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Analysis of Risk Factors for Hepatocellular Carcinoma Caused by Hepatitis

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Abstract:

Liver cancer is a malignant tumor, of which hepatocellular carcinoma (HCC) is the most common type, accounting for approximately 90% of liver cancer cases. HCC ranks sixth in cancer incidence and third in cancer mortality, causing significant impact on patients and society. HCC usually occurs in the setting of chronic liver disease and cirrhosis but can also occur in individuals without underlying liver disease. Therefore, understanding the risk factors of HCC can effectively help patients with treatment. The occurrence of HCC is closely related to many factors, among which hepatitis B and hepatitis C play a major role. This article mainly analyzes three risk factors: HBV, HCV, and non-alcoholic steatohepatitis (NASH). A comprehensive analysis of the intrinsic mechanisms of HCC caused by these three factors provides a reference for future treatment and diagnosis. Although the infection rates of HBV and HCV are declining significantly, their underlying factors cannot be ignored. In the future, research can focus more on exploring more risk factors.

Keywords: HBV; HCV; HCC; NASH.

1. Introduction

The liver is one of the most significant organs for humans due to its ability to synthesize most enzymes of the human body [1]. Globally, liver cancer is the third leading cause of cancer-related deaths [2]. HCC, the most common form of liver cancer, is a major cause of death for people with chronic liver disease and accounts for about 90% of cases of liver cancer.

The prevalence and causes of HCC differ greatly in different countries due to regional variations [3]. Most HCC has the highest occurrence in Asia, where it is the second leading cause of cancer-related deaths. In 2020,72.5% of global cases of liver cancer were found in the Asian population, and the most common type of primary liver cancer in Asia is still HCC [4]. While developing countries have traditionally reported a high rate of HCC cases, the prevalence of this condition has experienced significant growth in Western countries over the past thirty years [5].

Various risk factors contribute to the rise in HCC. Infections caused by hepatitis viruses (such as HBV, HCV, and HDV) represent a significant risk factor for the development of HCC. Hepatitis B virus (HBV) infection stands out as the primary risk factor for the development of HCC, contributing to approximately half of cases. The risk of HCV-related HCC has been significantly reduced to 30% with the achievement of sustained virological response (SVR) through the use of direct-acting antiviral agents (DAAs). NASH, linked to metabolic syndrome or diabetes, is increasingly emerging as the most rapidly expanding cause of HCC, especially in Western regions. Many other factors, including environmental factors, age, gender, and race also cause HCC.

This review focuses on the factors of HCC, covering its epidemiology, risk factors, and treatments. By integrating recent advances in liver cancer research, this review seeks to shed light on key areas for further investigation and intervention, ultimately contributing to the advancement of liver cancer management and patient care.

2. Risk Factors

2.1 HBV

HBV is a significant human pathogen that causes hepatitis. HBV infection causes serious medical and social problems worldwide and causes nearly 80% of liver cancer. In Asia and sub-Saharan Africa, the majority of HBV cases are observed, with HBV infection contributing to 60% of HCC cases, whereas in the Western regions, this proportion is only 20%. HBV infection was traditionally thought to manifest as acute, chronic hepatitis B or as a l presence of HBV surface antigen (HBsAg) in the blood for a long

period without pronounced hepatitis.

Recently, as shown in Figure, it was found that HBV infection has a fourth form, in which virus DNA can be found in the blood and liver tissue of patients without HBsAg being detected, which was called „latent HBV infection“ [6]. Hepatitis B is acute for most people and will last only six months. However, another form, chronic hepatitis B, will last for more than six months. Patients with chronic hepatitis B are at a higher risk of experiencing liver failure, cirrhosis, and liver cancer.

Reverse transcription is a method by which the enveloped virus HBV can replicate. Surface receptors specific to the liver include Na+-taurocholic acid co-transporting polypeptide (NTCP) and Solute carrier family ten member 1. NTCP facilitates HBV entry into hepatocytes. Following HBV entry into hepatocytes, the virus will incorporate itself into the host genome, impacting multiple associated pathways inside the host cells and ultimately influencing gene expression. A key factor in the pathophysiology of HBV-induced HCC is the aberrant expression of genes, which is intimately linked to the development of cancer cells [7]. However, following infection, HBV affects the cells and lowers their autoimmunity, which contributes to the development of HCC.

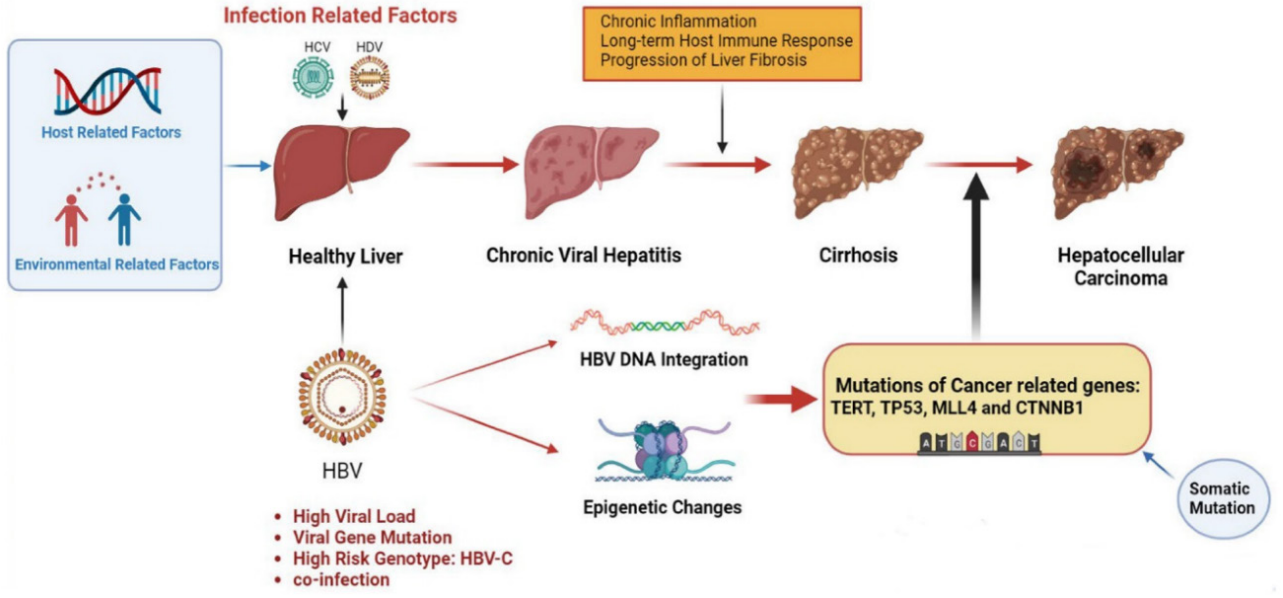

Fig. 1 Mechanisms of HCC due to viral infections [6].

2.2 HCV

About 71 million people globally are infected with HCV, and this infection accounts for about 30% of HCC cases. Hepatitis C infection is a leading cause of liver cirrhosis worldwide [6].

HCV was found in the 1980s, and since then, it has been studied extensively. HCV is an RNA virus and belongs to the Flaviviridae family of viruses. It spreads through blood, sexual contact, and mother-to-child transmission. It is shown that the phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway helps the HCV enter cells, replicate and translate by SREBPs. In comparison with HBV, HCV is also able to cause acute or chronic hepatitis [8]. However, HCV does not integrate its gene into the genome of host cells, which means that it does not directly cause mutations in host cell genes. HCC caused by HCV infection is primarily a persistent host immune response and prolonged inflammatory state due to the failure to successfully clear the virus after acute infection. This will further accelerate the process of fibrosis and cirrhosis of the liver tissue, ultimately contributing to the formation of hepatocellular carcinoma. In this process, the liver tissue is constantly damaged, which can eventually evolve into a malignant tumor. Therefore, for those infected with HCV, timely intervention, treatment, and surveillance are essential to reduce the risk of HCC [6].

The distribution of genotypes varies from population to population, but overall, types 1, 2, and 3 are the most prevalent. The large genetic diversity of the virus is one of the major challenges in developing a vaccine for HCV. This means that there are many different subtypes and variants of HCV, which makes it more difficult to design a vaccine against all of them. There is currently no vaccine for HCV, so antiviral drugs are used to fight the invasion of HCV. HCV is classified into seven genotypes and multiple subtypes. DAA drugs for the treatment of HCV infection have significantly improved the success rate of SVR in patients. Sustained viral response is a reli-

able indicator of HCV eradication and is associated with inhibition of liver disease progression and related complications, such as liver cancer. However, some studies have shown that despite obtaining SVR, some patients may experience HCV relapse after DAA treatment. The researchers found that HCV infection leads to the activation of EGFR signaling, which promotes the formation of aggressive invadopodia by tumor cells. As a result, HCV infection increases the aggressiveness of HCC tumors [7].

Although HCV is a hepatophilic virus, HCV infection is a systemic illness. Chronic hepatitis C virus infection does not only affect the liver but also has extra-hepatic activities in a variety of organs and tissues. The kidney is an important target of these extra-hepatic activities, which means chronic HCV is a risk factor for chronic kidney disease (CDK). It was found that SVR based on interferon is able to improve the outcomes of hepatic and extra-hepatic portions. In a French study, 668 patients with hepatitis C received antiviral therapy and achieved SVR. They were found to have a lower risk of infectious and cardiovascular events. It is also found that antiviral therapy can improve renal survival in HCV-infected patients and also reduce the rate of acute coronary syndrome and stroke [8]. One of the major causes of HCC is HCV, which is highly contagious around the world. Because of its genetic diversity and RNA nature, it is more difficult to develop vaccines against HCV against all subtypes and variants than HBV. The liver is not the only organ or tissue affected by HCV infection. These effects mostly affect the kidney and chronic kidney disease is predisposed by long-term HCV infection. While some research has indicated that SVR can partially mitigate this effect, more investigation is required to better understand relevant aspects in order to produce an HCV vaccine.

2.3 NASH

Enhanced HBV vaccination coverage and the widespread accessibility of antiviral therapy have resulted in a decline in the global burden of HBV-related liver cancer. Furthermore, the introduction of safe and efficacious antivirals for HCV is able to lower the incidence of HCC. Thanks to great advances in treatments for hepatitis B and C infections, their infection rates are steadily declining [9]. It is found that the frequency of NASH has increased in conjunction with the rise in rates of obesity and diabetes [10]. NAFLD is an epidemic liver disease worldwide, which affects more than a quarter of the global population. It is increasingly common in younger age groups and has become the most common chronic liver disease in children in many Western countries. It has also been found that more and more young people (under 40 years of age) have NASH and require liver transplant surgery. It is investigated that from 2010 to 2019, the Americas had the greatest increase in liver cancer incidence. NASH also experienced the most rapid growth as a cause of fatalities related to liver cancer worldwide. Researchers predicted that the prevalence of liver cancer resulting from NASH is going to rise in the upcoming decade across the United States, Europe, and Asia [10].

NASH-HCC patients do not respond to certain treatments, such as anti-PD-1 treatment. Using a diet-induced approach, the researchers created a mouse model that mimicked NASH-HCC in patients. In this experiment, mice with NASH-HCC showed unresponsiveness to anti-PD-1 treatment, whereas mice with HCC without NASH demonstrated a notable reduction in tumor size. The researchers examined CD8+ T lymphocytes within the livers of mice afflicted with NASH because of their significant involvement in this therapeutic approach. By performing intra-vital imaging, researchers found that CD8+ T cells within tumors of mice with NASH exhibited decreased velocity and reduced displacement distance. Metformin is involved in the regulation of glucose metabolism. It can reprogram CD8+ T cells, so the investigators conducted experiments to examine the impact of metformin on the stimulation and movement of CD8+ T cells. It was found that metformin maintains the activation and mobility of CD8+ T cells during immunotherapy for NASH-related hepatocellular carcinoma. Additionally, metformin restored the responsiveness of NASH-induced liver tumors to immunotherapy treatments. In conclusion, metformin is a treatment strategy to improve the damaged response to anti-PD-1 in mice with NASH-HCC [10].

To summarize, NASH is a liver disease that is increasingly common in young people and is now the most common chronic liver disease in children in many Western countries and the fastest-growing cause of liver cancer mortality worldwide. In addition, NASH-HCC patients do not respond to certain treatments. For example, anti-PD-1 treatment. This study found that metformin can improve the damage response of NASH-HCC mice against PD-1 while maintaining the activation of CD8+ T cells.

3. Conclusion

HCC is the most common type of liver cancer and is the fifth most common cancer globally. It is a global health problem that has increased in incidence and mortality. Multiple risk factors of HCC have been identified. Among them, the infectious factor is the most important. HBV and HCV belong to the infectious factor, which are also two main causes of HCC. HBV is able to integrate into the genome of the host cell, inducing HCC. Vaccines and antiviral drugs are used to treat HBV infections. In con-

trast to HBV, HCV is an RNA virus and is unable to integrate its genome into cellular genomes. It is the second most serious infectious factor of HCC, following HBV. There is currently no vaccine for HCV, so antiviral drugs are used to fight the invasion of HCV. Due to the utilization of DAAs for HCV, a growing quantity of patients have attained SVR. Although HCV is a hepatophilic virus, it will cause systemic effects, especially in the kidneys. SVR is also able to improve the outcomes of extra-hepatic portions. Notably, some patients obtaining SVR may experience HCV recurrence after DAA treatment. The percentage of HCC cases associated with NASH has seen a rapid rise since 2010 due to an increase in the obesity epidemic, especially in Western countries. It is predicted that in the United States, Europe, and Asia, the prevalence of liver cancer resulting from NASH is going to rise constantly. Metformin was found to be a treatment strategy that restored the responsiveness of NASH-induced liver tumors to immunotherapy treatments.

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