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Review

Hepatocellular Carcinoma Gene Expression: *The New Era, Where It goes*?

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ABSTRACT

Hepatocellular carcinoma is known to be a common primary liver malignancy and a serious leading cause of cancer-related mortality globally. Hence, ongoing recent advances in the genetic field regarding hepatocellular carcinoma paid researchers great attention to identifying various biomarkers to act as diagnostic and prognostic tools for the early detection of hepatocellular carcinoma and also developing targeted therapeutic agents that are indicated and available for advanced stages of hepatocellular carcinomas, however, their antitumor efficacy remains limited and under investigations. Therefore, our review summarized the genetic studies of liver cancer focusing on the somatic mutations, copy number variations, and epigenetic modifications that represent early alterations and oncodrivers in hepatocarcinogenesis, Moreover, the identification of genetic signatures and proteomic targets through hepatocellular carcinoma-related genome-wide screening, to show the ongoing clinical application of such analysis to facilitate diagnosis, prognosis and management of patients with hepatocellular carcinoma for a better outcome.

1. Introduction

Hepatocellular carcinoma (HCC) represents the most common primary liver malignancy and also the common causes of cancer-related mortality globally, its incidence is expected to increase significantly over the next decade. Multiple studies reported various HCC risks that vary geographically. Viral etiologies HBV/HCV (Hepatitis B virus/ Hepatitis C virus) are considered the common one. However, their risks of developing HCCs have been improved significantly with the advent of the HBV vaccination and HCV antiviral therapy [1,2]. Other serious factors that are growing in incidence globally include alcoholic liver disease, obesity, and non-alcoholic fatty liver disease (NAFLD). The mechanism of hepatocarcinogenesis of different risk factors relies mainly on chronic injury and lipotoxicity-induced oxidative stress leading to a vicious cycle of chronic hepatic inflammation and regeneration processes that eventually ends up with fibrosis, which increases the risks of genomic instability and carcinogenesis in a cirrhotic background [3,4]; However, these pathogenic mechanisms may also arise on a non-cirrhotic liver, especially in HBV and NAFLD. Currently, liver transplantation represents one of the chief curative therapies for resectable HCC; however, it is associated with 10–15% recurrence rates [5,6]. For unresectable tumors, oral multi-kinase inhibitors (MKIs) have been used, but their efficacy has been limited by the side-effects of toxicities and resistance. Recent studies of immunotherapy have shown promising results in improving the survival of advanced HCC cases opening the gate for selecting an effective HCC therapy that can improve long-term survival significantly [7,8].

2. HCC genetic analysis

Several genetic studies have shown significant progress regarding the genomic landscape of HCC including the somatic mutations, copy number variations, and epigenetic modifications that represent the oncodrivers and also contribute to disease prognosis. Moreover, advances in HCC-related genome-wide screening have led to the identification of genetic signatures and proteomic targets that also aid in the diagnosis and outcome [9] (see Fig. 1).

2.1. Somatic Mutations

It's known that over 30 somatic mutations may occur in the normal aging liver annually in response to genotoxic stress agents or arise randomly during DNA replication. During chronic hepatic inflammation of different etiologies, hepatocytes are susceptible to mutation-induced proliferation because of mitochondrial damage and endoplasmic reticulum oxidative stress. Furthermore, the viral etiology-related hepatic

Abbreviations: HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; lncRNAs, long non-coding RNAs; miRNAs, microRNAs; MKI, Multi-kinase inhibitor; NAFLD, Non-alcoholic fatty liver disease; OS, Overall survival; TERT, telomerase reverse transcriptase.

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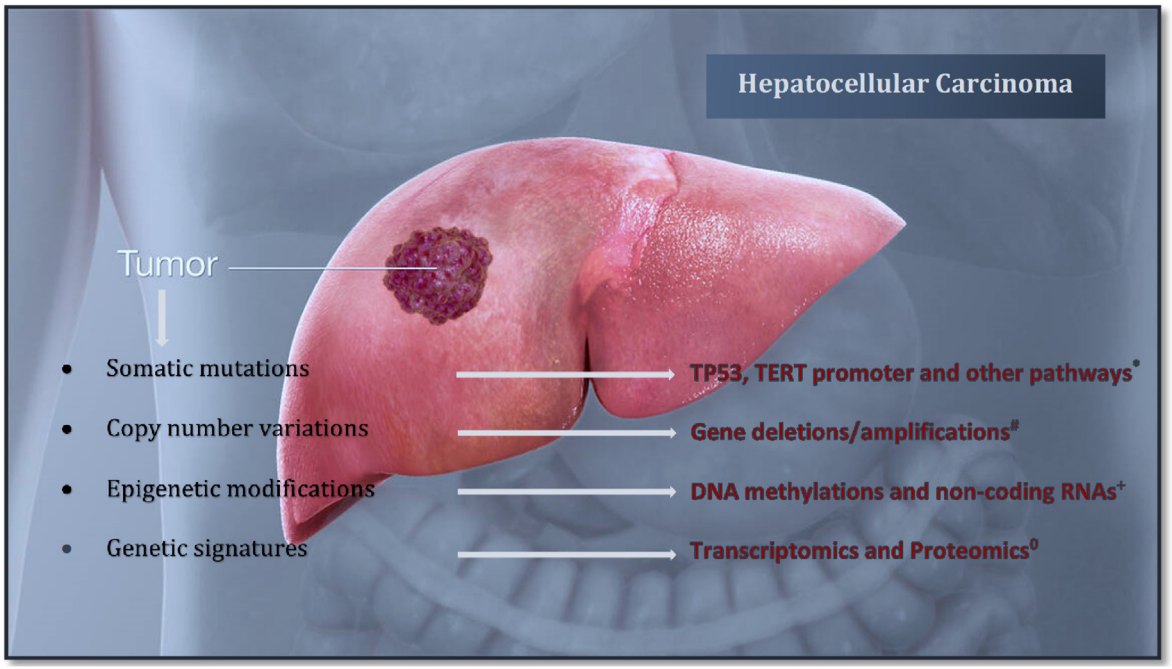

Fig. 1. Major genetic alterations in Hepatocellular carcinoma HCC [9]. *Other pathways include the Wnt/β-catenin, PI3K-AKT-mTOR, MARK, RPS6KA3 and MAP/ERK pathways. #Genetic amplifications involve CCND1, FGF19, MYC, MET, VEGFA, MCL1, UBE2Q1, EXT1, WNK2, JAGGED1. +Methylation aberrations as APC, CDH1 and non-coding RNAs include miRNAs and lncRNAs (miR-21, miR-221/222, and miR-224 high expressions). 0Transcriptomics involve proliferation clusters such as cyclins of A/B type, cell cycle division proteins (Hetero-hexamer DNA helicase MCM3–7, PCNA, DNA TOP2A, human hepatic cancer stem cell gene) while proteomics include upregulation of integrins, PDGF signaling, RHO, myosin, RB1, IL1.

injury may cause intracellular genomic integrations as seen in HBV, which is considered the serious one, while HCV causes double-stranded breaks that lead to missense mutations. Other etiologies-related hepatic injuries including NAFLD. and alcoholic liver disease result in HCC by causing direct damage to DNA through reactive oxygen species (ROS) and chronic inflammation. In practice, the serious driver mutations involved in HCC include major common pathways [10,11]: tumor suppressor genes, telomerase, and other several pathways that will be discussed in detail.

2.1.1. Tumor suppressor genes (genome guardian)

TP53 is responsible for cellular process regulation including angiogenesis and apoptosis. It's the most frequently altered gene in HCC as reported by the International Agency for Research on Cancer International Agency for research on cancer that over 29,000 mutations of TP53 have been studied in human cancers and also inactivated in around fifty percent of all HCCs that are mainly induced by aflatoxin B1, HBV, and HCV to a lesser extent. Furthermore, the gain of function gain of function mutations in HCC include TP53 V157F and TP53 R249S which are related to HBV and aflatoxin exposure [12,13]. Clinically, mutations in the TP53 family (p63 and p73) have been associated with aggressive behavior, in form of increased stem cell-like markers expression, advanced Edmonson grade, and high-risk of recurrence with low survival. Moreover, it may downregulate the immune response making HCC a potential target for immunotherapy [14,15]. The TP53-targeted therapies act by supplementing wild-type p53 or blocking its interaction with cytoplasmic partners. Oral cyclin-dependent kinase 4/6 inhibitor Palbociclib has been used in trials to inhibit p53 DNA-damage partner ataxia telangiectasia mutated. Also, the recombinant adenovirus p53 in combination with TACE has shown efficacy in increasing disease-free survival and overall survival (OS) in patients having HCC [16,17]. Other tumor suppressors include Hepatocyte-specific Arid1a/1b, which are components of SWItch/Sucrose Non-Fermentable complexes essential for DNA repair. ARID mutations have been found in the advanced stages of HCC with larger size and aggressive behavior as it is associated with increased angiogenesis. Therefore, these mutations have been vulnerable to immunotherapy and anti-angiogenic therapies in practice [18,19].

2.1.2. Telomerase

It lengthens telomeres and restores liver regeneration integrity upon activation of the telomerase complex, which is composed of telomerase reverse transcriptase (TERT) and telomerase RNA. The TERT promoter mutation is a common genetic alteration which occurs in dysplastic nodules and low-grade HCC, with an overall frequency of around sixty percent. Hence it plays a vital role in the earlier stages of carcinogenesis as it selects the onco-drivers for HCC that escape apoptosis with uninhibited telomerase activity [20]. Moreover, the loss of function of altered telomerase gene variants' predisposes to the neoplastic process as it impairs the healing phase response of hepatocytes to chronic inflammation accelerating the cirrhosis stage. Clinically, mutations in the TERT promoter have been related to shorter disease-free survival, OS, and late intrahepatic recurrence postoperative [21]. Furthermore, they have been frequently detected in the elderly group, African/European ancestry, and HCV/HBV etiology. Circulating DNA of TERT mutations may be of diagnostic value for screening high-risk patients having HCC and the TERT mutation-targeted therapies are still in clinical trials [22–25].

2.1.3. Other pathways

β-catenin is a multi-purposeful protein encoded by Catenin Beta 1gene that adheres the intracellular actin to adjoints and acts as a key nuclear effector of canonical Wnt signaling. It is mutated in around forty percent of HCC cases [26,27]. It has been related to the aggressive behavior of HCC, as it was detected in advanced histopathologic features with micro/macrovascular invasion, larger sizes, poor pathological grade, and tumor recurrence. Furthermore, mutations in any of the proteins responsible for activating or destroying β-catenin result in aberrant nuclear accumulation [28,29]. Other upregulated elements of the Wnt/β-catenin pathway detected in HCC including PRC1, AKIP1, and TXNDC12. So far, the involved genes and proteins in the Wnt/β-catenin pathway are in clinical trials to be used as therapeutic targets [30–32].

Other pathways that have been involved in carcinogenesis include PI3K/Akt/mTOR and RAS/RAF/MAPK pathways; their upregulation has been observed in around ten percent of HCC cases owing to the amplification of FGF19/CCND1 locus. First, the activated Akt/mTOR signaling has been detected in HCC tissues because of mutations related to activated PIK3CA and inactivated TSC1/C2. Furthermore, the identification of PTEN-related homozygous deletion in a subset of HCC cases as it encodes the inhibitor of PI3K kinase. On the other hand, The RAS family-related activated genes' mutations have been observed in HCC to a lesser extent unlike the inactivated forms of RP6SKA3 encoding RAS inhibitor RSK2 have been detected in around nine percent of liver cancer cases and thus inactivated release of RSK2 inducing the pathway constitutive activation [67,68].

In practice, RPS6KA3 and MAP/ERK pathways' mutations have been associated with poor differentiation, macrovascular invasion, and rapid proliferation [33,34]. Moreover, KEAP1 mutations detected by genome-wide screening represent the main cause of acquired resistance to oral MKIs. Altered HNF1A has been also detected in patients having HCC as it regulates cellular homeostasis and metabolism [35,36]. Lastly, the Janus kinases and signal transducers and activators of transcription are frequently altered in HCC promoting various neoplastic features that involve angiogenesis, proliferation, and metastasis. In practice, signal transducers and activators of transcription inhibitors are evaluated in clinical trials for HCC [37–39].

2.2. Copy number variations (CNVs)

They result from the loss/gain of either individual genes or entire chromosomal arms activating oncogenes that promote carcinogenesis. Frequent copy number alterations that have been identified in multiple HCC genetic studies include gains in chromosomal arms 1q and 8q and losses in 8p and 17p. Other known driver oncogenes that were significantly amplified in HCC include CCND1, FGF19, MYC, MET, VEGFA, MCL1, UBE2Q1, EXT1, WNK2, JAGGED1, and RB-regulated transcription factors E2F1 and F3. MYC amplification at 8q24.1 has been associated with poorly differentiated cells and promotes metastasis/recurrence as it upregulates MMP9 which breaks the extracellular matrix [40–45]. In practice, copy number alterations have shown a positive therapeutic response such as increased FGF19 was related to a complete response after sorafenib for HCC [46].

2.3. Epigenetic Modifications

DNA methylation, histone modification, chromatin remodeling, and non-coding RNAs cause epigenetic alterations that represent a serious event in early hepatocarcinogenesis. Various genetic meta-analysis studies have noted increased global hypomethylation significantly in CpG dinucleotides from 500 to 684 CpG sites in HCC compared to non-HCC tissues with worse OS [47,48]. A meta-analysis of 12 HCC genetic studies including 981 patients having HCC observed that CDH1 hypermethylation was significantly higher in HCC tissues and was correlated with worse OS [49]. Regarding non-coding RNAs including miRNAs and lncRNAs have shown promising results as epigenetic regulators in HCC studies, whereas higher expression of miR-21, miR-221/222, and miR-224 have related to rapid proliferation, while lower expression of miR-26, miR-122, and miR199 have been related to slow proliferation and angiogenesis suppression. Moreover, upregulated lncRNAs including HULC and HOTAIR have been observed in HCC studies as HULC may promote carcinogenesis and angiogenesis by inducing proliferation and activating the CREB transcription factor, while HOTAIR expresses CCL2 to maintain the tumor microenvironment and its loss has been associated with HCC response to chemotherapies [69,70]. On the other hand, histone alterations have been observed in HCC owing to dysregulations in the placement and removal of acetyl groups from these histone tails by HATs and HDACs. Upregulated HDACs 1/2 may predict mortality and also may promote doxorubicin sensitivity in patients having HCC , however, their role is not established yet [71]. Clinically, a study proved that six hypermethylated genes including NEBL, three FAM55C sites, GALNT3, and DSE were used as diagnostic biomarkers for HCC with 98% specificity [49,50]. Furthermore, the epigenetic alterations in HCC can be targeted by inhibiting DNA methyltransferases; First generations including azacitidine and decitabine have shown efficacy in reducing tumor burden in clinical trials, as they promote well cellular differentiation and response to MKIs. Regarding 2nd generations including guadecitabine and zebularine have shown longer half-lives in clinical trials compared to 1st generations [51–53]. Lastly, miRNAs have been tested as therapeutic targets in clinical trials to prove their efficacy such as anti-miR-221 Miravirsen [54,55].

2.4. Genetic signatures

2.4.1. Transcriptomics

Multiple clusters of various expressed genes have been identified as genetic signatures in HCC studies that hold promising results as diagnostic/prognostic markers and as therapeutic targets for HCC. The frequently known proliferation clusters include [56,57] cyclins of A/B type and cell cycle division proteins that regulate the cell cycle, Hetero-hexamer DNA helicase MCM3–7, PCNA, and DNA TOP2A. In clinical practice, the genetic signature of regulated c-MYC has been associated with poorer OS and poor cell differentiation. Moreover, the human hepatic cancer stem cell gene cluster has been related to the high expression of epithelial cell adhesion molecule, CK19, and Alpha-fetoprotein and also resistance to different chemotherapies [58,59]. Other clinically significant genetic signatures have been detected through two different algorithmic approaches that screen for various expressed genes in paired and unpaired HCC cell lines. For example, 8 genetic signatures (TK1, CTTN, CEP72, TRIP13, FTH1, FLAD1, CHRM2, and AMBP) have been identified in HBV-HCCs study. Also, Zhang et al. identified other 14 in the cell cycle-related genetic clusters (BIRC5, BUB1B, CDC45, DTL, GINS2, KIF23, KIF2C, MAD2L1, MCM4, OIP5, PLK4, PTTG1, and ZWINT) that predicts poor OS and recurrence [60,61]. So far, none of the genetic signatures has been validated or approved yet to be used in clinical practice, however, significant advances in this field have been done [62].

2.4.2. Proteomics

It' known that genetic, epigenetic, and post-translational dysregulation related to HCC has been associated with changes in the levels of protein expression and protein–protein interactions. Several HCC studies identified various protein targets related to earlier diagnosis; however, they were limited by smaller sample sizes and lack of validity. Lately, advances in high-throughput protein analysis techniques studies have identified detailed proteomic maps for HCC [63,64]. Proteomic and phospho-proteomic comparison between HCC of HBV and non-HCC tissues showed the upregulation of cell cycle division, integrins, PDGF signaling, RHO, myosin, RB1, IL1, MET pathways, and the identification of metabolic reprogramming. Moreover, most proteins involved in metabolic hepatic pathways, including gluconeogenesis, detoxification, and ureagenesis-ammonia, showed a dramatic decrease in tumor tissues. Clinically, various protein targets have been identified either for diagnostic or therapeutic purposes in several proteomic studies using absolute quantitation-based multidimensional liquid chromatography-tandem mass spectrometry techniques; PGK1 was detected in patients' serum to be proved as an independent predictor of HCC recurrence and OS. Currently, ongoing wide-scale proteomics' studies are adding to our knowledge regarding the activated functional pathways related to HCCs to identify diagnostic/prognostic biomarkers that hold promising results [65,66].

3. Future perspectives/limitations

The full picture of molecular pathogenesis underlying the different steps of hepatocarcinogenesis necessitates a proper evaluation of multi-regional genetic aberrations (HCC intra-tumoral heterogeneity) and omics-related data, hence further investigations with novel technologies

including WES/WGS sequencing are needed; WGS is a promising genomic database for understanding the genetic analysis in liver cancer research as various mutated genes are yet to be characterized for their molecular function and roles in cancer, opening the gate for future research in this direction to be translated into valuable biological insights. However, in practice, the targeted obtained sequencing data have a minor role in the whole-genome mutational profile which may miss other genetic aberrations related to tumor initiation/progression. Moreover, the detected mutations regarding tumor progression including certain trunk and branch mutations may be of low value. Lastly, regarding multistep carcinogenesis, it is important to understand the expression data not only the mutation data for yielding better results with the use of multi-omics approaches in clinical genome-based treatment [72,73].

4. Conclusion

HCC is a heterogeneous disease with a complicated genomic landscape that paid researchers great attention to developing diagnostic/prognostic biomarkers and molecular-targeted therapies for a better outcome. Hence, several HCC genetic studies have focused on identifying the major genetic onco-drivers of hepatocarcinogenesis; whereas TP53, TERT-related genetic aberrations and others associated with cell cycle regulation have been observed frequently mutated somatic genes. Moreover, global DNA hypomethylations, chromatin remodeling, and growth-associated signaling pathways have been dysregulated and aid in tumor progression. Lastly, omics-related studies particularly transcriptomics/proteomics may show promising results; however, further studies on larger scales through novel sequencing technologies are needed.

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Author contributions

N. B. collected the data, designed the research, and wrote the manuscript with critical final revision and editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data available statement

All data generated or analyzed from previous several studies as mentioned in references and if any data is needed, it will be available from the corresponding author on reasonable request.

Ethics statement

Ethics approval was waived for this study because no patients' data were reported.

Informed consent

Not applicable.

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