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Crosstalk Involved in Liver Inflammation and Hepatocellular Carcinoma

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Abbreviations:

HCC: hepatocellular carcinoma; CCA: cholangiocarcinoma; DAMPs: damage-associated molecular patterns; PAMPs: pathogen-associated molecular patterns; HSPs: heat shock proteins; mtDNA: mitochondrial DNA; LPS: lipopolysaccharide; KCs: Kupffer cells; HSCs: hepatic stellate cells; PRRS: pattern recognition receptors; NK: natural killer; LTβ: lymphotoxin beta; CXCL1: CXC-chemokine ligand 1; ER: endoplasmic reticulum; ROS: reactive oxygen species; OxS: oxidative stress; DCs: dendritic cells; Tregs: regulatory T cells; LSECs: liver sinusoidal endothelial Cells; MDSCs: myeloid-derived suppressor cells; TAM: tumor-associated macrophages; PD-1:programmed cell death protein 1; NAFLD: nonalcoholic fatty liver disease; MHC: major histocompatibility complex; NASH: non-alcoholic steatohepatitis

1. Abstract

Hepatocellular carcinoma (HCC) usually occurs at the background of inflammation and cirrhosis. Due to the unique anatomic location and the immunosuppressive environment of the liver, chronic inflammation causes intrahepatic cells death and elevated oxidative stress levels, leading to the occurrence and development of HCC. In addition, the failure of immune system regulation and surveillance plays an important role in the development of HCC. In this review, we discuss the relationship between liver inflammation and HCC development, and illustrate how these factors trigger intrahepatic cells injury, proliferation, and ultimately the development and maintenance of HC

2. Introduction

The liver is the sixth most common organ in the human body for primary cancer, and liver cancer is the fourth leading cause of cancer-related death worldwide [1]. Hepatocellular carcinoma (HCC) is the most common pathological type of primary liver cancer, accounting for 80-90%, followed by cholangiocarcinoma (CCA) accounting for 10-15%, and its incidence has an increasing trend. The less common liver malignancies include angiosarcoma and pediatric hepatoblastoma [2, 3]. The most important factor in the pathogenesis of HCC is liver-related chronic inflammatory disease, including chronic hepatitis virus infection, metabolically related inflammatory changes, and exposure to chronic toxins [4-6]. With the application of chronic hepatitis B virus vaccine and antiviral drugs, the incidence of chronic hepatitis virus hepatitis-related liver cancer has been greatly reduced in the East Asian society [7, 8]. However, HCC induced by lifestyle factors such as chronic

alcohol consumption, high fat diet and sedentary behavior is increasing, is especially common in Western societies [9, 10].

Due to the genetic diversity, metabolic complexity and heterogeneity of HCC, the most effective treatment is limited to local ablation, surgical resection, or liver transplantation at the early stage. For patients with advanced stage, the treatment outcome is still a great challenge [11]. In recent years, with the in-depth understanding of liver microenvironment and immune molecular signal network, new therapeutic strategies including immunotherapy have been gradually applied to the treatment of HCC [12, 13]. Combining immune checkpoint blockade with other therapies has profoundly affected the treatment status of primary and secondary liver cancer [14].

In this review, we summarize the relationship between chronic inflammatory diseases and hepatocellular carcinoma, with special attention to the roles of cell death, oxidative stress, and immune microenvironment in shaping malignant transformation of hepatocytes.

3. Liver Chronic Inflammation and Malignant Transformation

Tumor initiation process is that normal cells gain survival advantages and gradually accumulate carcinogenic mutations [15]. Hepatitis virus infection, fatty acid-mediated lipotoxicity, exogenous toxins, and excess iron deposition induce the intrahepatic cells damage, including hepatocyte and hepatic sinusoidal endothelial cells [2]. Liver chronic inflammation and injury induce unique regeneration and repair responses. This compensatory regeneration process helps to repair organ structure and maintain the function of liver [16-18]. However, proliferating cells are endowed with malignant potential as cells proliferate rapidly and oncogenic signaling pathways are induced in an environment conducive to the accumulation of genetic mutations [19, 20].

Chronic liver inflammation is triggered and maintained when the liver is continuously exposed to stimulation from damaged intrahepatic cells, as well as gut microbes and related products. These stimuli are classified as damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). The DAMPs are mainly induced by the damaged intrahepatic cells, including excess dietary lipids, apoptotic cell DNA, heat shock proteins (HSPs), hyaluronic acid and mitochondrial DNA (mtDNA). The PAMPs include antigens from gut microbiome, such as lipopolysaccharide (LPS), flagellin, peptidoglycan, and bacterial DNA [21, 22]. In addition, factors such as alcohol consumption, high-calorie diets, or viral infections, are all external triggers that alter the composition of the intestinal microbiome, disturb the balance of the microbiome, increase the number of pathogenic bacteria, and affect the barrier function of the intestinal mucosa, which can aggravate chronic liver inflammation [23].

Hepatocytes, Kupffer cells (KCs) and hepatic stellate cells (HSCs) express pattern recognition receptors (PRRS), including Toll-like receptors (TLRs), RIG-like receptors and NOD-like receptors, which can recognize DAMPs and PAMPs. Upon activation, it promotes the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, as well as chemokines such as MIP-1α and RANTE [24, 25]. Inflammatory mediators and DAMPS recruit platelets and immune cells, including pro-inflammatory monocytes, natural killer (NK) cells, neutrophils, and different types of T cells, accelerating the inflammatory response [26, 27]. In addition, the continuous repair of liver injury caused by chronic inflammation can activate hepatic stellate cells, leading to collagen deposition, fibrosis of the liver parenchyma and promote the occurrence of liver cirrhosis [9].

Chronic liver inflammation promotes the occurrence and development of HCC [28]. The proinflammatory cytokine TNF-α secreted by KCs triggers tumorigenesis by activating Wnt/β-catenin signaling and JNK signaling in the case of oxidative stress [29]. HCC can be induced by TNF-α mediated inflammation in the mouse model of Mdr2 (also known as Abcb4) knockout or diet induced obesity [30, 31]. Genes encoding lymphotoxin beta (LTβ), TNFSF14 and their targets CCL17 and CCL20 were overexpressed in human and mouse HCC tissues. Moreover, lymphotoxin activates the NF-κB signaling pathway, which promote the development of HCC [32]. Other inflammatory cytokines including IL-1β, IL-6, IL-11 and IL-23 are also involved in tumorigenesis [15]. Among these, IL-6 is the most relevant factor in diethyl nitrosamine-induced HCC development and serves as a reliable marker for predicting the transition from viral hepatitis to HCC [31]. Enrichment of angiopoietin-2 (Ang-2), vascular endothelial growth factor (VEGF), CXC-chemokine ligand 1 (CXCL1) and CXCL8 can stimulate angiogenesis, which are important factors in liver tumorigenesis [15].

4. Cell Death Mediated Responses in Liver Inflammation and HCC

Hepatocytes death is accompanied by chronic liver diseases such as hepatitis virus infection, non-alcoholic steatohepatitis (NASH), cirrhosis, and other processes, mainly in the form of apoptosis or necrosis (33, 34). Intracellular toxic conditions, such as high levels of ROS, DNA damage, or replication stress due to depleted regenerative capacity, activate intrinsic apoptosis [35-37]. Activation of oncogenes and intercellular fusion induce hepatocyte senescence. Without the effective elimination of genetic and immune surveillance systems, these senescent cells will transform into malignant cells [38]. Caspase 8 regulates chronic inflammatory induced cell death through catalytic cleavage function and acts as a scaffold for a multiprotein complex, independent of its catalytic domain, to achieve effective DNA damage repair. In preclinical models, complexes containing caspase 8 trigger γ-h2ax phosphorylation, controlling DNA integrity and thus potentially preventing malignant transformation [34].

Due to the destruction of intact cell membranes, dead liver cells release numerus injury-related molecular patterns. These "endogenous antigens", together with abnormal metabolites from biological products, excess alcohol, and fatty acid catabolism, lead to the breakdown of balanced immune tolerance properties [39-41]. KCs respond by turning on pattern recognition receptor signaling and producing a wide range of pro-inflammatory cytokines (including IL-1, IL-6, and TNF) and chemokines (CCL1, CCL2, and CCL5) [39], leading to increased expression of cell adhesion molecules ICAM1 and VCAM1 in LSECs and downregulating of platelet/endothelial cell adhesion molecule 1 (PECAM1), further recruiting monocytes, neutrophils, and platelets to the stressed sit [21]. Following activation of liver-resident innate immune cells, adaptive immune cells are recruited to the inflamed liver. The function of adaptive immune system in chronic hepatitis varies with pathology or diseases. Accumulation of CD4 T cells and CD8 T cells was detected in liver tissue of mouse NASH models and NASH patients [42, 43]. Activated CD8 T cells release inflammatory cytokines that aggravate the progression of NASH, and inhibition of CD8 T cell activation prevents liver injury in NASH mouse models [21, 44]. In the context of HBV infection, CD4 T cells have been identified as a major TNF producing population associated with liver injury [45].

5. Reactive Oxygen Species Mediated Responses in Liver Inflammation and HCC

Excessive consumption of high-calorie diet and alcohol disrupt the balance of lipid, carbohydrate, and protein metabolism in hepatocytes, leading to an unbalanced unfolded protein response and the release of lipotoxicity, accompanied with endoplasmic reticulum (ER) stress and mitochondrial dysfunction. For mitochondria and ER are the main sources of reactive oxygen species (ROS), these processes are associated with increasing ROS production and oxidative stress (OxS) [46, 47]. Sustained cell death and compensatory proliferation induced by inflammation exacerbate ROS and OxS, which leads to DNA damage and gene mutation in liver [42, 48, 49]. 8-oxo-7, 8-dihydro-20-deoxyguanosine (8-oxo-guanosine), and 8-nitroguanosine, which are induced by ROS, inhibit key enzymes in the DNA repair machinery, resulting in genomic instability(34). OxS regulates chronic liver inflammation by activating NF-kB signaling pathway and c-Jun N-terminal kinase (JNK)/IKK/p38 MAPK signaling pathway [50]. TP53 mutations induced by OxS are most common in HCC, which induce mismatch repair enzyme inactivation through remodeling epigenetics and hypermethylation of genes encoding mismatch repair proteins and tumor suppressors, initiating HCC [15, 51-53]. Activated immune cells are also a source of ROS production. ROS induced T-cell protein tyrosine phosphatase (TCPTP) to activate STAT1 and STAT3 signaling in NASH-induced HCC mouse model. STAT1 transcriptional activation up-regulates the expression of CXCL9 and lipoietin 2, recruiting neutrophils and T lymphocytes, and promoting liver inflammation. Activation of STAT3 drives malignant transformation of hepatic progenitor cells through the IL-6-STAT3 autocrine ring [54].

6. Innate Immune System Mediated Responses in Liver Inflammation and HCC

The immune system plays vital roles in protecting the normal physiology of the liver. However, in chronic inflammation, adaptive and innate immune cells can be the driving force of liver damage and carcinogenesis [55, 56]. As the central organ of systemic metabolism, the liver is continuously targeted by intestinal pathogens, microbial related molecular patterns, Toll-like receptors (such as TLR4 or TLR9) agonists, and a variety of metabolites. Although numerus immune cells subsets, such as NK cells and cytotoxic CD8+ T cells, play an important role in immune surveillance and anti-tumor immunity during the development and progression of HCC, however, several resident liver cell subsets, including Kupffer cells (KCs), dendritic cells (DCs), regulatory T cells (Tregs), maintain liver immunosuppression, and this immune inhibitory environment influents the T cell-mediated immune response [6].

In the process of tumor immune evasion in HCC, KCs and other non-parenchymal cells (such as HSCs and LSECs) produce an immunosuppressive environment by secreting ligands that bind inhibitory receptors of effector T and NK cells, thus facilitating the establishment and progression of HCC. Recruitment, activation, and expansion of Tregs, myeloid-derived suppressor cells (MDSCs), and neutrophils, as well as tumor-associated macrophage (TAM) and programmed cell death protein 1 (PD-1) depleted T cells, create a tolerogenic immune environment against tumor cells [57, 58].

KCs are the largest population of tissue-resident macrophages, which are characterized by the expression of PD-L1, low levels of costimulatory molecules (CD80 and CD86) and the activation of Treg cells and are important factors for hepatic immune suppression. In nonalcoholic fatty liver disease (NAFLD), KCs participate in chronic inflammation by producing ROS and proinflammatory cytokines, and recruiting Ly6-C+ infiltrating monocytes, platelets [21]. Intestinal pathogens polarize KCs to an anti-inflammatory state and reduce the major histocompatibility complex (MHC) expression of LSECs to limit their immune activation ability [39]. Depletion of KCs in vivo abolished the induction of hepatic tolerance to particulate antigens [59]. The polarization of macrophages is extremely heterogeneous. In the tumor microenvironment, TAM have an immunosuppressive phenotype [60], and promote tumor progression through tissue remodeling, such as angiogenesis and damage repair [61, 62]. Inflammatory macrophages and infiltrating monocytes can induce an antitumor response [63]. HCC antitumor responses could be improved by promoting the M2 type polarization of TAM to M1 type proinflammatory macrophages, thereby promoting a proinflammatory response against cancer

cells [64]. Although pharmacological blockade of tumor-associated macrophage activity appears to improve the prognosis of HCC patients, effective and selective targeting of these cells remains challenging [60, 65, 66].

There are two mainly subtypes of DCs in liver: conventional DC and plasmacytoid derived DCs [67]. Plasmacytoid derived DCs is characterized by low responsiveness to toll-like receptors (TLR) stimulation and low expression level of co-stimulatory molecules, which promotes the liver immunosuppression [67]. Conventional DCs (human CD 141+ or mouse CD 103XCR1+) exhibited a proinflammatory immunophenotype with high MHC-II expression and features associated with promoting CD8+ T cells activation [68, 69]. DCs in the liver, compared with the DCs in the spleen or other tissues, have a stronger ability in producing IL-10 and weaker ability in activating T cells, which is characterized as "immature", with the feature of down-regulating the level of MHC-II on the surface of monocytes, decreasing the antigen-presenting effect, and inhibiting the activation, migration and adhesion of inflammatory cells [39, 70].

The liver resident NK cells play important roles in infection and tumor immune surveillance. In the mouse liver, NK cells can be divided into two populations: conventional NK cells (which do not express CD49a (α1 integrin) and DX5 (α2 integrin)) and liver-specific resident NK cells (which express CD49a but do not express DX5) [71]. Liver specificity resident NK cells is similar to classic memory cells, having the function of producing a large number of IFN-γ with cytotoxicity [72]. Although these cells can be activated by proinflammatory factors, they are usually maintained in a hyporeactive state, which is caused by the liver immunosuppressive environment [73]. In peripheral blood and tumor tissues of HCC patients, the infiltrating NK cell population was significantly decreased. For the reason of abnormal expression of KLRC1 and its ligand HLA-E, the function of NK cells in cytokine production and cytotoxicity was significantly impaired [2, 74]. Moreover, hematopoietic stem cells can reduce NK cell activity through extracellular matrix (ECM) remodeling and influence HCC development in the context of fibrosis [75]. In addition, NKT cells are one of the important sources of IFN γ, which can activate NK cells and inhibit tumor growth [2]. However, it has been confirmed that CD4+ NKT cells can secrete T helper 2 cytokines and inhibit the proliferation of CD8+ T cells under in vitro and in vivo conditions [76, 77]. Therefore, the role of NKT cells in chronic liver inflammation and hepatocarcinogenesis remains to be further studied.

7. Adaptive Immune System Mediated Responses in Liver Inflammation and HCC

Failure of adaptive immune system-mediated surveillance is one of important reason for the primary tumor development [20]. Generally, increased tumor infiltration of CD8+ T cells predicts improved clinical outcomes for HCC patients. However, HBV-infected patients show accumulation of T reg cells in the liver, which with high risk of developing HCC [78-80]. Treg cells express high levels of CD25 (IL-2RA) and cytotoxic T-lymphocyte protein 4 (CTLA4) to compete with potential effector T cells for IL-2, CD80 and CD86 [81]. Treg cells also produce anti-inflammatory cytokines (TGFβ and IL-10) to maintain immunosuppressive features. A significant increase in senescent hepatocytes can be detected following antibody-mediated depletion of CD4+ T cells, indicating that adaptive immune responses are critical in monitoring cells with cancerous potential [82]. It is found that the infiltration of CD4+CD25+FOXP3+ T cells is significantly increased in the tumor microenvironment of patients with HCC, and the proliferation and function of CD8+ T cells are impaired, which predicts poor prognosis [83-85]. Consistent with this, the proportion of T reg cells relative to cytotoxic T cells within the tumor has the potential to be an independent predictor of HCC recurrence and patient survival [86]. Notably, a group of CD8+ T cells with high KLRB1 expression was found in early relapsed HCC. Compared with well-characterized CD8+ T cells in primary HCC, this group of CD8+ T cells showed lower anti-tumor cytotoxicity, low clonal expansion ability, and was associated with poor prognosis [87]. Since NASH is described as a liver disease triggered by CD8+ T cells, there is a contradiction with the treatment of immunotherapy in NASH-driven HCC, indicating the etiologic dependence of immune surveillance [88-90].

Recently, it has been found that 50% of cirrhosis patients and 60% of early-stage HCC patients have specific genetic signatures related to the immune system. These feature classes were divided into: hyperinvasive subtypes with increased numbers of effector T cells, immunosuppressive subtype with TGF-β signal activation and proinflammatory subtype with interferon (IFN)-γ signal upregulation. The immunosuppressive subtype was found in 10% of patients with cirrhosis and were associated with a 2.4-fold increased risk of HCC development. The other two subtypes in the case of cirrhosis of the liver showed increasing trend of HCC. These specific immune features of cirrhosis have been identified as independent risk factors for predicting HCC [91, 92].

8. Other Non-Parenchymal Cells

HSCs promote immune tolerance orientation in the liver through the production of anti-inflammatory cytokines such as TGFβ, which activates signaling pathways related to liver regeneration and promotes differentiation of monocytes into myeloid suppressor cells (MDSCs). MDSCs release immunosuppressive cytokines such as IL-10 and TGFβ and express arginase to suppress T cell proliferation [59, 93]. LSECs express PD-L1, pattern recognition receptors, and adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, mediating lymphocyte tissue infiltration and MHC I/II expression [6]. Insufficient expression of costimulatory molecules in LSECs after antigen presentation leads to T cell anergy, which further emphasizes its important role in hepatic immunosuppressive polarization [94, 95].

9. Concluding Remarks

In recent years, great progress has been made in our understanding of the mechanisms underlying the development and progression of HCC. The theory that liver chronic inflammation as a major driver of HCC development has been widely accepted. Factors associated with the persistent tissue damage including OxS, increased DNA damage, and pro-inflammatory microenvironment resulting from cytokine production and cell death, as well as dysfunctional immune system surveillance, lead to the development of liver cancer. Therefore, targeting and remodeling the inflammatory and immune microenvironment of liver, reversing the immunosuppressive environment of the liver, enhancing the infiltration of anti-tumor lymphocytes into the tumor, and re-establishing an effective immune surveillance and response to immune checkpoint blockade are the directions of future research.

10. Disclosure:

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