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Review article

Immune response involved in liver damage and the activation of hepatic progenitor cells during liver tumorigenesis

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ABSTRACT

Hepatocellular carcinoma (HCC) is a typical inflammation-related cancer. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are well-known leading causes of HCC. However, the mechanism of the induction of HCC by these virus is still being debated. This review will focus on the current knowledge of the pathogenesis of HBV- and HCV-induced inflammation and the role of such immune activation in the tumorigenesis of HCC. It is well established that the recruitment of certain number and type of immune cells to liver is essential for the resolution of HBV and HCV infection and the prevention of subsequent chronic persistent infection. However, in case that the immune response do not completely clear virus, persistent chronic infection occurs, and the perpetual immune response may contribute to chronic damages of the liver. Such chronic inflammatory damages further harm hepatocytes, but not hepatic progenitor cells (HPCs). Thus, following chronic damages, HPCs are activated and their dysregulated proliferation ensures survival in the hostile environment, contributing to the tumorigenesis of HCC. Furthermore, accumulating evidence also provides a strong link between HPCs and human hepatocellular carcinoma. Collectively, these findings support a notion that immune response is involved in liver damage during hepatitis virus infection, and the activation and dysregulated differentiation of hepatic progenitor cells promote the tumorigenesis of human hepatocellular carcinoma.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most aggressive human cancers and is the third leading cause of cancer-related deaths worldwide. It is reported that there are approximately 750,000 new cases of liver cancer per year globally [1]. Despite the recent advance in diagnosis and treatment of HCC, HCC is characterized with poor prognosis, with around 12% survival at 5 years [2]. And HCC still shows a propensity for recurrence and metastasis, remaining a highly lethal rate [3]. Research on the mechanism of HCC has revealed that hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection are major causes for HCC tumorigenesis [4]. It is estimated that 80% of all HCCs has a history of HBV and HCV infection [5]. Collectively, HCC is a typical inflammation-related cancer. However, the mechanism of inflammation-mediated cancer is still not clear.

HBV and HCV infection is the leading cause of the liver chronic viral infection worldwide. It is estimated that a billion people have been infected, and approximately 350 million are HBV carriers and 170 million are HCV carriers [5,6]. HBV acute infection in adult is usually inapparent, and the majority of acutely infected adults can clear the virus and recover completely from the infection. However, approximately 5–10% of acutely infected adults cannot completely clear the virus and eventually become chronically been infected.

HBV and HCV infection induced liver injury is attributed to the immune response to viral antigen rather than the direct injury of HBV and HCV replication [7]. During acute HBV infection, the recruitment of adequate T cells to liver is essential for resolution of HBV and HCV and prevention of chronic persistent infection. However, T cells are also involved in liver injury during HBV and HCV infection [8]. This is supported by accumulating studies, in particular, the typical study finding that HBV and HCV replication did not induce liver damage, until after the recruitment of T cells to liver [9].

The intrahepatic stem cells, also known as hepatic progenitor cells (in humans) or the oval cells (in rodents) are small epithelial cells with an oval nucleus. Hepatic progenitor cells (HPCs) are able to differentiate into hepatocytes and bile duct epithelia. HPCs are scarcely detectable under physiological conditions, while numerous animal and human models of liver damage have shown the proliferation of oval cells [10]. These human liver damage diseases are closely associated with inflammation condition, particularly hepatitis B, C virus infection.

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In rodents, the observed oval cell is commonly accompanied by immune cells and cytokines, as well as treatment with carcinogens [11]. The liver parenchymal is mainly consisting of numerous mature hepatocytes. The cellular response of the liver to different injuries requires the regenerated hepatocytes, which result from the proliferation of hepatocyte and differentiation of hepatic progenitor cells [12,13]. However, the study indicated that activated immune cells and cytokines can impair the regenerated hepatocytes after liver damage rather than hepatic progenitor cells [14,15]. Thereby, the activation and proliferation of hepatic progenitor cells contribute to the reconstruction of the damage liver. However, more and more evidences support that HPCs are involved in the pathogenesis of HCC in animal models [16,17]. And clinical studies have probed the hepatic progenitor cells in human hepatocellular carcinoma [18]. Taken together, these findings indicate that during the pathological process of liver injury, the activated immune response results in liver hostile environment, which is favorable for the survival of hepatic progenitor cells rather than the regenerated hepatocytes. And abnormal dedifferentiation of hepatic progenitor cells may lead to the tumorigenesis of human hepatocellular carcinoma.

2. Immune-mediated liver damage resulted in hepatocellular carcinoma

2.1. Immune-mediated HCC in HBV and HCV infection

HBV and HCV are known to be hepatotropic virus. And HBV and HCV-mediated hepatocellular injury has been extensively investigated to understand the effect of HBV and HCV on the hepatocytes. Studies found that HBV and HCV could persistently replicate in cultured cells without obvious cell damage and death [19–21]. Furthermore, clinical study found that HBV infected patients with immune-tolerant phages still maintain a normal level of alanine aminotransferase (ALT), which is an indicator of liver injury [22]. Since, HBV and HCV infections arise with a massive of immune response. It is suggested that HBV and HCV themselves are not cytopathic for infected hepatocytes, but immune response may be involved in liver injury in viral hepatitis.

Accumulating studies suggest that adaptive immunity response to HBV and HCV infection contributes to liver damage [23]. After active virus replication, it was observed that virus-specific cytotoxic T lymphocytes (CTL) are efficiently and timely activated to clear virus [24]. However, subsequent study indicates that CTL not only clear virus but also induce liver cell destruction. Firstly, it was observed that Hepatitis B virus (HBV) transgenic mice did not experience hepatocellular damage until the transfer of HBV-specific $CD8^+$ T cells [9]. Furthermore, the finding that the intrahepatic strength of T cells obviously increased the severity of tissue injury in HBV patients and chimpanzees study [25]; The level of stimulated cytokines such as IL-6, IL-12, IL-17, TNF-α also indicate the severity of liver damage in HBV infected patients [26–28]. In addition $CD4^+$ T cells are the inducers of effective $CD8^+$ T cell and also contribute to liver pathogenesis by maintaining virus-specific $CD8^+$ T cell function [29]. Recently study also indicated that the interaction of platelet and $CD8^+$ T cells also aggravated the cytotoxicity of CTL in the infected liver [30].

NK (natural killer) cells are rare populations in peripheral lymphoid but constitute the majority of innate immune cells in the liver. Many studies have investigated NK cells response to viral infections. It is found that NK cells are involved in both viral clearance and liver damage of viral infection [23,31–37]. It is believed that NK cells produce IFN-γ to clear virus. However, the chronic persistence of HCV and HBV infection decreased IFN-γ production by NK cells, but increased cytotoxicity of NK cells, contributing to liver injury [23]. In addition, authors indicated that NK cells were involved in improving $CD8^+$ T cell responses against HBV infection, enhancing the cytotoxicity of $CD8^+$ T cells [38].

These abovementioned inflammatory cells released various cytokines and chemokines which may favor HBV-associated hepatocellular carcinoma tumorigenesis [39]. The chronic hepatic inflammation and regeneration caused by HBV resulted scarring in the liver [40]. Hepatic fibrosis was characterized by the accumulation of 'scar' extracellular matrix [41]. Fibrosis developed in the process that normal lobules are replaced by architecturally abnormal nodules, resulting mainly from regenerative hyperplasia, separated by fibrous tissue [42]. The late stage of progressive fibrosis, called cirrhosis, had favored the tumorigenesis of hepatocellular carcinoma (HCC) [43]. Cirrhotic transformation of the liver was required for tumorigenesis of HCC in HBV patients [44]. Recent research demonstrated thatTh17/Treg imbalance was an indicator of liver cirrhosis process and a risk factor for HCC occurrence in HBV patients [45].

2.2. Immune-mediated HCC in autoimmune hepatitis (AIH)

The healthy liver keeps some elements of inflammation, which are involved in metabolic, detoxification activities, inducing appropriate immune response. However, an abnormal immune response can lead to pathological inflammation and disrupt tissue homeostasis, arising with liver tumorigenesis. Autoimmune hepatitis (AIH) is a chronic self-perpetuating inflammatory disease, with acute liver injury [46]. The mechanisms of acute liver injury are not completely understood. But it is well known that the enhanced immune responses are involved in the progressive destruction of the hepatic parenchyma in autoimmune hepatitis. And immunosuppressive therapy can prolong survival in severe cases of AIH [47]. It is suggested that cytokines, such as tumor necrosis factor (TNF-α) and IFN-γ, contribute to pathogenesis of live injuries [48–50]. Another finding indicates that B cells also play an active role in the pathogenesis of AIH. B cells can be antigen-presenting cells (APCs) and result in the activation of T cells, furthermore, activating inflammation [48]. And studies in mice and recent clinical studies have indicated that B cell targeted therapies can significantly affect autoimmune disease [51]. Collectively, during autoimmune hepatitis, enhanced immune responses induce liver injury. AIH patients may develop HCC in the consistent inflammatory state [52]. Yeoman et al. has reported that cirrhosis in AIH is the sine qua non for HCC tumorigenesis, which subsequently occurs at a rate of 1.1% per year and affects men and women in equal proportions [53].

3. Role of inflammation in hepatic progenitor cell activation

3.1. Role of immune cells and non-parenchymal cells for the activation of HPC

Following liver acute injury, repair of lost tissue is typically dependent in proliferation of hepatocytes. However, during chronic liver injury, regeneration of liver tissue mainly relies on the hepatic progenitor cells (HPCs) [10,54]. Recently, the study indicated that liver cell proliferation can be impaired by the secreted cytokines of natural killer (NK) cells, such as interferon gamma (IFN-γ), T helper 1 (T_h1)-type cytokine [14]. Other findings that natural killer T (NKT) cells showed a significant cytotoxicity towards regenerating hepatocytes [15]. Thereby, it appears that the activation of immune response may show negative effect for hepatocellular survival.

Inflammation environment in liver may show positive effect for HPC. Authors indicate that the activation and proliferation of HPC occur usually in human liver diseases with inflammation condition, such as Hepatitis B, C, alcoholic and non-alcoholic liver disease [54]. Furthermore, the finding that infiltration of inflammatory cells is immediately followed by HPC proliferation during chronic liver injury [54,55]; and anti-inflammatory agents reduced the HPC in liver injury models [56,57]; other authors indicated that there was a correlation between the degree of inflammatory infiltration and number of oval cells [58,59]. Collectively, it is believed that immune response can promote activation of HPCs, and the main effector cells are shown below.