Chapter 1

Introductory Chapter: Etiology and Pathogenesis of Hepatocellular Carcinoma

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1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent malignant tumor of the liver with hundreds of thousands of new cases diagnosed each year. Men are up to 3 times more likely to develop HCC compared to women. HCC encounters a higher incidence in countries with low socio-economic status and with improper access to healthcare. These countries also associate high alcohol intake among the population as well as increased incidence of hepatotropic viruses or human immunodeficiency virus (HIV). On the other hand, screening and surveillance of patients at risk have determined the upturn of survivability in HCC patients.

2. Risk factors

HCC has several well-known risk factors, which have been proven to strongly associate with the development of HCC. The most common etiological risk factors are hepatotropic viruses: hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) and a suggestive evidence is revealed by similar distribution of HCC in areas where these viruses also encounter increasing incidence and it is considered that up to 90% of the diagnosed HCCs develop in context of hidden cirrhosis [1, 2]. Other risk factors that are highly involved in the hepatocellular carcinogenesis also include autoimmune hepatitis, nonalcoholic fatty liver disease (NAFLD), obesity and diabetes, tobacco and alcohol abuse, environmental toxins, and iron overload.

2.1. Cirrhosis

Cirrhosis is the main underlying cause for most HCC cases, with HBV, and HCV infection often involved in the development of cirrhosis. Approximately 70–90% of liver cancers occur on cirrhosis, and in Western countries, the HCC ratio on cirrhosis exceeds 90%. The likelihood of developing HCC in viral B cirrhosis is 2.4% per year, and viral C cirrhosis is 5–7% per year. In Europe, HCC incidence is 1.5–3/100 cirrhosis per year. Male gender, advanced age, long duration of the disease and the severity of the disease are the main risk factors for developing cancer in cirrhosis alongside etiology of cirrhosis [3].

The progression from cirrhosis to HCC is a complex process. Cirrhosis is the outcome of any chronic hepatic illness and it is outlined by debilitation of regenerative capacity of the liver through declining proliferation of the hepatocytes [4]. Telomere dysfunction and alterations of cellular micro- and macroenvironment have been proven to enhance cellular proliferation [5]. Telomerase dysfunctions determine chromosomal instability and reduced regenerative liver capacity with decreased hepatocyte regeneration. It has been proven that telomeres are shorter in hepatocytes from a cirrhotic liver compared to a normal liver. Also, shorter telomeres are associated with the progression of liver fibrosis [6].

Several mouse models studies have suggested that telomerase dysfunctions have been associated with early-stage liver cancers but not with high-grade HCCs, which tends to indicate that telomere dysfunction cannot determine alone the development and progression of HCC in cirrhotic livers [7]. Van Gijssel et al. supported this idea by using a rat model in which they decreased hepatocyte proliferation with various hepatotoxic compounds that also increased carcinogen-induced tumor forming [8]. Activation of stellate cells in liver cirrhosis can increase products of oxidative stress, several growth factors as well as cytokines with further roles in reducing hepatocyte regeneration, and development of HCC [9]. Outbreaks of dysplasia occur in regeneration nodules, followed by neoplastic transformation. HCC rarely develops on the noncytotoxic liver and this is particularly common in HBV infection, hemochromatosis or HCV infection. The existence of viral infection or portal hypertension can increase the odds of developing HCC for patients with primary biliary cirrhosis [10].

2.2. HBV infection

HBV is regarded as the main etiological factor that generates multiple pathological changes inside the liver structure, being responsible for the development of HCC over time [11]. However, in order to correctly assess the risk of carcinogenesis triggered by chronic HBV infection, multiple variables need to be considered, like a virus or host-related factors and also the patient's lifestyle [12]. A major study published Chen CJ et al. evaluated the risk of developing HCC in 3653 patients who were positive HBV infection and negative for hepatitis C antibodies. The authors concluded that recorded serum levels of HBV DNA higher or equal to 10,000 copies/mL are a significant risk predictor for the development of HCC, no matter the Hepatitis B antigen level and liver cirrhosis [13].

In highly endemic regions, HBV is mainly transmitted from mother to child during birth (perinatal exposure). In developed countries, HBV infection is primarily contracted through parental contact with infected blood or through sexual contact [14]. Co-infection with HBV

is found in 9% HIV-infected patients, resulting in an increased risk of developing HCC compared to chronic HBV infection alone [15]. At the time of writing, there are 10 genotypes of human HBV named from A to J. The last genotype (J) was described in 2009 by Tatematsu K et al. [16], while the highest risk of developing HCC is linked with genotype C [17].

The prevalence of HBV carriers associates geographically with the distribution of HCC. Epidemiological studies indicated a 200-fold increase in HCC risk in Taiwanese HVB men compared to HBV-negative men [18]. Cirrhosis developed from chronic HBV infection is globally the most important etiologic factor of HCC.

Hepatocarcinogenesis generated by chronic HBV infection is a multistep process that implies rearrangement of the intracellular DNA leading to inflammation of the hepatocytes, accompanied by an increased rate of proliferation [19]. After the integration of viral DNA into the host's genome, the telomerase reverse transcriptase is altered and multiple genes involved in the malignant process suffer various insertional mutations [20]. If the inflammation process continues to affect the hepatocytes, the liver will respond to injury with necrosis of the affected areas, followed by compensatory regeneration and hepatic fibrosis, therefore, altering the entire hepatic architecture, leading to cirrhosis [21]. Recent studies enhance the importance of HBV X protein, suggesting that pathways like p38MAPK and PI-3 K/AKT are used in order to increase the invasive potential of HBV infection [22, 23]. The association of HBV infection with HCV or HVD or with increased alcohol intake or aflatoxin consumption increases the carcinogenic risk of HBV [24].

2.3. HCV infection

Chronic hepatitis C infection is a major risk factor for developing HCC. In developed countries, HCV is the important risk factor for HCC. HCV-associated HCC patients are usually significantly older than those with HCC associated with HBV infection [16].

The evolution over time of the viral infection in a few countries is pledged for the massive increase of HCC incidence. The major spread of HCV infection took place in Japan around the 1930s and in the US in the 1960s. These assessments are consistent with epidemiological observations and allow the estimate that HCC prevalence will increase in the US over the next 2–3 decades when it is likely to match that in Japan [25]. HBV co-infection, present in 3–13% of patients with viral hepatitis C, is associated with a HCC risk of 3–4 times the incidence of each infection [26]. It is considered that the survivors of the Hiroshima and Nagasaki nuclear bombs that were HCV-positive had a much higher risk of developing HCC in the absence of cirrhosis. It was suggested that the radiation had a mutagenic effect and C virus stimulated cell proliferation in these patients [27]. Almost all HCV-related hepatocarcinomas occur due to cirrhosis or chronic inflammation. It is therefore, believed that HCV is an indirect carcinogenic agent by induced inflammatory and necrotic lesions. Core protein influences various cellular functions, including apoptosis, and suppresses p53 activity [28–30].

2.4. Autoimmune hepatitis

The risk of developing HCC for patients with underlying autoimmune hepatitis still remains unclear. Development of HCC in the absence of cirrhosis or viral hepatitis is rather rare or

isolated [31]. A recent meta-analysis concluded that the risk of HCC is much lower for patients with autoimmune hepatitis and cirrhosis than for patients with cirrhosis from viral hepatitis or primary biliary cholangitis [32, 33]. Development of HCC from autoimmune hepatitis with corticosteroid-therapy should mainly impose searching for associated viral chronic hepatitis or any other HCC risk factors that can promote carcinogenesis [34].

2.5. Tobacco and alcohol abuse

Tobacco and alcohol abuse represent important HCC risk factors and exposure to both risk factors can increase HCC susceptibility. The mechanism involves generation of reactive oxygen species (ROS) and a decrease of antioxidants, which induces oxidative stress [35].

Alcohol chronic intake is associated with HCC development due to the several mechanisms such as creation of acetaldehyde-DNA; formation of cytochrome P450E1-associated ROS species; iron overload, which can lead to further ROS formation and p53 gene mutation or activation of factor-KappaB-involved in the promotion of inflammatory response; oxidative stress promotion; and decreased metabolism of vitamin A, which determines the promotion of hepatocyte proliferation as well as initiation and development of liver fibrosis [36]. Alcohol interferes with hepatocarcinogenesis by inducing an already demonstrated precancerous lesion, such as liver cirrhosis or by modifying carcinogenesis initiated by other agents such as HBV or HCV or environmental carcinogens following hepatic enzyme induction or by altering cell membranes [37].

2.6. Environmental toxins

Aflatoxin b1 derived from a fungus (Aspergillus flavus) is a major risk factor in some tropical and subtropical regions. Aspergillus flavus is ubiquitous and contaminates cereals (corn, rice, and sorghum), hazelnuts, etc., stored in humidity conditions. Epidemiological data have shown a strong correlation between aflatoxin intake and HCC incidence in some countries in Asia and Africa. Since 1993, the International Agency for Research on Cancer recognized aflatoxins as a human carcinogen (group IA) [38]. Advanced age, smoking, alcohol, and HBV infection may increase the carcinogenic risk of aflatoxin [39].

2.7. Obesity, diabetes and nonalcoholic fatty liver disease (NAFLD)

Obesity represents an important public health problem, with a massive increase in the past years and with staggering estimations of approximately 300 million obese worldwide. Obesity elevates the risk of all types of cancer, including HCC [40]. One study performed in Denmark on a cohort of 43.965 obese patients estimated the relative risk of liver cancer to 1.9 in comparison to the general population [41]. Two Swedish population-based cohort studies also showed an increased risk of HCC among obese [42, 43].

In another US study, Nair et al. evaluated the importance of obesity in over 19,000 patients diagnosed with cirrhosis and liver transplants, with an overall incidence for HCC of 3.5%. The study suggested obesity as a statistically independent risk factor for liver cancer in patients with alcoholic and cryptogenic cirrhosis [44]. Furthermore, a recent case–control study

indicated synergy between increased alcohol intake, smoking, and obesity [45]. In 2014, an American study regarding the incidence of hepatocellular carcinoma in Texas Latinos concluded that the incidence of liver cancer is somehow higher than other regions in the US, suggesting risk factors related to increased obesity and diabetes rates, as well as environmental, cultural and socioeconomic factors, and possibly genetic predisposition [46].

The mechanism by which obesity leads to cancer is unclear; insulin resistance and its subsequent inflammatory cascade, and insulin growth factor (IGF)-1 seem to be implicated [47]. In a study published in 2010, Michael Karin's team addressed the mechanism by which the obesity can lead to cancer by studying the development of HCC induced by diethylnitrosamine (DEN) or fat diet in mice [48, 49].

Although this is not entirely proven, a number of studies indicate that NAFLD is the link between obesity, diabetes, and HCC. In time, NAFLD can lead to fibrosis and finally, cirrhosis. Approximately 60% of patients with obesity have simple steatosis or steatosis with mild inflammation and around 25–30% have nonalcoholic steatohepatitis (NASH) [50].

Further mechanisms involved in the development of HCC at obese patients were addressed by Villanueva et al. by studying the molecular links between inflammation and liver cancer uncovering the reported role of lymphotoxin signaling in HCC development. The involvement of oxidative stress in developing HCC in obese patients was studied by Zhang, Kaufman et al., who underlined that the accumulation of intracellular lipids increases the demand on the endoplasmic reticulum (ER), which integrates several metabolic processes, therefore inducing ER dysfunction that leads to the production of ROS, provoking oxidative stress and activation of inflammatory pathways (NF-kB and JNK signaling). Another effect of oxidative stress is that can also induce DNA damage that leads to genomic instability that prompts the mutations that favor the development of neoplastic cells [51–53]. Carbohydrate metabolism alterations are frequently encountered at patients with cirrhosis [54].

Since 1986 at least 10 case-control and 5 prior cohort studies from seven different countries reported a connection between diabetes and HCC, promoting the idea that diabetes is an important and consistent risk factor for HCC [55–57]. However, the current studies have not established if diabetes precedes HCC.

The association among obesity, diabetes, NAFLD, and HCC has been assessed by El-Serag et al. in two large studies that substantiated the increased risk of HCC by obtaining results, which showed a doubling number of cases with HCC in patients with diabetes in contrast with nondiabetic patients in a 10–15 year observation period, explaining that the rising incidence of HCC in the US in the past 30 years is connected to an ever-growing prevalence of obesity and diabetes [58, 59].

Since the incidence of obesity and diabetes is in a continuous growth in the world, Kelly, and co. study demonstrated a direct established relationship between diabetes and HCC risk. The biological mechanism of diabetes implicated in hepatocarcinogenesis is not entirely established. Increased serum levels of insulin are at this point the most researched mechanism for the link between diabetes and cancer, though only high levels of insulin are not enough to cause HCC. Levels of insulin-like growth factor-1 (IGF-1) have been linked with increased

risk for pancreatic cancer [60–62]. Most studies indicate that serum IGF-1 levels were linked with the high-risk of HCC, and also that IGF-1 can promote tumor cell growth [63–66]. This was often linked to cell proliferation in pancreatic cancer and similar effects could be observed in HCC [62, 67].

As diabetes and obesity continue to be an ever-growing worldwide concern, we can anticipate a near future increase in the prevalence of NAFLD-related HCC [68]. If liver cirrhosis is present, NAFLD patients have a substantially higher risk to develop HCC [69]. Obesity is linked with a low-grade inflammatory status and also an increased production of cytokines like IL-6 or TNF-alpha [70]. Multiple potential carcinogenic mechanisms are also involved, such as reduced levels of adiponectin [71, 72], hepatic lipid accumulation with possible energy support required for massive tumor growth [73] or normal intracellular signaling means affected by lipotoxicity [74].

2.8. Iron overload

Almost two thirds of the total iron pool is present in hemoglobin while the rest of it is stored, mostly inside the liver, with the help of an intracellular protein called ferritin, which can bind up to 4500 molecules of iron per molecule of ferritin. Transferrin is a glycoprotein responsible for binding the circulating iron within the plasma [75]. Iron overload has been mainly associated with hereditary hemochromatosis (HH) and dietary iron overload (DIO).

Iron overload is frequently linked with an abnormal secretion of hepcidin [76, 77]. Recent studies performed on rats, which underwent a high-iron diet also confirm the possibility to develop HCC in the absence of liver cirrhosis, therefore, excessive iron is capable to generate oxidative tissue damage alone by accelerating the development of free radicals [78, 79]. DIO has been reported in some countries located in the southern and central part of Africa, mainly in the rural parts and highlights the link between the consumption of large volumes of home-brewed alcohol using iron containers, and development of iron overload [79].

3. Conclusion

HCC is a complex pathogenesis link with various risk factors. Liver cirrhosis is, unsurprisingly, an important risk factor for HCC development, regardless of the cause, whereas chronic HBV and HCV infections are the most significant developing factors for liver cancer worldwide. Therefore, frequent causes of cirrhosis are indicated as risk factors for HCC. The common factors affecting the progression to HCC in patients with cirrhosis are host and viral related with the involvement of external risk factors such as smoking, alcohol, and aflatoxins.

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