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REVIEW

HCV-related hepatocellular carcinoma: From chronic inflammation to cancer

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Abstract Hepatitis C virus (HCV) infection is a worldwide health problem because of its incidence and pathogenicity. It might evolve into chronic disease, cirrhosis, and/or hepatocellular carcinoma (HCC) and the outcome is mainly determined by the host immune response. For viral clearance, combined innate and adaptive immune responses are required; resolution requires a vigorous, durable, polyclonal $CD4^+$ and $CD8^+$ T-cell response, with an increase in virus-specific $CD8^+$ T cells or cytotoxic T lymphocytes. Failure of efficient immune response can lead to chronic inflammation, tissue remodeling through cell growth, apoptosis and/or necrosis and induction of oxidative stress. Development of fibrosis and/or cirrhosis plus a microenvironment conducive to genomic instability mutations will promote neoplastic transformation. System governance derives from cellular (regulatory cells) and humoral (cytokines and chemokines) immune networks. Therefore, HCC pathogenesis may be a model to study the disease progression from chronic inflammation to cancer allowing design of new strategies targeting the immune response, thereby modifying disease outcome.

Abbreviations: APC, antigen presenting cells; CTL, cytotoxic T lymphocyte; DC, dendritic cell; FasL, Fas ligand; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HLA, human leukocyte antigens; iDC, immature dendritic cell; IFN, interferon; IL, interleukin; mDC, mature dendritic cell; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; NF-κB, nuclear factor-κB; NK, natural killer (cells); NKT, natural killer T (cells); PAMP, pathogen-associated molecular pattern; TCR, T-cell receptor; TGF, transforming growth factor; Th, T-helper (cells); Th0, naive T-helper (cells); Th1, T-helper type 1 (cells); Th2, T-helper type 2 (cells); TNF, tumor necrosis factor; T_{reg}, regulatory T-helper (cells).

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Contents

Introduction

Liver cancer is the fifth most common cancer in men and the eighth most common in women, with an estimated 711,000 new cases worldwide in 2007 [1]. More than 80% of cases occur in developing countries, with China alone accounting for more than 55% of the total. Rates are more than twice as high in men and are the highest in West and Central Africa and in Asia. In contrast, incidence rates are the lowest in developed countries, except in Japan. Among primary liver cancers occurring worldwide, hepatocellular carcinoma (HCC) is the most common, accounting for 70–85% of cases [2]. In the United States, 22,620 new cases of liver and intrahepatic bile duct cancer have been estimated in 2009 [3]. The incidence rates are increasing; overall HCC age-adjusted incidence rates tripled between 1975 and 2005, rising from 1.6 per 100,000 to 4.9 per 100,000 [4].

In addition, HCC is one of the most fatal cancers, with 5-year relative survival rates of less than 11%, even in developed countries. Between 1990–1991 and 2005, death rates increased (from 5.27 to 7.76 per 100,000) for liver cancer in both men and women in the United States [3]; 18,160 deaths have been estimated in 2009 [3].

Analysis of HCC mortality in Europe confirmed large variability in this region, with favorable trends in various European countries over the last decades, particularly in women and in young adults. The highest male mortality rates were in France (6.8), Italy (6.7), and Switzerland (5.9), while the lowest ones were in Norway (1.0), Ireland (0.8), and Sweden (0.7); the highest female mortality rates were in Italy (1.9), Switzerland (1.8), and Spain (1.5) and lowest in Greece, Ireland, and Sweden (0.3) [5]. The highest rates of HCC in Europe, primarily due to infection with hepatitis viruses, have been registered in the Campania region, Southern Italy [6]. In this region, incidence rates of 38.3/100,000 in males and 14.3/100,000 in females and mortality rates of 35.3/100,000 in males and 17.6/100,000 in females were reported [7].

HCC variability

Hepatitis B (HBV) and C (HCV) infection are the most important HCC risk factors, being implicated in more than 70% of HCC cases worldwide.

HCV possesses three important clinico-biological and pathogenic features distinctive from HBV that are relevant to hepatocarcinogenesis [8]. First HCV yields chronic infection (10% of HBV cases versus 60–80% of HCV), probably because of the immune evasion by HCV quasi-species generated from high rates of replication errors. The second key difference is the greater propensity of HCV to promote liver cirrhosis compared with HBV: 5–10% of HCV-infected patients develop liver cirrhosis after 10 years of infection, approximately 10- to 20-fold higher than HBV. Third, HCV is an RNA virus without a DNA intermediate; thus, it cannot integrate into host genomes [8]. HBV infection leads to the development of HCC through direct and indirect pathways as it has the ability to integrate into the host genome affecting cellular signaling and growth control. Since HCV does not integrate into the host genome HCC is mainly induced through indirect pathways: chronic inflammation, cell deaths and proliferation. Thus HCC is almost exclusively found in cirrhotic HCV patients while HCC is sometimes found in HBV patients without significant liver cirrhosis [9,10].

Finally, in contrast to HBV, effective vaccination against the HCV is not available to date. Three factors contributed to this: the high propensity of HCV to promote chronic persistent infections [11], evidence that convalescent humans and chimpanzees could be readily reinfected following re-exposure [12] and the considerable genetic heterogeneity of this positive-stranded RNA virus [13].

By considering the above, this review focuses on the HCV-related HCC, emphasizes the role of chronic inflammation and pro-tumoral microenvironment in hepatocarcinogenesis [14,15] and suggests new perspectives for therapeutic interventions. The immune system can spontaneously clear the virus and virus-specific neutralizing antibodies and cell-mediated responses are detected [16,17].