Oncoinformatics and Mutational Analysis of Human Liver Cancer

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Abstract

Liver cancer is a major cause of cancer-related deaths worldwide, surpassing other forms of cancer in terms of mortality rates. Liver cancer encompasses various aggressive tumor types, including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA), as well as rare forms such as fibrolamellar carcinoma and hepatoblastoma. The incidence and mortality rates of iCCA are also rising globally, with variations among different racial and ethnic groups. Chronic liver damage plays a central role in the development of both HCC and iCCA, creating a pro-oncogenic state that facilitates the transformation of cells and the progression of liver cancer. Extensive research has revealed the genetic complexity of liver cancer, with frequent somatic mutations observed in genes such as TP53, MYC, and WNT/beta-catenin pathway-related genes. Mutations in the promoter region of the telomerase gene (TERT) have also emerged as a predominant mechanism activating telomerase and are detected in a significant proportion of hepatocellular carcinomas. Epigenetic modifications, including DNA methylation and histone modifications, contribute to liver cancer development and progression. This review aims to consolidate the current understanding of liver cancer biology, focusing on genetic alterations, tumor heterogeneity, and the role of key cellular players in tumor initiation and perpetuation. By integrating these multifaceted aspects, a comprehensive understanding of liver cancer can be achieved, leading to improved strategies for combating this challenging disease.

Keywords: Bioinformatics, Liver cancer, hepatocellular carcinoma, intrahepatic cholangiocarcinoma, genetic complexity, Data compiled , somatic mutations, telomerase, DNA methylation, histone modifications.

INTRODUCTION

Liver cancer is a significant contributor to fatalities related to cancer globally. Nowadays, it's responsible for more cancer deaths than any other factor. This kind of cancer is increasing in both prevalence and fatality. Every year, approximately 700,000 lives are claimed by liver cancer across the globe [1, 2]. This form of cancer encompasses a range of aggressive tumors that display distinct variations in ethnicity, causes, and geographic distribution. The primary types of liver cancer include HCC (Hepatocellular carcinoma) and iCCA(intrahepatic cholangiocarcinoma).Furthermore, there are two uncommon types of malignant tumors of liver that typically arise in young adults and i.e. fibrolamella and hepato-blastoma

carcinoma.HCC is among the rapidly growing cancers in terms of both its occurrence and mortality worldwide. It is observed to be more prevalent in males compared to females. It is a diverse condition that typically emerges in individuals with liver cirrhosis, which can be caused by a range of factors [3]. These include infections like hepatitis B virus, hepatitis C virus, excessive alcohol consumption, or metabolic syndrome. The incidence and mortality rates of intrahepatic cholangiocarcinoma, which is the second most common primary liver cancer, are on the rise worldwide. Notably, this type of tumor shows consistent variations among diverse racial and ethnic groups, with Hispanic and Asian populations exhibiting the highest occurrence [4].While Hepatocellular carcinoma and intrahepaticcholangiocarcinoma are associated with distinct causative agents, both of these primary liver cancers are intricately connected to chronic liver damage. This damage is caused by various chronic liver diseases, leading to continuous harm to liver cells and an increased turnover of cells. This heightened cell turnover creates an environment conducive to errors during the ongoing repair processes. Consequently, the hepatic microenvironment undergoes significant changes, giving rise to an oncogenic microenvironment.This altered microenvironment promotes the transformation of liver cells, creating a pro-oncogenic state and facilitating the development of liver cancer [5].

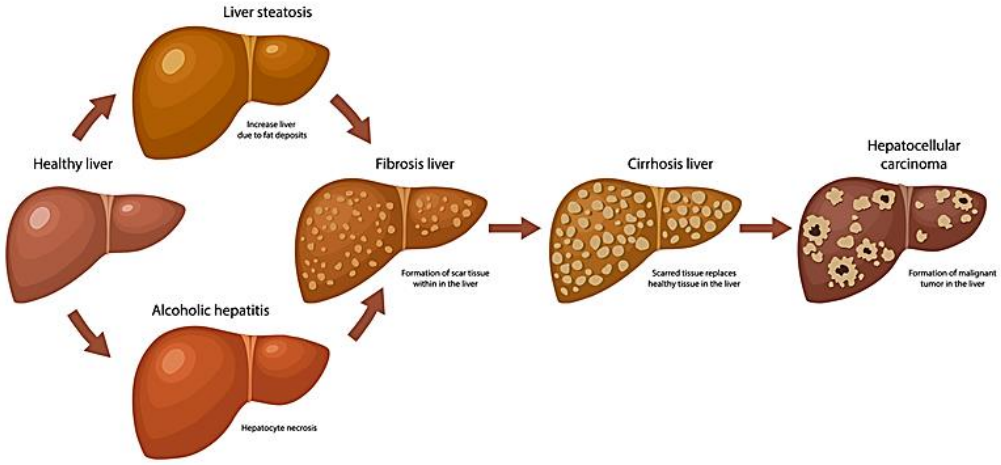

Figure 1: Stages of Liver Cancer

In the case of early-stage tumor detection, there are several treatment possibilities available. These options encompass surgical removal, local ablation techniques, or even transplantation ofliver. However, as the cancer advances into more advanced stages, the range of treatment interventions becomes limited. In such scenarios, alternative therapeutic approaches like chemoembolization or the administration of sorafenib have shown promising but moderate enhancements in terms of patient survival [6-8].Extensive cellular and molecular investigations have revealed that adult hepatocytes serve as the primary cell source for liver tumors. The process of hepatocarcinogenesis involves multiple potential pathways. One pathway involves the direct transformation of hepatocytes into hepatocellular carcinoma (HCC) through the gradual accumulation of specific genetic mutations. Another pathway entails de-differentiation into precursor cells, which subsequently undergo genetic alterations to develop into HCC. The malignant transformation of these cells gives rise to intrahepatic

cholangiocarcinoma. These diverse pathways shed light on the intricate mechanisms underlying the development of liver tumors [9].

Within this comprehensive review, we aim to consolidate the present comprehension of liver cancer biology. Our focus lies in delving into the intricacies of genetic alterations, investigating the complex nature of tumor heterogeneity, and unraveling the secrets behind identifying and characterizing the cells that play a pivotal role in initiating and perpetuating these tumors. By assimilating these multifaceted aspects, our aim is to offer a holistic and comprehensive understanding of the captivating realm of liver cancers.

GENETIC COMPLEXITY OF LIVER CANCER:

A multitude of somatic genetic abnormalities have been identified in hepatocellular carcinoma, encompassing a range of mutations, copy number alterations of genes, and rearrangements within and between chromosomes. Notably, certain genes critical to cancer progression, including TP53, MYC, WNT, beta-catenin, as well as cell-cycle related genes cyclin D1 and cyclin-dependent kinase inhibitor 2A, frequently exhibit alterations at the genetic level. These observations shed light on the pivotal role played by these genes in the development and progression of HCC [10-12].Moreover, there exists a subset of genes that are frequently affected by alterations in liver cancer, playing vital roles in various cellular processes. These include genes responsible for maintaining telomere stability [13], as well as genes involved in epigenetic mechanisms [14]. Additionally, genes associated with remodeling of chromatin are also commonly affected [15]. These genetic modifications offer insights into the intricate mechanisms that regulate telomeres, epigenetics, and chromatin structure, emphasizing their significance in the context of liver cancer.

1. Mutations in genes:

Recognized as potential catalysts for the development of cancer, specific genes often exhibit recurring somatic mutations. In most cases, the rate of mutation per genome in hepatocellular carcinomas is about average, comparable to that observed in other solid tumors. For instance, HBV virus exhibits a relatively elevated mutation rate due to its replication process involving RNA-mediated RT. Notably; HBV RT lacks a proofreading function, further contributing to the occurrence of mutations [17-19].Unlike HBV, HCV is not a retrovirus RNAthat is not incorporated into the host genome and only exists as a single-stranded entity. However,an elevated mutation rateis a direct result of the dsDNA breaks induced by HCV infection. Cells infected with HCV demonstrate an increased frequency of mutations in specific genes, including BCL-6, CTNNB1, TP53, and immunoglobulin genes [20].

2. Mutation in promoter of telomerase:

Situated at the ends of linear chromosomes, telomeres play a crucial role in safeguarding chromosomes against undesirable fusion and degradation caused by enzymes. Telomerase, a protein complex consisting of the telomerase reverse transcriptaseand the telomerase RNA component, actively participates in maintaining the integrity and length of telomeres [21]. In most fully developed adult cells, the expression of telomerase is typically repressed or suppressed [22].When telomeres undergo significant shortening, a DNA damage response is activated. This response can lead to either programmed cell death, or a state of cellular senescence. This process is detrimental to liver health because it prevents the liver from regenerating its normal structure, contributing to fibrosis and, ultimately, cirrhosis [23].The TERT promoter region has emerged as the predominant site of mutations observed in HCC.

These mutations represent the most prevalent genetic alterations in HCC and serve as the primary mechanism for activating telomerase.TERT promoter region mutations are detected in a significant proportion, ranging from 30% to 60%, of hepatocellular carcinomas [24, 25].

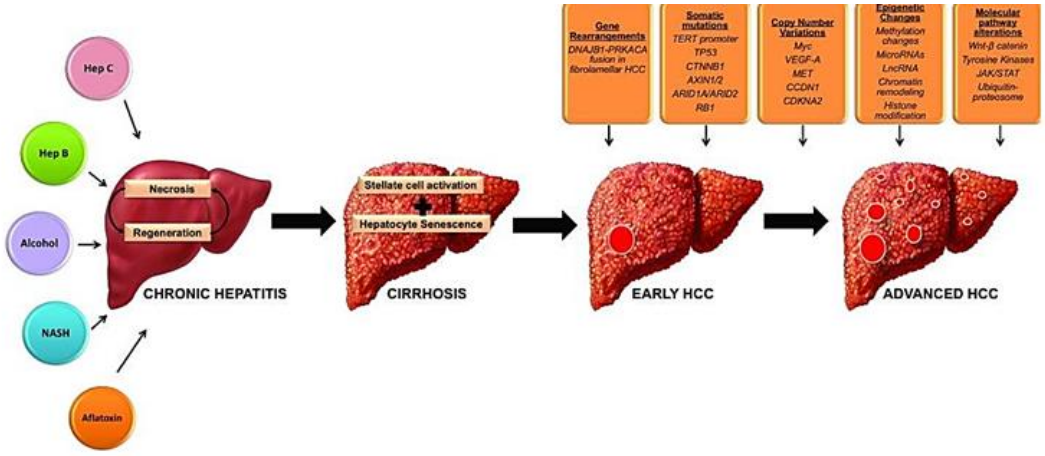

Figure 2: Pathogenesis of liver cancer

3. **Mutations in TP53 pathway:**

TP53, a tumor suppressor, plays a critical role in safeguarding cellular integrity and thwarting the onset and advancement of diverse cancer types. It is frequently observed that multiple cancers manifest reduced levels of p53 or harbor mutations in the TP53 gene.In its wild-type form, p53 exerts a crucial role in promoting apoptosis and inducing cell cycle arrest. However, the occurrence of inactivating mutations in the p53 gene, as well as alterations in other key pathway components, disrupts these vital functions [26, 27].

4. **Additional Somatic Mutations and Hepatitis B Virus Integrations in Hepatocellular Carcinoma:**

A notable finding in HCC is the frequent involvement of eleven key pathways, which play crucial roles in the development and progression of the disease. These pathways include alteration in WNT/beta-catenin pathway, PI3K-AKT-mTOR pathway dysregulation, TP53/cell cycle pathway abnormalities, MAPK pathway perturbations, hepatic differentiation pathway modifications, epigenetic modification, chromatin remodeling pathway irregularities etc.[28].

5. **Epigenetic modifications:**

Epigenetics delves into the realm of inheritable alterations in gene expression that transpire without any modifications to the DNA sequence itself. This intricate field plays a pivotal role in the development of cancer by influencing a multitude of mechanisms, including gene transcription, the stability of chromosomes, and the differentiation of cells.Epigenetic modifications encompass a range of chemical modifications, such as methylation, hydroxymethylation, and acetylation, which occur in precise regions of DNA. These modifications wield profound influence over gene activity, exerting a significant impact on the progression of cancer [29, 30].

Methylation of DNA:

Aberrant methylation patterns in hepatocellular carcinoma encompass the targeting of numerous gene regions, showcasing hypo-methylationi.e. global and site specific and site-

specific hyper-methylation. In liver cancer, global hypo-methylation causes chromosomal and genetic instability by disrupting nuclear structure and function. On the other hand, regional hyper-methylation frequently leads to the tumor suppressor genessilencing, further contributing to the progression of HCC [31].During the process of liver carcinogenesis, factors like chronic HBV and HCV infections can contribute to the deregulations of methylation patterns.These viral infections have the potential to disrupt the normal methylation processes in the liver, thereby influencing the development and progression of liver cancer. The deregulated methylation observed in these cases is believed to play a significant role in the molecular mechanisms underlying hepatocarcinogenesis [32, 33].In hepatocellular carcinoma, deregulated methylation often manifests through various mechanisms. One prevalent example is the hyper-methylation of the CDKNA2 promoter, which results in p16suppression, a crucial regulator of cell cycle and tumor suppressor.This event is commonly observed in HCC and contributes to the development of tumors.Additionally, the methylation of GSTP1 and E-cadherin promoters, as well as the deregulation of DNA methyltransferases (DNMTs) mediated by HBx, further contributes to the dysregulated methylation patterns in HCC. These alterations in methylation play a significant role in HCC development [34–38].

Role of Histone Modifications:

Histones play a crucial role in controlling the activity of genes by influencing the accessibility of chromatin. The state of chromatin, whether open or closed, is determined by histones.To achieve this regulation, various chemical modifications are added to specific sites on the histone tails, which extend from the nucleosomes. Elevated amounts of tri-methylated histone H3 lysine 4 have demonstrated a connection to decreased overall survival and unfavorable prognosis in hepatocellular carcinoma. Additionally, a separate investigation found that increased levels of H3 lysine 4 were associated with aggressive characteristics of tumors. Furthermore, for a worse prognosis in HCCthese high levels of H3 lysine 4 served as a predictive factor [39, 40].

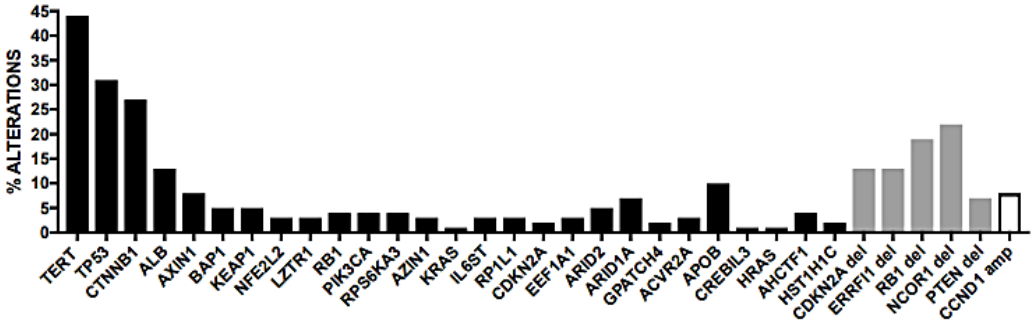

Figure 3: Major alteration in genes of different ethnicity

The Cancer Genome Atlas Research team has recently released a detailed report on their extensive investigation into the genomic makeup of hepatocellular carcinoma. They conducted a comprehensive analysis and found that 26 genes exhibited frequent mutations in this cancer type. Notably, driver mutations were identified in these above genes [41, 42].

SIGNALLING PATHWAYS THAT PLAY ROLE IN LIVER CANCER

Cancer is characterized by abnormalities in various signaling pathways, and hepatocellular carcinoma (HCC) is no exception. Several specific pathways have been identified to be

disrupted in HCC, contributing to its pathogenesis. Among these pathways are those involved in regulating the signaling of growth factors such as insulin-like growth factor, epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, and hepatocyte growth factor among others. These deregulated pathways play a significant role in the development and progression of HCC [43].

1. WNT/β-catenin signaling pathway:

The disruption of the Wnt pathway is a common occurrence in HCC, making it one of the most frequently affected pathways. The Wnt pathway involves a family of nineteen ligands and ten transmembrane receptors that interact with each other. This interaction can result in the activation of either the canonical or non-canonical Wnt pathway. Activation of the Wnt pathway in HCC is frequently associated with specific mutations. The most prevalent mutations involve CTNNB1, which leads to the stabilization of β-catenin. Mutations in AXIN1 and AXIN2, which normally act as negative regulators of the Wnt pathway, also contribute to pathway activation. Furthermore, the tumor suppressor gene APC is often inactivated, further promoting the activation of the Wnt pathway in HCC [43].

2. VEGF and other pathway of angiogenesis:

In HCC, the tumor is characterized by abundant blood vessels, and the process of angiogenesis plays a significant role. Neoangiogenesis, which is driven by factors such as VEGF and angiopoietins, is crucial for the promotion and maintenance of new blood vessel formation in HCC.Researchers have utilized these principles to develop effective therapeutic approaches for treating HCC. Despite the presence of a well-developed vascular network, areas of hypoxia can still be found within the tumor due to the disorganized formation of capillaries and the presence of leaky blood vessels.The presence of hypoxia in HCC triggers the activation of growth factors like HIF 1 and 2 as well as IGFs. These factors play a crucial role in promoting tumor angiogenesis by activating specific genes that respond to hypoxia.This process ultimately contributes to tumor development and its metastasis [44-49].

3. JAK/STAT pathway:

STATs can be triggered into action by a range of cytokines, hormones, and growth factors. This activation occurs when JAKs phosphorylate the tyrosine residues on STATs. When activated, STATs initiate the transcription of specific genes called suppressors of cytokine signaling (SOCS).Adhesion to phosphorylate JAKs and their corresponding receptors is an essential function of the SOCS genes, effectively putting a brake on the pathway.This regulatory mechanism serves to maintain a balanced and controlled cellular environment.The activation of STATs by JAKs triggers a cascade of cellular processes. Disruption or malfunctioning of the inhibitors involved in this pathway can contribute to various ailments, like cancer.Notably, inactivation of SOCS1 and SSI-1, as well as triggering of the JAK/STAT pathway, has been observed in cases of HCC.These molecular alterations play a role in the development and progression of HCC, highlighting their significance in the context of this disease [50,51].

CONCLUSION

To summarize, liver cancer is a major global health issue with high mortality rates surpassing other forms of cancer. Its incidence is increasing, resulting in the deaths of approximately 700,000 individuals annually. Different types of aggressive liver tumors, including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA), as well as rare

variants like fibrolamellar carcinoma and hepatoblastoma, contribute to the overall burden of the disease. HCC, especially, is rising rapidly and is more prevalent among males, often occurring in individuals with liver cirrhosis caused by factors such as viral infections (hepatitis B and C), alcohol consumption, or metabolic syndrome.The rates of iCCA are also escalating globally, with variations observed among different racial and ethnic groups. Chronic liver damage resulting from various liver diseases plays a pivotal role in the development of both HCC and iCCA. The continuous turnover of liver cells in this damaged environment creates an environment conducive to oncogenic transformations, leading to the development of liver cancer.Treatment options for early-stage liver cancer include surgical removal, local ablation techniques, or liver transplantation. However, as the cancer advances, the range of available interventions becomes limited. Alternative approaches such as chemoembolization or targeted therapy with sorafenib have shown some improvements in patient survival.Extensive research has shed light on the genetic complexity of liver cancer. Frequent somatic mutations, including alterations in genes such as TP53, MYC, and genes related to the WNT/beta-catenin pathway, are commonly observed. Mutations in the promoter region of the telomerase gene (TERT) have emerged as a primary mechanism activating telomerase and are prevalent in a significant proportion of hepatocellular carcinomas. Epigenetic modifications, including DNA methylation and histone modifications play crucial roles in the development and progression of liver cancer.A comprehensive understanding of the genetic alterations, tumor heterogeneity, and key cellular processes involved in liver cancer initiation and progression is vital. The presence of genetic abnormalities, frequent somatic mutations, and dysregulated pathways underscores the importance of specific genes and molecular mechanisms in liver cancer. Epigenetic modifications, particularly DNA methylation and histone modifications contribute to the disruption of gene expression and are associated with poor prognosis in liver cancer patients.By consolidating current knowledge and integrating these multifaceted aspects, we can gain a holistic understanding of liver cancer biology. This comprehensive review aims to provide insights into the genetic complexity, tumor heterogeneity, and cellular mechanisms underlying the development and progression of liver cancer. Enhancing our understanding of these aspects will contribute to more effective strategies in combating this challenging disease.

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