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Tumor Immune Microenvironment as a New Therapeutic Target for Hepatocellular Carcinoma Development

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Abstract

Development of hepatocellular carcinoma (HCC) is driven by a multistep and long-term process. Because current therapeutic strategies are limited for HCC patients, there are increasing demands for understanding of immunotherapy, which has made technological and conceptual innovations in the treatment of cancer. Here, I discuss HCC immunotherapy in the view of interaction between liver resident cells and immune cells.

Keywords: Hepatocellular carcinoma, Tumor immune microenvironment, Liver resident cells, Hepatic immune cells

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HEPATOCELLULAR CARCINOMA AND ITS THERAPEUTIC OPTIONS

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death and sixth most common cancer worldwide (Villanueva, 2019). HCC arises from chronic liver inflammation driven by hepatitis B or C virus infection, alcohol consumption, and non-alcoholic fatty liver disease (El-Serag & Rudolph, 2007). Other risk factors may include metabolic disorders, toxin exposure or genetic dysregulation (El-Serag, 2011). Most of the risk factors lead to the sequential progression from hepatic steatosis to steatohepatitis, fibrosis, cirrhosis, and eventually HCC.

From many decades, clinical treatments for HCC were differentially performed in each stage (Villanueva, 2019). Surgical resection or liver transplantation is a very common treatment in the early stage of HCC, but frequent relapses appear. In the intermediate stage of HCC, radiation therapy and chemotherapy can be performed. However, resistance to chemotherapy makes difficult to overcome HCC. Scientists moved to focus on systemic therapies and Sorafenib was approved by Food and Drug Administration (FDA) as a first systemic agent for the advanced HCC patients. But still, the efficacy of systemic therapies is not sufficient and there are side effects such as diarrhea, fatigue, and hypertension (Llovet et al., 2008). Thus, the elucidation of a novel treatment for HCC still remains a big challenge.

Because of the heterogeneities of HCC, recent studies have highlighted the crosstalk between tumor cells and their surrounding microenvironments. Tumor microenvironment (TME) is composed of a variety of non-tumor cells, including hepatic stellate cells (HSCs), immune cells, endothelial cells, and non-cellular components such as extracellular matrix, growth factors, cytokines, and chemokines (Yang et al., 2011). Understanding TME in depth gives a better idea to develop novel targets for HCC treatment.

FUNCTIONS OF LIVER RESIDENT CELLS IN HEPATOCELLULAR CARCINOMA

Cancer cells actively interact with the TME to modulate tumor growth, invasion, and metastasis. Cancer-associated fibroblasts (CAFs), the most abundant cell types in TME, originated from HSCs (Bu et al., 2019). In normal liver, HSCs maintain a nonproliferative and quiescent phenotype. When there is a liver injury, HSCs become activated and transdifferentiating into myofibroblasts, leading to the development of hepatic fibrosis (Khomich et al., 2019). Activated HSCs secrete α-smooth muscle actin, collagen (extracellular matrix protein), matrix metalloproteinases (MMP), proteoglycans, chemokines, and growth factors (Friedman, 2008), consequently, CAFs play crucial role in the development and progression of HCC (Rombouts & Carloni, 2013).

Endothelial cells, another type of liver resident cells, control cell stability and angiogenesis (Dudley, 2012). There are some studies showing that endothelial cells in normal and tumor tissues have molecular and functional differences. Tumor-associated endothelial cells show an irregular shape, enhanced motility, rapid cell turn over, and high expression of CD105 and PDGFR (Benetti et al., 2008). Such phenotypes could increase angiogenesis and metastasis.

CAN IMMUNOTHERAPY BE A SUITABLE TREATMENT FOR HEPATOCELLULAR CARCINOMA (HCC)?

Because of the poor safety and limited success of multiple kinase inhibitors, such as sorafenib, clinicians and researchers have begun to seek new alternatives to HCC therapy. Malignant HCC with pathological diversity and chronic course is particularly affected by the immune system, so the recent clinical success of immune checkpoint inhibitors, including programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), has led to the application of immunotherapies to HCC (Wörns & Galle, 2017). This interest also stimulated basic HCC immunobiological research.

PROS AND CONS OF THE IMMUNE RESPONSES IN HEPATOCELLULAR CARCINOMA (HCC); PROTUMORIGENIC OR IMMUNOSURVEILLANCE?

HCC is immune-mediated disease driven by chronic inflammation. There are many subtypes of immune cell associated with TME, including tumor-associated macrophages (TAM), dendritic cells, myeloid-derived suppressor cells (MDSCs), neutrophils, mast cells, natural killer (NK) cells, natural killer T cells (NKT), T cells, and B cells (Lu et al., 2019). Increasing literatures have shown that the functions of immune cells are controversial in HCC TME (Hou et al., 2020). Here, the recent studies about the role of immune cells during HCC development are summarized in Table 1.

1. Protumorigenic immune cells

Most of immune cells are commonly observed in tumor and secrete lots of cytokines and chemokines affecting HCC development (Fu et al., 2019). Thus, these cells are known as immunosuppressive cells working in a tumor-supportive manner.

When macrophages come around the tumor area, these cells take the M2 phenotype and are referred to as TAM. M2 macrophages inhibit anti-tumor immunity and promote cancer proliferation, angiogenesis and extracellular matrix (ECM) remodeling (Mantovani et al., 2008). M2 macrophages strongly release all of the high levels of metastatic cytokines, including interleukin

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Table 1. The functions of immune cells during hepatocellular carcinoma development

Characteristics	Types of immune cell	Cytokines/Chemokines	References
Protumorigenic	Regulatory T cells	IL-10 and TGF-β	13
	M2 macrophages	IL-10, Arg1, PD-L1	16–19
	MDSCs	CD34, CD33, CD15 and CD16	20–27
	TAN2	CCL2 or CCL17	32
	Natural killer T type I	OPN	37, 38
	T helper cells (Th9, Th17, Th22, and T follicular helper)	IL-17, IL-22	39–42
Immunosurveillance	$CD8^+$ T cells	TGF-β- or IL-10	43–45
	$CD4^+$ T cells	IFN-γ	46
	B cells	Granzyme B, CD20	51–53
	Natural killer T type II	IFN-γ, IL-4, TNF-α	47
	Dendritic cells	IL-12	48–50
	M1 macrophages	IL-6, IL-1β, TNF-α	17

IL, interleukin; TGF-β, transforming growth factor-beta; PD-L1, programmed death-ligand 1; MDSCs, myeloid-derived suppressor cells; TAN2, tumor-associated neutrophils N2; CCL2, C-C motif chemokine ligand 2; OPN, osteopontin; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor-α.

(IL)-6, IL-1 and TNF-α (Huang et al., 2021). In general, TAMs tend to accumulate in the hypoxic regions of the tumor, producing angiogenic factors such as VEGF, TGF-β, and MMP (Murdoch et al., 2004). TAM is therefore an important component of the microenvironment in HCC and is associated with poor prognosis in HCC patients.

MDSCs are heterogeneous population of immature bone marrow cells that accumulate in response to various cytokines and growth factors in a TME (Kumar et al., 2016). In TME, CAFs produce MDSC-promoting cytokines (IL-6, VEGF, M-CSF) and chemokines (CXCL12/SDF1, CCL2/MCP-1) and inhibit the T cell-dependent immune response by enhancing the recruitment of MDSC (Mace et al., 2013; Deng et al., 2017). In addition, during tumor formation, MDSC can induce Treg differentiation and expansion (Kalathil et al., 2013) or interfere with DC, NK and macrophage differentiation and impair their functions (Hoechst et al., 2009; Hu et al., 2011). In humans, MDSC expresses several markers such as CD34, CD33, CD15 and CD16 (Almand et al., 2001) and major factors involved in MDSC-mediated immune suppression are arginase, iNOS, TGF-β, IL-10, and Indoleamine-2,3-dioxygenase (IDO) (Ziani et al., 2018). These evidences suggest that MDSC contributes to the immune suppression network through multiple mechanisms in tumor growth, angiogenesis and metastasis and is a potential immunotherapy target for HCC (Lu et al., 2019).

According to a recent study, tumor-associated neutrophils (TANs) can promote tumor growth, metastasis, and tumor vascularization by releasing cytokines in TME (Murdoch et al., 2008, Kitamura et al., 2015). TANs can be polarized into two subtypes, N1 (antitumor) and N2 (protumor), depending on the presence of TGF-β (Fridlender et al., 2009). N1 neutrophils are induced upon TGF-β blocking, express immune activated cytokines and chemokines, low levels of Arg 1 and can kill cancer cells. In contrast, N2 neutrophils are induced after exposure to high TGF-β levels and are characterized by expression of CXCR4, VEGF, and MMP9, and inhibit $CD8^+$ T cell function by several mechanisms (Leliefeld et al., 2015). Zhou SL and his colleagues found that CCL2 or CCL17-expressing TANs recruit macrophage and Treg cells to promote HCC progression and resistance to sorafenib (Zhou et al., 2016).

In addition, cancer cells can avoid immune system using immunosuppressive inflammatory cells, such as regulatory T cells (Tregs) (Mougiakakos et al., 2010). Treg cells support cancer progression

and metastasis including breast cancer and liver cancer, by suppressing various types of effector lymphocytes including $CD8^+$ T cells (Togashi et al., 2019). Previous reports have shown that Treg cell numbers were increased in tumors and peripheral blood of HCC patients (Ormandy et al., 2005; Yang et al., 2006). Increased intratumoral Tregs maintain immune resistance and prevent inflammation by expressing multiple T cell depletion markers including PD-1, LAG-3, CCR4, GITR, and TIM-3, or by expressing anti-inflammatory cytokines such as IL-10 and TGF-β (Lu et al., 2019). Consequently, these evidences are likely that Treg inhibition serves as an important biomarker of inducing an immune response to HCC.

NKT cells have two different subsets (types I and II) that recognize different antigens presented by CD1d molecule. The action of each NKT cells plays a contrary role in HCC (Zhu et al., 2018). Type I NKT cells are numerous in mice and produce Th1- and Th2- type cytokines. Some studies have been published that these cells promote chronic injury in HCC by recruiting HSCs and neutrophils. On the other hand, type II NKT cells are more abundant in humans than type I cells and they express TCR-α- and TCR-β chains consequently to prevent liver disease (Bandyopadhyay et al., 2016). In chronic liver disease, the action of different subsets of NKT cells are closely interconnected, therefore, it is important to develop a drug that can identify specific subset of NKT cells.

Furthermore, mast cells can contribute to the development of highly suppressive MDSCs and Tregs within TME (Ziani et al., 2018). There are increasing evidences for the pro-tumorigenic functions of T helper cells, such as Th9, Th17, Th22, and T follicular helper (Zhang et al., 2009; Jiang et al., 2011; Chen et al., 2016; Tan et al., 2017).

2. Immunosurveillance

Several studies have shown that some immune cells including $CD8^+$ cytotoxic T lymphocytes (CTLs), $CD4^+$ T cells, B cells, NK cells and DCs are critical to block tumor development. These immune cells are involved in the antitumor immune responses in HCC. Understanding the characteristics of these cells could lead to the development of cancer immunotherapy.

Since most tumor surveillance has the effect of recognizing tumor antigens by $CD8^+$ T cells (CTLs), understanding of CTLs is important for the control of anti-tumor immunity. Several studies have found that low population of intratumoral CTLs is associated with a worse prognosis in HCC patients (Fu et al., 2007; Gao et al., 2007). Fibrotic liver directly reduces CTLs and expresses TGF-β- or IL-10-mediated anti-inflammatory cytokines and accelerates HCC through interaction with PD-L1 on Kupffer cells (Wu et al., 2009). Together with CTLs, $CD4^+$ T cells also have been previously shown to inhibit the progression of HCC through immune surveillance of senescent hepatocytes (Kang et al., 2011).

NK cells, which play a major role in innate immunity, play an important role in host defenses against natural cytotoxicity and stimulation by cytokines such as IFN-g (Yang et al., 2010). These cells help control viral hepatitis, liver fibrosis and liver tumor formation by directly killing infected and damaged cells, and increased density of NK cells is associated with HCC cell apoptosis and reduced tumor cell proliferation (Yang et al., 2011). The team reported that inferior NKG2D, TNF-related apoptosis-inducing ligand and IFN-g expression against NK cells from ethanol fed mice attenuated cytotoxicity against HSC. These studies suggest that liver NK cells play an important role in mediating liver immune function and immune defense mechanisms against HCC.

Dendritic cells (DC) are well known as phagocytic antigen-presenting cells leading activation of T cells and immune responses (Pham et al., 2022). Teng et al. suggest DC vaccination with PD-L1 inhibitor can be used as a new therapy method for HCC (Teng et al., 2020). Moreover, recent studies support the function of DC as effective treatment for HCC by secretion of cytokines such

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as IL-12 (Ormandy et al., 2006).

Like the immune cells described above, B cells in tumors were found to be in close contact with $CD8^+$ T cells. They are also correlated with granzyme B and IFN-c (Garnelo et al., 2017). Previous studies have reported that circulating IgA is detected in non-alcoholic steatohepatitis (NASH) patients (McPherson et al., 2014). IgA^+ cells with high expression of PD-L1 and IL-10 interfere with the activation of cytotoxic $CD8^+$ T lymphocytes to suppress immune surveillance and promote HCC progression (Shalapour et al., 2017).

CONCLUSION

In conclusion, the article delves into the complex landscape of HCC and its therapeutic options. The efficacy of traditional treatments of HCC is limited and it needs for novel and targeted therapeutic approaches. The article emphasizes the importance of understanding the complexities of the TME in HCC. Based on the results of current strategies, it is expected that future advancements will significantly enhance the treatment outcomes for HCC.

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