Commentary

Epigenetics of cancer: the role of histone methyltransferase, SETDB1, in cancer metastasis

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Cancer has a significant impact on society and the economy than all other disease, according to a report from the American Cancer Society. Alteration in histone methylation is a frequent event during tumor development and progression. In the past decade, numerous studies have demonstrated that SETDB1 (as known as KMT1E, ESET) is a histone H3K9 methyltransferase and contribute significantly to tumor initiation and progression. More recently publication on *Hepatology*, Wong and colleagues (1) has focused on the molecular epigenetic events mediated by histone methylation that leads to cancer metastasis in human hepatocellular carcinoma (HCC), ultimately *in vitro* and *in vivo* experiments to discover "the cellular and molecular role of SETDB1 in human HCC metastasis". Mechanistic investigations indicated that SETDB1 expression is regulated through chromosomal, transcriptional, and posttranscriptional levels in HCC. These findings defined the essential role of the SETDB1 in cancer metastasis, which may provide a novel therapeutic target for cancer metastasis.

Cancer is the major problem for the life course of the human health. In the United States, cancer causes about one-fifth of the deaths each year. Worldwide, between 100 and 350 out of 100,000 people die of cancer each year. Based on Globocan estimates, about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide (2). Despite its clinical importance, it is little known about the detailed molecular mechanisms of cancer. Cancer is a group of diseases characterized by abnormal cell growth with the potential to invade or spread to other parts of the body. Most cancers have lost one or more genome maintenance and repair system due to genome instability and mutation. Many studies have indicated that the cancer has been considered as a complex disease, which involves both genetic and epigenetic alteration. Epigenetic regulation of gene expression is a dynamic and reversible process with DNA methylation, histone modifications, and chromatin remodeling. Recently publications have indicated that aberrant epigenetics are a frequent event during tumor development and progression, especially histone modification. Covalent histone modifications have been implicated in the development and progression of various cancers (3). These histone modifications include acetylation (Ac), methylation (Me), phosphorylation, ubiquitination and sumoylation, play key roles in gene regulation. Among the histone modification, histone methylation is strongly associated with carcinogenesis and poor prognosis. For example, loss of histone H3 lysine 9 dimethylation (H3K9Me2) has been found in both prostate and kidney cancer and is associated with poor prognosis (4,5). Importantly, histone H3 lysine 9 trimethylation (H3K9Me3) serves as a diagnostic marker of both recurrence and distant metastasis in lung, gastric, and bladder cancer patients (6-8).

Histone methylation status is dynamic, and regulated by either methyltransferase (HMTs) or demethylase (HDMTs). There are several examples in current literature that have provided clear indications that HMTs are playing important role in cancer metastasis. For example, Suv39h1,

a histone H3K9 methyltransferase (H3K9MT), is highly expressed and functions as an oncogene in hepatocellular and colorectal cancer metastasis (9,10). G9a (as known as EHMT2), a H3K9MT, is over-expressed in lung, prostate and hepatocellular cancers (11). Suppression of G9a and Suv39h1 causes cell growth inhibition in prostate cancer (12) and induces lung epithelial cells transformation (13). Another H3K9MT, SETDB1 (as known as KMT1E, ESET), which regulates H3K9 methylation, a hallmark of gene repression. One study shows that SETDB1 and the DNA methyltransferase DNMT3A interact directly and localize to promoters silenced in cancer cells (14). Other studies have found that SETDB1 is a H3K9MT involved in the transcriptional silencing of euchromatic genes in cervical and breast cancer cells (14,15). These findings suggest that SETDB1 acts as a repressor in cancer cells. Whether it plays a role in the progression of tumorigenesis remain largely unknown. Ceol and colleagues using the zebrafish model have demonstrated that SETDB1 is a pro-oncogene for melanoma development (16). Recently publications have indicated that SETDB1 was found to be a bona fide oncogene undergoing gene amplification-associated activation in lung tumorigenesis (17). The same study also showed that ectopic expression of SETDB1 in A549 cells significantly promoted cell invasion. Strikingly, Rodriguez-Paredes and colleagues reported that the 18 genes have been identified that significantly increased upon SETDB1 depletion in both H1437 and DMS-273 cells. Among the 18 genes, 11 genes are known to promote cell invasion in a variety of cancers; these include *ANXA3*, *IL-6*, *IL-11* (18,19). These studies indicate that SETDB1 plays important role in cancer initiation and progression; however, the mechanism by which SETDB1 regulates metastasis remains to be elucidated. Recently published on *Cancer Research*, Wu and colleagues (20) indicated that SETDB1 is down-regulated in highly metastatic lung cancer cells and significantly decreased in the metastatic state. *In vivo* xenograft experiments have observed that loss of SETDB1 in noninvasive lung cancer cells promotes cellular invasion. Furthermore, mechanistic investigations demonstrate that SETDB1 cooperates with SMAD2/3 to repress metastasis through *ANXA2* in TGFβ-mediated lung cancer metastasis (20). Taken together, the results were indicated that SETDB1 may play different roles in cancer metastasis.

The current paper by Wong *et al.* (1) indicated that up-regulation of SETDB1 by multiple mechanisms in HCC promotes cancer metastasis. The authors have demonstrated that RNA expression of SETDB1 was associated with various clinicopathological features and survival rates in HCC patients. Up-regulation of SETDB1 was correlated with the tumor microsatellite formation in the adjacent non-tumor and a poorer 5-year overall-survival rate. In Hep3B and MHCC97L cells, stable knockdown of SETDB1 suppressed cell proliferation and overexpression of SETDB1 enhanced cell proliferation and colony formation abilities of MIHA cells by in vitro. *In vivo* orthotopic experiments have indicated that stable knockdown of SETDB1 in MHCC97L cells reduced the tumor size of HCC formed in a mouse model. Mechanistic investigations indicated that expression levels of SETDB1 via miR-29 negative regulator and SP1 were positively correlated with human HCC. These data suggested that SETDB1 as an oncogene that is functionally important for tumor growth and metastasis in HCC. This study adds to our knowledge and represents an important role of SETDB1 in human HCC. In addition, mechanistic investigations indicated that SETDB1 expression is regulated through chromosomal, transcriptional, and posttranscriptional levels in HCC. The finding from these mechanistic studies will determine the extent to which upstream regulator could be used as a new biomarker for early diagnosis in human HCC patients and, possibly, to guide of other solid malignancies. In summary, the findings from several studies address the cellular, molecular, and biological functions of SETDB1 which may help improve our understanding of cancer progression in metastasis and develop feasible treatments. These studies will shed new light on epigenetic mechanisms in cancer metastasis and may provide useful targets/pathways for cancer diagnosis and therapy.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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