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EDITORIAL

Recent insights on risk factors of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is a disease prevalent in many populations worldwide. It initiates many economic and health problems in management modalities and leads to increasing mortality rates. Worldwide, trials have attempted to discover specific early markers for detection and prediction of the disease, hoping to set a more precise strategy for liver cancer prevention. Unfortunately, many economic, cultural and disciplinary levels contribute to confounding preventive strategies. Many risk factors contribute to predisposition to HCC, which can present individually or simultaneously. Previous articles discussed many risk factors for hepatocellular carcinogenesis; however, most of them didn't consider collectively the most recent data relating to causes. In this article, the pathogenesis and risk factors of HCC are discussed. Most of the intermediary steps of HCC involve molecular and transcriptional events leading to hepatocyte malignant transformation. These steps are mainly triggered by hepatitis B, C or transfusion-transmitted virus, either alone, or with other factors. Diabetes seems to be a major contributing risk factor. Schistosomiasis, a blood infestation, mostly affects Nile basin inhabitants leading to bladder, renal and hepatic cancers. Alcoholism, food and water pollutants and some drugs can also lead to HCC. Additionally, some hereditary diseases, as hemochromatosis, α-1-antitrypsin deficiency and tyrosinaemia are known to lead to the development of HCC, if not well managed.

Key words: Hepatocellular carcinoma; Hepatitis C virus; Hepatitis B virus; Transfusion-transmitted virus; Schistosomiasis; Risk, Alcoholism and hereditary diseases

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INTRODUCTION

Hepatocellular carcinoma (HCC) is ranked to be the most common cancer in many countries[1]. Recently, HCC was reported to be the fifth most common cancer in males, the eighth common cancer in females and about 560 000 cases are discovered per year, more than 80% of which occur in the developing countries. Having very poor prognosis, it represents the third leading cause of cancer death worldwide; more than one-half of them in China. Generally, HCC is more frequent in men than in women and the incidence increases with age[2]. Like other cancers, it is a multistep process, involving many genetic alterations, which eventually lead to malignant transformation of hepatocytes. Most liver diseases lead to cirrhosis. Within 15-40 years, chronic hepatitis leads to cirrhosis. Mostly, HCC develops among 70%-90% of cirrhotic patients, while only 10% of HCC patients have a non-cirrhotic liver, or even have inflammatory lesions[2]. According to the WHO mortality database of the early 1980s, the highest rates were found in Mexico and Chile, France, Italy, Portugal, Austria,

Hungary and Romania. Unfortunately, figures are rising in many European countries, including, in the UK, Wales and Scotland, possibly due to increased consumption of alcohol[3]. Alcoholic liver diseases and hepatitis C infection, being primary etiologies for liver cirrhosis, are the major causes of the rising HCC mortality rates[4].

PATHOGENESIS OF HUMAN HCC

Being implicated in more than 70% of HCC cases world wide, liver cirrhosis is the major risk factor for HCC development. Liver carcinogenesis may last for decades, through progressive accumulation of different genetic alterations eventually leading to malignant transformation. Thus, chronic liver injury initiates increased liver cell turnover, triggering oxidative DNA damage and inflammatory events. This leads to formation of dysplastic and macroregenerative nodules, which are considered to be neoplastic[5].

A-MOLECULAR PATHWAYS AND THEIR POSSIBLE RELATIONSHIP TO HCC

The underlying steps in human hepatocarcinogenesis: there are at least four molecular pathways that regulate either proliferation or death.

1-Irregular expression of β-catenin

β-catenin is a nuclear protein that regulates the cell cycle. Its irregular expression, resulting from β-catenin gene mutations, is implicated in HCC. In addition, alteration to the Wnt signaling pathway plays a role in more than 50% of HCCs[6]. Wnt molecules are a large family of cysteine-rich secreted glycoproteins that control development in organisms, ranging from nematodes to mammals. Interestingly, accumulated intra-nuclear β-catenin form complexes with proteins such as Wnt ligands and Frizzled receptors, leading to unrestricted cell cycling[7].

2-Up-regulation of many growth factors

Insulin-like growth factor (IGF), insulin receptor substrate 1, hepatocyte growth factor (HGF) and transforming growth factor β (TGF-β) have been implicated in the development of HCC[8].

3-Transformation from pre-neoplastic to HCC nodules

HCC is a highly vascular tumor, always accompanied by neo-vascularization. Thus, overexpression of angiogenic factors, vascular endothelial growth factor (VEGF) and angiopoietin-2, is another pathway for HCC genesis[9,10].

4-Mutations in transcription factors controlling the cell cycle

Transcription factors such as phospho-retinoblastoma (pRb), P53, TGF-β and β-catenin participate in hepatocellular carcinogenesis[11]. Mutations in these factors deprive the cell control over the cell cycle, leading to uncontrolled mitosis and cancer.

B-RISK FACTORS THAT LEAD TO HCC

HBV infection

This DNA virus is the most frequent etiology of liver cancer. There is strong epidemiological evidence correlating HCC to HBV infection. This was shown by positive results in HCC patients for both HB surface antigen (HBs Ag) and HB core antibodies (HBc antibodies) or both together[12]. However, patients with negative hepatitis B serum markers, although showing symptoms of chronic hepatitis or cirrhosis, were proved to have active intrahepatic replicating virus. This is conventionally known as occult HBV infection[13].

HCV infection

In developing countries, the major concern in HCC is chronic HCV infection. Chronic HCV infection mostly leads to hepatic cirrhosis before developing HCC[14]. Additionally, occult HCV was also reported in patients with chronic un-explained hepatitis[15]. Thus, both occult HBV and HCV infections contribute to HCC prevalence. These can be detected by the invasive biopsy technique, which is the sole diagnostic tool in occult uncertain infections.

Generally, the prevalence of HCV-infection is accepted to be a major morbidity factor in hepatic carcinogenesis. In developing countries, the mode of transmission of HCV is diverse. Old habits of injection, shaving, circumcision, blood transfusion, labor and surgical viral transmission, frequently created many infected generations who carry the infection for many years, although the modes of transmission were greatly minimized by hygienic and cultural development. However, these old-infected populations constitute classic candidates for long standing infection, cirrhosis and HCC. HCV is a member of the Flaviviridae family of enveloped, positive-stranded RNA viruses, genus Hepacivirus. It is a completely cytoplasmic-replicating virus that induces oncogenic transformation[16]. An increasing body of evidence suggests that HCV has a direct pathway in promoting malignant hepatocyte transformation. However, it also now established that many viral proteins are implicated in malignant transformation and HCC development. Of these proteins, core proteins, NS3, NS4, were shown to have transformation potential in tissue culture[17-20]. These viral proteins, in addition to the viral RNA, interact with many host-cell factors, while still regulating the viral life cycle. They modulate host-cell activities such as cell signaling, transcription, transformation, apoptosis, membrane rearrangement, vesicular trafficking and protein translation. This ultimately misleads the host transcription factors, disturbing cell mitosis and protein synthesis, leading to carcinogenesis[2]. On the other hand, the HCV core has immunosuppressive activities through interaction with the complement receptor C1qR on the T cells leading to chronic infection[21].

Transfusion-transmitted virus

Another possible risk factor for HCC, found in patients

with HCV-related liver disorder is transfusion-transmitted virus. These viral DNA traces were only discovered by fine *in situ* PCR in liver biopsies, which could be described to be neither HBV nor HCV material[22,23].

Diabetes mellitus

Liver cirrhosis, which is a functional liver damage (characterized by a decrease in serum albumin level below 4 g/dL and increased prothrombin time), is always higher in HCC patients with diabetes, than among those without a history of diabetes. Thus, there is a positive correlation between the history of diabetes mellitus and HCC, which was not confounded by any other HCC risk factor, as observed by Lagiou and co-workers[24]. A number of possible mechanisms explained this association. Most non-insulin dependent diabetics show hyper-insulinemia. Thus, insulin or its precursors may interact with liver cells to stimulate mitogenesis or carcinogenesis[25,26]. Another possible pathway is that a p53 mutation (an apoptotic factor) was noticed frequently in HCC patients with diabetes rather than non-diabetics, this could provide an evidence for a molecular mechanism involving this common association[27].

Hereditary hemochromatosis

Hereditary hemochromatosis is an autosomal recessive condition characterized by excessive iron deposition in hepatocytes due to an increased intestinal absorption. Thus, liver disease is the commonest cause of death in patients with hereditary hemochromatosis[28]. Among hemochromatotic patients, 6% of men and 1.5% of women are at absolute risk of liver cancer[29]. However, a cross-sectional study showed that progression to HCC among hemochromatotic patients is mostly variable from one population to another, depending mainly on exposure to environmental factors that synergize the current underlying gene mutation[30].

Schistosomiasis among Egyptian Nile basin population

Many cross-sectional studies on wide Egyptian sectors frequently correlated HCV infection and intravenous treatment for schistosomiasis, which is a common parasitic infestation frequently constituting a serious predisposing factor for hepatic fibrosis[31]. Many HCC cases were also diagnosed among long standing bilharziasis.

Exposure to chemical carcinogens

Environmental pollutants such as aflatoxin B, a product of mold commonly contaminating badly stored foods, as well as insecticides, were reported to be classical sources for hepatocarcinogenesis[32]. Other known chemical carcinogens are chlorination byproducts in drinking water. Uncontrolled water chlorination converts many organic traces in water into dangerous intermediates, such as di-and tri- chloroacetic acids, which are experimentally known to induce HCC[33]. Additionally, a rarely encountered chemical contaminant to drinking water, the algal toxin, microcystin, which is found in pond-ditch waters, can induce primary liver cancer[34]. However, many other chemical contaminants, such as solvents, food additives, drugs and hormones, are thought to contribute to HCC. Recent studies strongly suggested that bile acids might be pro-inflammatory and oncogenic agents. Thus, chronic exposure to bile acids plays an important part in inflammation and hepato- and cholangiocellular carcinogenesis[35].

Alcoholism

Alcohol is a very common source for steatohepatitis (fatty liver), cirrhosis and eventually HCC[36]. In developed countries, alcohol drinking seems to be the most common source for HCC. Alcohol either directly initiates HCC after its oxidation into acetaldehyde, which is genotoxic, or indirectly through the development of cirrhosis[37]. Epidemiological studies suggested a strong synergistic effect of alcohol on both HBV and HCV infections in developing HCC[38].

Congenital disorders

Alpha-1-antitrypsin deficiency and tyrosinemia might be complicated by the development of HCC[39]. Thus, dietary or pharmacological management of hereditary tyrosinemia might offer a strategy for prevention of HCC in these cases[40]. On the other hand, alpha-1-antitrypsin is an acute-phase protein that is produced by liver cells. Hereditary deficiency of this protein is mostly due to liver production of the abnormal protein that cannot be released into the plasma. Accumulation of the protein in hepatocytes can lead to liver damage. This can trigger hepatitis in neonates, end-stage liver disease, cirrhosis and HCC in adults[41].

Recent insights on laboratory detection of HCC

Recently, I published a review of the laboratory markers useful in diagnosing HCC, either specific RNAs or serum proteins. These included molecular markers such as hepatoma specific alpha fetoprotein (HS-AFP) mRNA, hepatoma specific gamma glutamyl transferase (HS-GGT) mRNA, transforming growth factor β1 (TGF-β1) mRNA, insulin-like growth factor-Ⅱ (IGF-Ⅱ) mRNA, heat shock protein (HSP) and methylated apoptotic factors (such as p53-mRNA). Serum markers such as AFP, alpha-L-fucosidase (AFU), GGT, TGF-β1, IGF-Ⅱ, anti-p53 antibodies and des-gamma-carboxy prothrombin (DCP) in addition to less common markers such as r-glutamyl transpeptidase (r-GT), tumor necrosis factor alpha (TNF-α), pancreatitis-associated protein (PAP), serine-threonine kinase 15 (STK-15) and plasma glutamate carboxypeptidase (PGCP) were also studied.

The most important conclusion was that the use of AFP, AFU and methylated p53-mRNA together could give a 100% early prediction of HCC development in risky subjects. This short panel of three markers is the recommended to ensure optimal HCC prediction with the highest priority to other studied markers[42].

CONCLUSION

Initiation of HCC is often mediated by complex mole-

cular and transcriptional cascades leading to hepatocyte malignant transformation. These molecular changes include, irregular expression of β-catenin, up-regulation of many growth factors, transformation from pre-neoplastic to HCC nodules and mutations in transcription factors controlling the cell cycle. This cascade is mostly triggered by individual or confounding risk factors. These risk factors include hepatitis B or C, blood transfusion transmitted viruses, diabetes, Schistosomiasis, alcohol intake/alcoholism, food and water pollutants, as well as exogenous and endogenous carcinogenic chemicals. Some hereditary diseases such as hemochromatosis, α-1-antitrypsin deficiency and tyrosinaemia might lead to the development of HCC if not properly managed.

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