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TO EVALUATE THE CLINICOPATHOLOGICAL IMPORTANCE OF SETDB1DEREGULATION IN HUMAN HCC

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Abstract

Similarly, the "frequent up-regulation of G9a in various HCC sample cohorts has also been confirmed and verified. In this study, upregulation of G9a was found to be related with HCC disease progression, cancer aggressiveness, and the development of more malignant tumour phenotypes. The functional analysis revealed that shRNA knockdown and CRISPR/Cas9 deletion of G9a both decreased HCC cell proliferation in vitro and affected the tumorigenicity of xenograft HCC in vivo when administered subcutaneously. The depletion of G9a resulted in a substantial reduction in HCC cell migratory capacity as well as the induction of cell senescence. The pharmacological inhibition of G9a by small molecule inhibitors UNC0638 and BIX01294 resulted in a reduction in HCC cell proliferation as well as a change in the shape of the cells. We demonstrated that the frequent up-regulation of G9a in human HCC was caused by gene copy number increase on chromosome 6p21 and the loss of miR-1, as demonstrated by mechanistic studies. Also of note, up-regulation of G9 epigenetically suppressed miR-1 production, resulting in the formation of a feedforward regulatory loop between the two genes. In human HCC, we discovered a putative tumour suppressor RARRES that was epigenetically silenced by G9a" and enhanced tumour cell proliferation. We discovered this by using RNA-Seq and GSEA analysis. We discovered that SETDB1 and "G9a are new oncogenes that are commonly up-regulated in human HCCs when the findings were taken together. It was discovered that their upregulationin human HCCs was caused by a variety of processes occurring at the chromosomal, transcriptional, post-transcriptional, and post-translational levels. Their carcinogenic activities may also be linked to epigenetic silencing of tumour suppressors that are downstream of them. It appears that SETDB1 and" G9a may be potential therapeutic targets for the treatment of HCC, based on our findings.

Keywords: HCC, SETDB1, PTEN, Methyltransferases, Hyperactivation.

1. INTRODUCTION

The great majority of "HCC patients had a history of chronic liver disease and cirrhosis, which was often the result of chronic infection, such as hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol misuse, or nonalcoholic steatohepatitis (NASH). As well as aflatoxin B1, obesity, and some hereditary metabolic abnormalities, there are other risk factors to consider.

Cirrhosis is the most important risk factor for the development of HCC, with approximately 70 percent to 90 percent of HCC cases having a recognized background of cirrhosis. Cirrhosis is primarily caused by heavy alcohol consumption, HBV and HCV infection, and is the most common cause of HCC. Almost half of all HCC cases globally are linked with

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HBV infection, while a quarter of all HCC cases are associated with HCV infection. When normal hepatocytes are destroyed, fibrous tissue is replaced, and nodules and lumps develop as a result of the regeneration of injured tissues. Cirrhosis can be classified as a chronic disease or a chronic illness. Due to excessive renewal of liver tissue, increased DNA synthesis and more DNA rearrangements occurred. As a result, the DNA became more prone to mutation and provided a more selective environment for the formation of malignant nodules. HCC development is not always the outcome of liver cirrhosis, despite the significant incidence connection between cirrhosis and the progression" of the disease. The fundamental processes that lead to the progression of cirrhosis to HCC are still unclear, and they may entail a mix of several etiologies. The existence and severity of liver cirrhosis, on the other hand, are significant indicators for patients in determining treatment options and prognosis for the disease.

HBV infection can result in chronic and acute liver damage, and it is the most common cause of liver cancer. The risk of getting "HCC in HBV carriers has been found to be 100 times higher than the risk of developing HCC in non-carriers. The regional distribution of HBV infection and the geographic distribution of HCC are highly overlapping. HBV is responsible for more than half (340,000 instances, or 54.4 percent) of all HCC cases globally, with the majority of cases occurring in Asia, Africa, and the western Pacific.

HBV is a virus having 3.2 kilobytes of partly double-stranded DNA on its genome. A HBV infection causes damage to hepatocytes and chronic inflammation, which leads in a reduction in hepatocyte proliferation as well as the development of fibrosis and cirrhosis (cirrhosis of the liver). The cirrhosis that results from this process accelerates the accumulation of DNA mutations in the host genome, which ultimately results in abnormal genetic alternations, chromosomal instability, and an imbalance in the expression of oncogenes and tumour suppressor genes. HBV, on the other hand, has been shown to induce HCC in the absence of cirrhosis. In addition to mutagenesis, HBV DNA may be incorporated into the host genome and induce genome rearrangement and" genomic instability, as well as abnormal gene expressions, which are all consequences of HBV infection. Furthermore, the HBx protein produced by HBV interferes with gene activities involved in cell cycle and proliferation regulation, apoptosis, DNA repair, and signaling transduction pathways such as the nuclear factor kappa B and protein kinase C pathways, among others. HBx has also been shown to produce global genome hypermethylation and inactivate the tumour suppressor gene IGFBP3, according to a recent research.

Chronic inflammation, cell "death, and proliferation are the primary mechanisms by which HCV infection leads to HCC. As a result, virtually all HCV-associated HCC patients are also affected by cirrhosis, but HBV-associated HCC cases are occasionally not affected by cirrhosis. Patients who are HCV carriers have a 17-fold increased chance of developing HCC compared to those who are not carriers [26]. A total of 31.1 percent (195,000) of all HCC cases globally were caused by HCV, with the vast majority occurring in Middle and Northern Africa. In contrast to HBV, HCV is an RNA virus with a genomic size of around 10 kb that cannot be integrated into the host genome. As a result, HCV"

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may have contributed to HCC through indirect mechanisms. "NS3" and "NS5A" are non-structural proteins encoded by the HCV genome, and they are thought to be the main and unique pathogens in the development of HCV-associated HCC. "Both of these proteins produce inflammation and oxidative stress by activating the STAT-3 and NF-kappa B pathways, which have been linked to the development of hepatocarcinogenesis. Aside from that, the NS5A protein directly interacts with the p53 protein, inhibiting its ability to prevent tumour growth and repair DNA. It has also been suggested that the HCV core proteins are involved in HCC through interfering with immune system surveillance by suppressing T-cell proliferation. Through their entry into host cells, HCV core proteins trigger the production of oxidative stress, which activates the p38 mitogen-activated protein kinase (MAPK) and the nuclear factor-kappa B pathway, resulting in changes in the cytokines-induced inflammation and apoptosis pathways. When comparing patients with wild-type core proteins to patients with mutations of core proteins, the genome analysis revealed that the mutations of core proteins are linked with HCC. In addition to the congenic proteins, HCV has been linked to obesity" and metabolic dysregulation, both of which are associated with HCC caused by fatty liver disease.

2. LITERATURE REVIEW

Because epigenetic controls exert "their functions primarily through the regulation of gene transcription and the structure of chromatin, an understanding of chromatin structure is essential for understanding epigenetic regulation. It is the combination of DNA, proteins, and RNA that is structured and packed into repeating units known as nucleosomes, which are found in the nucleus of the cell. It has been determined that the nucleosome is made up of 147 base pair (bp) of double stranded DNA that is wrapped around an octamer of four core histone proteins: histones 2A, 2B, H3, and H4. Hippocampal histones and DNA can be enzymatically or chemically changed with epigenetic marks, which can affect the structure of chromatin by altering its electrostatic state or interactions with other chromatin-binding proteins, among other things. When the chromatin structure changes, it has an impact on the accessibility of transcription factors to promoter regions, and as a result, it has an impact on gene expression. In a non-dividing cell, chromatin may be found in two different functional states: euchromatin (transcription active) and heterochromatin (transcription passive) (transcription inactive). It is the area of the genome where nucleosomes are loosely organized in an open conformation, making DNA accessible to transcription factors, which can then activate the transcription process. Hitherto, heterochromatin is a genomic area in which DNA has been tightly packed into extremely condensed" forms that are inaccessible to transcription factors or chromatin-associated proteins and is therefore inaccessible to these proteins. It is believed that the transcription of genes in these regions is impeded. Heterochromatin is the predominant state of DNA, and it is essential "for chromosomal stability as well as protection against mutations and translocations. The dynamic states of chromatin structures are critical for controlling the activation and function of the genome, which in turn affects the cellular behaviours.

A process in which methyl groups (-CH3) are added to DNA from the cofactor S-adenosyl-

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L-methione (SAM) to the 5-position of cytosine in a CpG dinucleotide context is catalysed by a family of DNA methyltransferases (DNMTs). DNA methylation is one of the most important processes in the cell's metabolism. DNA methylation and demethylation are important regulators of gene expression and chromatin structure in a normal mammalian cell. The transcription of genes with high levels" of DNA methylation in the promoter region is typically repressed. Somatic cells have the ability to transmit DNA methylation patterns to daughter cells with great fidelity, which is why they are called somatic cells. Normally, the DNA methylations that accumulate "during cell division and differentiation are permanent and unidirectional in order to prevent cells from changing into another cell type or reverting to their stem cell state. Because of this, DNA methylation is required for proper development and is involved in a variety of molecular and cellular processes, including genomic imprinting and the inactivation of the X chromosome.

A gene's transcriptional activity was reduced in normal cells due to the methylation of cytosine at CpG islands in its promoter region, which occurred in normal cells. The promoter methylation patterns, on the other hand, are frequently changed in tumour cells. DNA methylation patterns in the promoter region of tumour suppressor and oncogene genes are abnormal, and are associated with a variety of cancers. These abnormal DNA methylation patterns, which are typically hypermethylation and hypomethylation, cause expression alternations of tumour suppressor and oncogene genes. The most important mechanism of hypermethylation-related transcriptional inactivation is the inhibition of RNA polymerase and transcriptional factor binding to the promoter" of the gene. It has been demonstrated that the recruitment of m5CpG-binding domain (MBD) proteins, which selectively bind to methylated DNA sequences, inhibits the binding of transcription factors to promoters, therefore repressing gene transcription. The abnormal DNA hypermethylation of tumour suppressor genes was discovered in a large number of cancers over the course of their multistep carcinogenesis and progression. "It has been discovered that a huge number of tumour suppressor genes have been" silenced by promoter hypermethylation, and the list of these genes is constantly expanding.

3. RESEARCH GAP

The formation of HCC, "like many other cancers, is a multistep process that involves the accumulation of genetic and epigenetic alterations that result in the inactivation of tumour suppressor genes and the activation of cancer-causing genes. Genetic alterations have been widely researched in the last few decades, and the function of numerous important changed genes and pathways in the development of HCC has been well defined, as we have detailed in the preceding sections (1.1.3). The exact significance of epigenetic alternations, on the other hand, remains a mystery. Since genetic changes affect the DNA sequence of the genome, which involves mutations, chromosome" gain and loss, are theoretically irreversible processes, and "correcting" them is difficult and risky, which may raise safety concerns, it is important to understand how genetic "changes affect the genome. Increasing evidence has shown that epigenetic alterations play a significant role in the onset and progression of cancer in recent years. In contrast to genetic control,

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epigenetic regulation affects gene transcription and chromatin structure without affecting DNA sequence in the genome. Involving several layers of regulatory mechanisms at both the transcriptional and post-transcriptional levels, it results in the formation of a complex regulatory" network that may be used to fine tune gene expression levels. This epigenetic regulatory network was disrupted in tumours, resulting in an imbalance in the expression "of oncogenes and tumour suppressor genes, which ultimately contributed to the development of cancer malignancies. Most significantly, epigenetic alterations are reversible, making them a promising target for the development of cancer therapeutics. Because of this, gaining a better knowledge of the underlying processes of epigenetic alternations in HCC will aid in the discovery of new therapeutic targets as well as the development of innovative drugs for the diagnosis" and treatment of HCC.

Aberrant DNA methylation, "histone modification, chromatin remodeling, and non-coding RNAs are the epigenetic alterations that play a role in cancer development and progression. In this section, we will provide a brief overview of the roles played by these three components in human HCC.

Because epigenetic controls exert their functions primarily through the regulation of gene transcription and the structure of chromatin, an understanding of chromatin structure is essential for understanding epigenetic regulation. It is the combination of DNA, proteins, and RNA that is structured and packed into repeating units known as nucleosomes, which are found in the nucleus of the cell. It has been determined that the nucleosome is made up of 147 base pair (bp) of double stranded DNA that is wrapped around an octamer of four core histone protein histones 2A, 2B, H3, and" H4. Hippocampal histones and DNA can be enzymatically or chemically changed with epigenetic marks, which can affect the structure of chromatin by altering its electrostatic state or interactions with other chromatin-binding proteins, among other things. "When the chromatin structure changes, it has an impact on the accessibility of transcription factors to promoter regions, and as a result, it has an impact on gene expression. In a non-dividing cell, chromatin may be found in two different functional states: euchromatin (transcription active) and heterochromatin" (transcription passive) (transcription inactive). "Euchromatin" refers to the area of the genome where nucleosomes are loosely organized in an open conformation, allowing DNA to be readily accessible to transcription factors, which can then activate transcription. Hitherto, heterochromatin is a genomic area in which "DNA has been tightly packed into extremely condensed forms that are inaccessible to transcription factors or chromatin-associated proteins and is therefore inaccessible to these proteins. It is believed that the transcription of genes in these regions is impeded. Heterochromatin is the predominant state of DNA, and it is essential for chromosomal stability as well as protection against" mutations and translocations. The dynamic states of chromatin structures are critical for controlling the activation and function of the genome, which in turn affects the cellular behaviors.

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4. RESEARCH OBJECTIVE & METHODOLOGY

According to the procedures "outlined, the putative SETDB1 promoter region was amplified from the normal liver cell line MIHA and cloned into the pGL3-Basic luciferase reporter vector (Promega) to test for SETDB1 promoter activity. Transient co-transfection of luciferase reporter constructs and the pGK- Renilla luciferase control vector into Hep3B cells was accomplished using the FuGENE 6 transfection reagent (Roche). It was determined that the SETDB1 promoter was active using Dual luciferase assay reagent II (Promega) and that the activity was normalised to the activity of the Renilla luciferase control. Dr. Karen Sze produced the SP1 expression construct as well as the three SP1 binding sites luciferase reporter, which have both been previously" published. Santa-Cruz provided both the control and SP1 specific siRNAs used in this study. Mithramycin A, an SP1 inhibitor, was obtained from Sigma-Aldrich for this study.

Wild-type and mutant miR-29 "binding regions in the SETDB1 3'UTR were cloned into the pmirGLO Dual-luciferase miRNA target expression vector in order to study SETDB1 post-transcriptional regulatory mechanisms (Promega). For the purpose of positive control, the miR-29a complement gene was also cloned into the pmirGLO vector. Applied Biosystems provided the miR-29a precursor as well as a miRNA negative control for this study. The miR-29 precursor and the luciferase reporter construct were transfected consecutively. Firefly and Renilla produced luciferase signals 48 hours" after being transfected, and this signal was observed.

The PTEN knockout cell lines were "created in the MHCC97L and BEL7402 cell lines by utilising Transcription activator-like effector nucleases (TALENs) that targeted the PTEN coding region in the genome to knock out the gene. Fundamentally speaking, the engineered TALE repeated domain recognised the coding sequence of PTEN, and the DNA cleavage domain caused double stand breaks (DSB) right" after the start codon of the PTEN coding sequence, and then the DSB was "repaired by non-homologous end joining (NHEJ) mechanism, which introduced InDel mutations and caused frameshift mutations in PTEN. The TALEN plasmids targeting PTEN were obtained from The Genome Engineering Laboratory at Seoul National University, which is located in South Korea. In a nutshell, the TALEN plasmids targeting the PTEN coding region were transiently co-transfected into MHCC97L and BEL7402 cells in the same" manner. After 48 hours of transfection, the cells were exposed to puromycin selection "at a concentration of 2g/l for another 48 hours, or until all of the untransfected control cells died. The surviving cells were counted and planted into 10-cm dishes at a density of 400 cells per dish, and they were then cultured at 37oC in a cell incubator for 3 to 4 weeks, until a single colony "of cells had developed. The single colony was picked up and grown to a larger size in order to test the knockout effect further.

Through the use of Western Blotting, we were able to determine the knockdown impact of PTEN in BEL7402. All of the single colonies picked up from the dish were expanded and subjected to PTEN protein expression detection using rabbit polyclonal anti-PTEN antibody (Abcam). The knockout effect of PTEN in MHCC97L was screened using

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MeltDoctorTM High-Resolution Melting (HRM) Reagents (Life Technologies) for gene editing detection. In a nutshell, all of the single colonies obtained from TALEN-PTEN transfected MHCC97L cells were grown and subjected to genomic DNA extraction in the same manner. Then, using 100 ng of genomic DNA as a template, 10 ul of" 2x MeltDoctorTM HRM reagent, 0.4uM of target site specific primers, and "nuclease-free water were combined to form a final volume of 20 ul. The PCR mixture was "then applied to a StepOneTMPlus Real Time PCR machine for DNA amplification and high resolution melting curve runs, following which it was discarded. The results were examined using HRM analysis software 3.0, and the variations were automatically identified by the programme. PTEN-HRM-F ATCAGCTACCGCCAAGTCCA and PTEN-HRM-R AGTCTTTCTGCAGGA AATCCCATA are the HRM primers used for this gene.

5. DATA ANALYSIS & FINDINGS

Our findings revealed that SETDB1 was the most significantly up-regulated epigenetic regulatory gene in human HCC, as revealed by the RNA-Seq analysis described above (P = 1.2 10-6, FDR = 5.7), out of the 341 up-regulated epigenetic regulatory genes in human HCC identified by the RNA-Seq analysis described above. When" 16 pairs of HCC livers were compared with their matching NT livers, the median expression of SETDB1 rose by 3.18 times, indicating a substantial increase. "As indicated by the mapped RNA-Seq reads on the SETDB1 genome sequence displayed in the UCSC genome browser, a typical instance (229T/NT) had a 2.64-fold increase in SETDB1 expression in HCC when compared with its NT counterpart when compared with its NT counterpart. In addition, we discovered that, among the three SETDB1 isoforms, transcript variation" 1 was the most prevalent form expressed in human HCCs and associated NT livers.

SETDB1 was found to be significantly up-regulated in 50 pairs of HCC samples included in the TCGA RNA-Seq dataset (P 0.001), which is consistent with previous findings. In this sample set, 40 percent (20/50) of the participants had at least a 2-fold increase in SETDB1 expression (Figure 3.3B). On the other hand, there were no examples of down-regulation. This finding corroborated our first discovery and encouraged us to investigate the possibility of SETDB1 upregulation in a wider cohort of participants. We" next used quantitative real-time PCR (qRT-PCR) to examine changes in the expression of SETDB1 in an enlarged sample set that included 92 paired primary HCC and their matching non-tumor liver samples (NT), as well as "5 normal livers (NL). Similar to our earlier results, high levels of SETDB1 expression were detected in primary HCCs when compared to their non-tumorous counterparts and normal liver tissues (P 0.001, Figure 3.3C), which is consistent with our prior findings. The median expression of SETDB1 in primary HCCs was 1.84 and 2.3 times greater than the median expression in NT and NL samples, respectively, compared to the NT and NL samples. It was shown that the transcription factor SETDB1 was upregulated in 45 percent (41/92) of primary HCCs, with 27 instances exhibiting a moderate increase (> 2 folds) and 14 cases exhibiting a significant increase (4 folds) in the expression of SETDB1. Contrary to this finding, down-regulation of SETDB1 was detected" in 12 percent (11/91) of the patients, with no instances reaching

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the 4-fold cut off point.

SETDB1 was shown to be "commonly up-regulated in primary HCCs at the mRNA level, as demonstrated in several sample cohorts, according to the findings. Following that, we used immunohistochemistry (IHC) to analyse the protein expression of SETDB1 in formalin-fixed paraffin-embedded (FFPE) tissue sections to determine if the up-regulation of SETDB1 can be observed at the protein level as well. To conduct this study, we employed both tissue slices with well-defined HCC and non-tumor liver boundaries and a tissue microarray series that included 89 pairs of primary HCC samples and non-tumorous counterparts. Our findings revealed that the SETDB1 protein was predominantly expressed in the nucleus of HCC cells, and that it was significantly up-regulated as" compared to non-tumorous neighbouring hepatocytes. A tissue "microarray revealed that SETDB1 was overexpressed in 39 percent (35/89) of patients, whereas only 5 instances exhibited down-regulation of the protein.

Moreover, more extensive data mining of the TCGA RNA-Seq dataset revealed that up-regulation of SETDB1 was also observed in the majority of other tumour types, including Bladder urothelial carcinoma (BLCA), Breast invasive carcinoma (BRCA), Colorectal adenocarcinoma (COADREAD), Head and Neck squamous cell carcinoma (HNSC), Kidney renal clear cell carcinoma, Kidney renal papillary cell carcinoma. It was concluded from this study that up-regulation of SETDB1 is a common occurrence in cancer and that it may play an essential role in the start and development of cancer.

Our findings showed that SETDB1 was commonly up-regulated in human HCC, both at the mRNA and protein levels, when taken together. In addition to human HCC, deregulation of SETDB1 has been found in nine additional kinds of malignancies that have been investigated using TCGA RNA-Seq. These findings prompted us to investigate the functional functions of SETDB1 in the development of human" HCC.

6. CONCLUSION

Using transcriptome sequencing, "we discovered that dysregulation of epigenetic regulators was frequent in human HCC. This was discovered after examining the expression of 591 epigenetic regulators in this cancer. SETDB1 was identified as the epigenetic regulator that was highly up-regulated in the majority of HCC sample cohorts, and this up-regulation was confirmed in a number of other HCC sample cohorts as well. HCC development, cancer aggressiveness, and a poor survival rate in individuals with HCC were all found to be significantly related with upregulation of SETDB1. In terms of function, SETDB1 was shown to be an oncogene that was required for HCC cell proliferation and metastasis, as established by our in vitro and in vivo models of the disease. The molecular processes that lead to the frequent up-regulation of SETDB1 in human HCC have been established at the chromosomal, transcriptional, post-transcriptional, and post-translational stages, respectively. Gene copy number increase at 1q21 on chromosome 1 was shown to be related with greater expression of SETDB1 when studied genetically. On the transcriptional level, the hyperactivation of SP1

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increased the promoter activity of SETDB1, resulting in the activation of the gene's expression. Because the loss of the miR-29 family has a positive effect on SETDB1's post-transcriptional degradation, it has the potential to promote its up-regulation. SETDB1 was shown to be controlled by the PI3K/Aktsignalling pathway at the post-translational level. The loss of PTEN or treatment with insulin induced PI3K/Aktsignalling, which resulted in an increase in SETDB1 expression. The elevated level of SETDB1 seen in human HCC was a result of the interaction of these many levels of regulatory mechanisms.

In this study, we established that SETDB1 is a new oncogene that is commonly up-regulated in human HCCs. Cancer proliferation and metastasis are facilitated in human HCC by up-regulation of SETDB1 via molecular processes at the chromosomal, transcriptional, post-transcriptional, and post-translational levels, all" working together.

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