, chronic alcohol consumption and aflatoxin-B contaminated food, and shows higher incidence in cirrhotic patients. Current therapy is as yet very limited, thus American and European guidelines recommend implementation of surveillance programs in high risk patients. Liver transplant and interventional radiology are still the most efficient treatments while chemoembolization represents the choice for unresectable HCC. The sole drug currently showing some survival benefits in HCC patients in advanced stages and preserved liver function is sorafenib, an inhibitor of tyrosine kinases affecting proliferation and angiogenesis (1). Novel pharmacological approaches against HCC are strongly needed.

Along with various genetic causes, recent findings described HCC onset and progression deeply correlated to epigenetic modifications [reviewed by (2)] of both DNA and histones (i.e., methylation and hydroxymethylation of DNA cytosine residues and acetylation, ribosylation, phosphorylation, ubiquitination, sumoylation, methylation, deamination and proline isomerization of histone tails). These local modifications control gene specific transcriptional activity and often, in HCC as well as other tumor types, aberrant patterns of epigenetic marks cause the silencing of tumor suppressor genes (3). Notably, epigenetic modifications are reversible, thus representing attractive targets in therapeutic approaches. For these reasons, each enzyme that bears activity of chromatin modifier and appears correlated to tumor onset and progression holds promise for therapeutic targeting in cancer treatment. Of note, some drugs against epigenetic modifiers have already been used in clinical trials with interesting results. For example, the histone deacetylase inhibitors belinostat and, more recently, resminostat have been assessed in the treatment of HCC patients and have shown signs of efficacy (4,5). In particular, resminostat treatment resulted in a control rate of the disease close to 90% in patients with confirmed progression on prior sorafenib treatment (5).

Notably, Wong and colleagues (6) correlated the upregulation of the methyltransferase SETDB1 with HCC progression, aggressiveness and poor prognosis; moreover they also provided evidence regarding the functional role of SETDB1-...

SETDB1 is a new promising target in HCC therapy

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mediated repression are tumor suppressors RASSF1A and P53BP2 (14). As a parallel activity, SETDB1 acts as protein methylase and, interestingly, a recent report pointed to a role in HCC for this enzyme in the methylation of the tumor suppressor p53 (15).

Wong and colleagues started their study by whole-transcriptome sequencing (RNA-seq) comparing the expression levels of a large set of the known chromatin modifiers in HBV-associated primary HCC to correspondent NT livers. Overall, several epigenetics regulators were found modulated, highlighting the relevance of epigenetic mechanisms in controlling aberrant HCC gene expression. In particular, SETDB1 was found significantly upregulated at both RNA and protein levels; this result was confirmed in several in vitro models of HCC. Notably, SETDB1 expression levels were also associated to clinicopathological features and survival rates of patients and this analysis suggested its overexpression to have a prometastatic role and a correlation to poor prognosis. To investigate the possible direct functional role of SETDB1 in HCC, these authors knocked-down the expression of this enzyme in two cell models (Hep3B and MHCC97L) and tested the effects of its silencing; SETDB1 knockdown was found to be able to suppress proliferation in vitro and reduce tumor size in vivo orthotopic livers. Moreover, coherently with the finding of an up-regulation of SETDB1 in patients’ metastases, its knock-down was found to attenuate HCC lung metastasis in orthotopic implants in nude mice. RNA-seq was then used to investigate the global transcriptional modulation in SETDB1 knock-down cells and, as expected, the enriched target genes identified by these analyses belong to multiple pathways often deregulated in cancer, including those involved in the control of cell-cell adhesion. Data were further validated by ChIP and RT-qPCR analysis.

This study also focused on mechanisms of SETDB1 upregulation in HCC and, of note, multiple levels of control have been identified. Firstly, the SETDB1 gene copy gain was found at chromosome 1q21 (this chromosomal region is frequently amplified in human HCC). Secondly, aiming at the identification of putative consensus binding site for transcriptional regulators on SETDB1 gene they performed an in silico analysis that allowed for identification of the specificity protein 1 transcription factor (SP1); its role as transcriptional activator of SETDB1 gene was further confirmed by luciferase reporter assay and inactivation by mithramycin A treatment or siRNA silencing. Finally, the post-transcriptional regulation of SETDB1 was found to be mediated by the down-regulation of the microRNA-29.

Overall these data are of interest not only for the clarification of the oncogenic role of SETDB1 in HCC development but also because these results integrate with other recent findings contributing to the identification of SETDB1 as a new relevant marker of HCC. In fact, recently Fei and colleagues (15) identified in the SETDB1-mediated di-methylation of the tumor suppressor p53 a mechanism by which this methyltransferase executes its role in HCC.

Moreover, SETDB1 has been found to interact with the DNA methyltransferase DNMT3A (14). Interestingly, miR-29 family members are also known to target DNMT3s in HCC cells (16): low levels of miR-29 and DNMT3A modulation have been correlated to HCC aggressiveness (17) and the treatment with a DNMTs inhibitor is able to impair metastasis (18). On the other hand, miRs-29 levels are controlled to maintain the differentiated hepatocyte phenotype (19). Thus, miR-29 family members control methylation activity on both histones and DNA.

In our view, while more efforts are needed to better clarify the role of SETDB1 in all HCC stages, particularly with respect to specific cancer-related targets, the provided evidence indicates this enzyme as a promising target in future therapy. Therefore, further development of specific inhibitors suitable to clinical use is opportune.

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Footnote

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