

Genetic implications of viral hepatitis-associated hepatocellular carcinoma: A clinico-pathological overview

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Hepatocellular carcinoma (HCC) is the fifth most frequent malignancy worldwide with higher burden of cancer related-mortality in the developing nations [1]. The epidemiologic variations of HCC accounted for the predominant etiological factors in different geographic regions. Also, within the same region there exist marked variations in the incidence of HCC depending upon socio-demographic, etiologic and ethnic diversity [2]. The age-adjusted incidence rate (per 100,000) of liver cancer in males was highest among East (31.9) and South-Eastern Asian (22.2) population. On the other hand, South-Central Asia (3.7) recorded the lowest incidence rates [3]. The southern Europe comprised the medium-high incidence of HCC, whereas South and Central America, and other European countries are considered as low-incidence region [4]. There is considerable evidence suggesting that human hepatocarcinogenesis is a multistage process with the involvement of multiple risk factors.

Molecular basis of virus-related Hepatocarcinogenesis

An etiological association between hepatitis viruses and HCC has been clearly established, although the relationship is complex and might involve several contributing factors. In particular, HBV, HCV and alcohol are the main etiological agents of HCC. HBV seems to play a direct role in liver cell transformation through persistent expression of HBx and the large envelope protein, which is thought to disrupt the cellular transcription mechanism lead to liver tumorigenesis [5]. The role of HBV mutations and genotypes in disease progression continues to be of great interest. Viral mutation particularly, at the Basal Core Promoter (BCP) region (T1762/A1764), high serum HBV DNA level and HBeAg status has higher predictability of developing HCC [6]. Similarly, HCV plays critical role in hepatocarcinogenesis either indirectly through immune-mediated chronic inflammation or by disrupting the host immune-regulatory pathways [7]. HCV genotype 1b has been reported to be independently associated with higher risk of HCC [8]. Unlike in hepatitis C virus (HCV) infection, the relationship between different HBV genotypes and risk of future disease is not well established.

Epigenetic Alterations in HBV and HCV-Related HCC

HBV (and HCV)-related hepatocarcinogenesis involves a combination of direct as well as indirect mechanisms. Notably, the prolonged immune response in hepatocytes against HBV (or HCV) activates chronic inflammatory response, DNA damage due to oxidative stress, and subsequent cellular proliferation that substantiates function of exogenous carcinogenic factors [9]. The published literature reported a higher frequency of chromosomal aberrations and involvement of p53 gene inactivation in patients with HBV-related HCC. This is mainly attributed to the development of mutations, hepatic progenitor cells genes overexpression, and activation of the AKT pathway [5]. Gene silencing and differential gene-expression patterns in HCC patients have been reported due to hypermethylation of the promoter region of various tumor-suppressor genes such as RASSF1A, p16/INK4A, SOCS-1, IGFBP3, APC, E-cadherin, and GSTP1 [10]. Moreover, Micro RNAs are important biomarkers of regulation of hepatic functioning and are either upregulated (miR-18, miR-21, miR-221) or down regulated (miR-122, miR-223, miR-125) in HCC patients [11]. The current evidence supports the role of chronic HBV (and HCV) infections playing in stimulation of chronic necroinflammation and host immune mechanism leading to hepatocarcinogenesis [5].

Molecular classification of HCC

The clinico-pathological classification and staging of liver cancer is primarily based upon immunohistochemical findings, presence of etiological agents and clinical features, but these classifications lack accuracy and precision for appropriate management and prognostication [12]. To overcome this problem current researcher advocates for molecular classification approaches, based on expression pattern of signature genes by microarray and identification of novel single nucleotide polymorphisms (SNP). This approach has potential clinical utility for developing novel classification system for HCC that can readily predict therapeutic response and guide clinical decision-making for personalized management [13]. However, the robust understanding of the molecular classification of liver carcinoma necessitates further consideration of novel genomics and transcriptomics signatures for clinical translation of the molecular findings.

Molecular therapeutic targets of HCC

Novel molecular targeted therapies are meant to focus on groups of HCC cases with similar genetics characteristics. The objective of targeted therapy is to inactivate the oncogenic expression, revive tumor suppressor genes, and effective blockade of the signaling

pathways involved in hepatocellular proliferation, thereby correcting abnormal signal transduction and induction of apoptosis [14]. Currently, various candidate genome-based therapeutic targets for HCC have been identified using high throughput technology such as microarray, whole-genome mutational analysis, CHIP-chip analysis, and next-generation sequencing systems [13].

In summary, HCC has a multifactorial etiology with concomitant effect of viral hepatitis mediated chronic inflammatory response, oxidative stress, endogenous (oncogenes, growth factors and tumor suppressors) and exogenous carcinogenic factors in human hepatocarcinogenesis. Therefore, it is important to consider epigenetic alterations, genomic and proteomic signatures to identify suitable prognostic biomarkers and therapeutic targets to overcome the molecular complexity of HCC. Finally, better understanding of the molecular basis of virus-related hepatocarcinogenesis will help to develop more targeted therapeutic options to cure HCC in future.

Competing interests

None declared.

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