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The Increasing Relevance of Histone Lysine Methylation for Hepatocellular Carcinoma Pathogenesis and Treatment

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Abstract

Hepatocellular carcinoma (HCC), the most frequent type of primary liver cancer, is a very important cause of cancer-related death worldwide. Epigenetic mechanisms and, particularly, histone methylation, are known to play a role in HCC development and, therefore, are promising targets for specific therapies. In this Mini Review I will briefly mention and discuss a panel of histone methyltransferases and demethylases that have been associated to HCC and I will also draft some future perspectives on this field.

Keywords: Hepatocellular carcinoma; Liver; Cancer; Epigenetics; Histone methylation

Abbrevations: HCC: Hepatocellular Carcinoma; KO: Knockout; SMYD: SET and MYND Domain-Containing Proteins; DEN: Diethylnitrosamine

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and it is the second most common cancer-related cause of death worldwide. There is a general trend towards increasing incidence of HCC, especially in Asia and Africa, although in other areas there is a plateau or even a declining trend. Incidence and mortality rates are very similar, since HCC has bad prognosis worldwide. HCC is more common in male than in women and the most important risk factors are hepatitis B virus, hepatitis C virus, excessive alcohol consumption, ingestion of aflatoxin B1-contaminated food, cigarette smoking, high iron intake, metabolic syndrome, diabetes, obesity and nonalcoholic fatty liver disease, as well as genetic predisposition, while coffee might have a protective effect against HCC [1]. Treatment options include surgical therapies and drugs with anti-proliferative and anti-angiogenic effects [2]. First-line pharmacological treatment includes the multikinase inhibitors sorafenib [3,4] and lenvatinib [5]. Although no epigenetic drugs have been approved for the treatment of HCC to date, epigenetic mechanisms are nowadays considered key for the development of the disease [6,7]. Epigenetics can be defined as the study of chromatin modifications that do not involve alterations in the DNA sequence. These modifications of chromatin could be mitotically or meiotically heritable or non-heritable and may or may not affect gene expression. Epigenetic modifications, i.e. posttranslational modifications of histones and non-histone proteins, DNA methylation and regulation by non-coding RNAs, among others, are associated with physiological and pathological processes, including cancer [8,9]. Posttranslational modifications of histones control the accessibility of DNA to transcription factors and components of the DNA replication and repair machinery, among other regulatory molecules, and form what is known as the "histone code", i.e. the combination of one or multiple histone modifications that give rise to specific biological outcomes [10,11].

Among all the different epigenetic mechanisms, we will focus on histone methylation, i.e. the addition of a methyl group to basic residues (mainly lysine and arginine) by enzymes with methyltransferase activity, whose action can be reverted by demethylases, and its role in hepatocellular carcinoma [12].

Discussion

Histone methylation has been associated with carcinogenesis, since aberrant expression of lysine methyltransferases, lysine demethylases and arginine methyltransferases alters histone methylation or demethylation status and can contribute to tumour promotion, most probably due to the addition of gene activation marks to oncogenes and the incorporation of repressive to tumor suppressor genes [13,14].

Some examples of histone lysine methyltransferases whose dysregulation has been related to HCC development are Suv39H2 (by targeting H3K9me2/3) [15], GLP1 and G9a (both generating H3K9me1/2) [16,17], SETDB1 (which also acts on H3K9me2/3) [18,19], PRDM2 (acting on H3K9me1/2/3) [20] and PR-SET7 (by methylating H4K20me1) [21].

Regarding PR-SET7, a study demonstrated that knockout (KO) mice devoid of PR-SET7 mRNA and protein in the liver from postnatal stages spontaneously develop HCC. Due to the inability of PR-SET7-KO hepatocytes to proliferate, ductal progenitor cells become the source of newly-generated hepatocytes that would dedifferentiate to cancer stem cells [22]. Drugs inhibiting PR-SET7 are available, but have only been tested in basic studies [23]. Furthermore, the mRNA expression of lysine methyltransferase SMYD3, a member of the SET and MYND domain-containing proteins (SMYD), correlates with poor clinical prognosis of human HCC [24]. SMYD3 function has been studied in a chemically-induced hepatocellular carcinoma in mice. Liver-specific SMYD3 KO mice were subjected to treatment with the liver carcinogen diethylnitrosamine (DEN) and delayed carcinogenesis was observed in the KO mice compared to wild-type (WT), leading to the conclusion that SMYD3 is required for liver carcinogenesis. SMYD3 activation of transcription in specific promoters was related to H3K4me3 [24]. Remarkably, selective small-molecule inhibitors of SMYD3 already exist, although they have only been used in basic research [25]. Finally, it is worth mentioning some examples of histone lysine demethylases dysregulated in the context of HCC are JMJD1A (targeting H3K9me1/2 [26] are JARID1B (by acting on H3K4me1/2/3) [27], among others.

Conclusion

Specific targeting of epigenetic mechanisms that control liver cancer progression, such as histone methyltransferases or demethylases, by inhibiting those which add activation marks to oncogenes and hyperactivating those which are involved in the addition of repressive marks to tumour suppressor genes, is a promising therapy for HCC, a disease with poor survival rates. Despite the absence of epidrugs (drugs targeting epigenetic modifiers) in the clinics, many efforts are currently made to translate all the knowledge acquired in basic epigenetic studies to the bench side [8,14].

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