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Opinion

During Hepatocarcinogenesis, DNA Methylation Regulates a Set of Long Non-Coding RNAs that Compromise Hepatic Identity

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Abstract

Hepatocarcinogenesis is a long-term process that results in hepatic function decline. Our goal is to learn more about the processes involved in this disease process so that we may help create novel diagnostic markers and treatment targets. We discovered a group of Long non-coding RNAs (lncRNAs) that are highly downregulated in Hepatocellular Carcinoma (HCC) and are associated with the grade of tumour dedifferentiation and patients' poor prognosis in this study. Our findings suggest that they are linked to hepatic differentiation, and that at least a subset of those lncRNAs is necessary for the expression of other hepato-specific genes required for liver function. Furthermore, we show that DNA methylation silences the expression of these lncRNAs in HCC. Overall, we discover linked epigenetic changes that are implicated in the progression of liver cancer and identify potential new biomarkers.

Long noncoding RNAs (lncRNAs) are becoming more prominent in cancers, such as Hepatocellular Carcinoma (HCC). The mechanism implicated in the HCC inhibition of a group of lncRNAs, as well as their contribution to the hepatocarcinogenesis process, are described here. Several human HCC cohorts were used to validate the top 35 lncRNAs downregulated in HCC (Top35 LNDH). We show that their inhibition is linked to promoter hypermethylation in HCC human cell lines compared to primary hepatocytes and in HCC human cell lines compared to control tissue. Demethylating HCC human cell lines also resulted in the expression of these lncRNAs. The Top35 LNDH were generated in well-differentiated HepaRG cells and were preferentially expressed in the adult healthy liver compared to other tissues including foetal liver. Surprisingly, knocking down these genes interfered with the production of other hepato-specific genes. Finally, Top35 LNDH expression is associated with a higher grade of tumour differentiation and, more crucially, a better patient prognosis. Conclusions: Our findings show that the Top35 LNDH are not only part of the genes that make up the hepatic differentiated signature, but also play a role in its formation. Furthermore, their downregulation by DNA methylation happens during the hepatocarcinogenesis process, jeopardising hepatocellular differentiation and the prognosis of HCC patients.

Keywords: lncRNAs • Epigenetics • DNA methylation • Hepatocellular differentiation • Hepatocellular carcinoma

Introduction

Hepatocellular Carcinoma (HCC) genesis and progression is a multistep process in which the underlying hepatic insufficiency is linked not only to hepatocellular loss but also to the dedifferentiation of the remaining liver parenchyma [1,2]. The loss of liver differentiation has been shown to facilitate the development of HCC and to determine the prognosis of HCC patients. Furthermore, individuals with poorly differentiated or undifferentiated HCCs had a poorer prognosis than those with well-differentiated HCCs, according to various clinical data. A fully differentiated cell's distinct phenotype is the outcome of the expression of a diverse but distinct set of genes that determine its identity and consequently function. Multiple mechanisms control gene expression in a cell-type and temporal-specific way [3]. Epigenetic processes are among them, determining chromatin shape and accessibility, and hence dictating gene activity state. DNA methylation, post-translational histone modifications, nucleosome remodelling, and Non-Coding Rnas (ncRNAs) are all examples of epigenetic chromatin control. The epigenomic landscape and, hence, the transcriptome identity of a cell will be determined by the right expression of a variety of epigenetic proteins (writers, readers, and erasers) and ncRNAs. As a result, disruption of these epigenetic pathways jeopardises cell development and leads to human diseases such as cancer. We previously found a list of Long Non-Coding Rnas (lncRNAs) that are unregulated in several kinds of malignancies, including HCC [4]. In this study, we focused on the 35 top-ranked lncRNAs that were found to be downregulated in HCC and confirmed their downregulation in separate human HCC cohorts. We show that another epigenetic mechanism, DNA methylation, regulates the expression of these epigenetic actors on a mechanistic level. The downregulation of this group of lncRNAs in HCC is caused by promoter DNA hypermethylation [5]. We further show that this group of lncRNAs is selectively expressed in adult healthy livers, where they are not only part of the genes that make up the hepatic differentiation signature, but also necessary for the transcription of additional hepatic-specific genes. As a result, we demonstrate that the amount of expression of this group of lncRNAs in HCC patients is related to the degree of hepatic differentiation and patient prognosis [6]. As a result, our findings support the link between epigenetic mechanisms like DNA methylation and lncRNA expression and liver differentiation, and show that hepatocarcinogenesis is linked to DNA methylation-mediated downregulation of a set of lncRNAs that are required for hepatic differentiation and function [7].

Discussion

DNA methylation, post-translational histone modifications, non-coding RNAs, and 3D genome structure are all epigenetic processes that tightly govern gene expression in a cell-type and dynamic way. Thus, epigenetic alterations play a crucial role in organism development, controlling cell lineage decisions and later preserving the transcriptome landscape as it progresses toward a terminally differentiated state. Because of this epigenetic fine-tuned regulation of gene expression, epigenetic changes are important events in tumour initiation and are known to have an influence on all cancer hallmarks. Dysregulated DNA methylation, for example, has been identified as one of the early stages in carcinogenesis, reprogramming gene expression patterns and increasing chromosomal instability. Furthermore, deregulation of the levels of numerous lncRNAs has been linked to the development and progression of cancer in recent years. In this context, we previously found a list of lncRNAs deregulated in many tumour types using a pan-cancer comparison. We discovered that lncRNAs were unregulated in tumors in a more tumor-specific way than mRNA, and that upregulated lncRNAs in tumors were preferentially expressed in healthy organs such as the testis, brain, digestive tract, or blood/spleen. We wanted to know more about the top 35 lncRNAs that were downregulated in HCC in the current study (Top35 LNDH). First, we verified their downregulation in two more in silico and experimental HCC cohorts, as well as their greater expression not only in the peritumoral but also in healthy liver tissue. In fact, as compared to normal livers, some of the lncRNAs analysed were already downregulated in the peritumoral and cirrhotic tissue, indicating that those lncRNAs play an early role in liver carcinogenesis. A similar mechanism may be responsible for the downregulation of the Top35 LNDH. In this regard, cancer cells DNA methylation landscape is characterised by aberrant DNA methyltransferase expression, widespread DNA hypomethylation, and focused hypermethylation of CpG islands, which are found in around 70% of human gene promoters. Hypermethylation of the promoter is linked to a reduction in transcription initiation. The reduced expression of these Top35 LNDH in HCC is related to promoter DNA hypermethylation, according to in silico

methylome data, targeted bisulfite sequencing, and in vitro investigations in cultured cells treated with the demethylating drug DAC. We found that HCC 1 patients with lower levels of Top35 LNDH have greater methylation levels in the promoters of these lncRNAs and higher levels of DNMT1, DNMT3A, and to ensure the cell's proper function. In fact, cancer aetiology now recognises the capacity to avoid or escape from terminal differentiation as a significant component [2]. Expression of transcription factors such as HNF-1 and 4 alpha (HNF1 and HNF4) and C/EBP and metabolic proteins and enzymes such as albumin, Cytochrome P450 (CYP) isoforms, Fructose-1,6-Bisphosphatase 1 (FBP1), or MAT1A, among others, play a role in hepatocellular identity and function. In this investigation, we discovered that, like other genes, Top35 LNDH expression is strongly elevated during liver development. Furthermore, we discovered that a subset of the Top35 LNDH was preferentially expressed in the liver compared to other tissues, supporting the hypothesis that lncRNAs are more tissue specific than mRNAs. These findings showed that Top35 LNDH expression may play a role in adult liver identity. show that Top35 LNDH expression not only corresponds to hepatic differentiation, but is also essential for the production of hepato-specific genes. We discovered that silencing four Top35 LNDH genes reduced the increase of CYP3A4 and ALB expression induced by a DNA demethylation agent. The expression of the diverse cell-type collection of genes is driven by a distinctive epigenetic landscape, and the mechanism of action of some epigenetic medicines is linked to the restoration of liver differentiation. In HCC cells, hypermethylation of the promoter regions of CYP3A4, ALB, and FBP1, among others, occurs, and demethylating therapies result in considerable promoter demethylation and elevation of their expression levels. We show that DNA methylation regulates the expression of the Top35 LNDH, and that their induction is essential for the demethylation-dependent induction of at least CYP3A4 and ALB. More research is needed to properly unravel the molecular mechanism behind this reliance. Although there are few examples in this context, an elegant report highlighting the potential complexity of these mechanisms has described how the lncRNA SNHG6 is a negative regulator of MAT1A protein expression in hepatoma cells by triggering the miR1297/FUS pathway to regulate nucleocytoplasmic shuttling of MAT1A mRNA, while activating MAT2A mRNA expression by suppressing miR-1297 direct binding to MAT2A 3'UTR In any case, our findings show that maintaining the transcriptome responsible for liver identity requires a coordinated sequence of epigenetic processes including DNA demethylation and the production of lncRNAs. The loss of liver identity and the degree of differentiation of hepatic cells have an influence on patient care and prognosis from a clinical standpoint. As a result, we discovered that HCC patients with the lowest level of Top35 LNDH expression had a considerably poorer prognosis than those with a greater level of Top35 LNDH expression. Individual expression of a substantial number of these lncRNAs has been found to correlate with overall survival, suggesting that using their expression to predict patient progression warrants further investigation. Furthermore, the successful care of cancer patients is contingent on early detection and appropriate treatment. As previously stated, the mechanism of action of several epigenetic medicines is dependent on their differentiation impact. so, tumours that are more differentiated will have a restricted response. To establish if the amount of expression or methylation status of any or all of the Top35 lncRNAs discovered might be employed as biomarkers for targeted treatment, more research is needed. The degree of tumour dedifferentiation has a negative correlation with the progression and prognosis of HCC patients. The expression of genes that define the completely differentiated cell state and, hence, its function is governed by a number of methods. We identified a group of lncRNAs (Top35 LNDH) as part of the hepatic differentiated signature, whose expression is suppressed by DNA methylation during hepatocarcinogenesis. Importantly, the absence of this Top35 LNDH limits the expression of other hepato-specific genes and is linked to patient prognosis. These findings show the intricacy and interconnectedness of many epigenetic processes involved in gene expression and hepatic differentiation, as well as the influence that their control might have on the course of liver disease and the prognosis of HCC patients.

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