

# Regulatory T cells and their associated factors in hepatocellular carcinoma development and therapy

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**Regulatory T cells and their associated factors in hepatocellular carcinoma development and therapy**

Zhang CY *et al.* Role of Tregs in HCC

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15

## Abstract

Liver cancer is the third leading cause of cancer-related death worldwide with primary type hepatocellular carcinoma (HCC). Factors, including carcinogens, infection of hepatitis viruses, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD), can induce HCC initiation and promote HCC progression. The prevalence of NAFLD accompanying the increased incidence of obesity and type 2 diabetes (T2D) becomes the most increasing factor causing HCC worldwide. However, the benefit of current therapeutic options is still limited. Intrahepatic immunity plays critically important roles in HCC initiation, development, and progression. Regulatory T cells (Tregs) and their associated factors such as metabolites and secreting cytokines mediate the immune tolerance of the tumor microenvironment in HCC. Therefore, targeting Tregs and blocking their mediated factors may prevent HCC progression. This review summarizes the functions of Tregs in HCC-inducing factors including alcoholic and non-alcoholic fatty liver diseases, liver fibrosis, cirrhosis, and viral infections. Overall, a better understanding of the role of Tregs in the development and progression of HCC provides treatment strategies for liver cancer treatment.

**Key Words:** hepatocellular carcinoma, regulatory T cells, alcoholic fatty liver disease, non-alcoholic fatty liver disease, treatment, clinical trials

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**Core Tip:** Liver cancer is the third leading cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC) is the primary type of liver cancer. Factors, including carcinogenic infection of hepatitis viruses, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD), can induce HCC initiation and promote HCC progression. The prevalence of NAFLD accompanying the increased incidence of obesity and type 2 diabetes (T2D) becomes the most increasing factor causing HCC worldwide. However,

the benefit of current therapeutic options is still limited. Intrahepatic immunity plays critically important roles in HCC initiation, development, and progression. Regulatory T cells (Tregs) and their associated factors such as metabolites and secreting cytokines mediate the immune tolerance of the tumor microenvironment in HCC. Therefore, targeting Tregs and blocking their mediated factors may prevent HCC progression. A better understanding of the role of Tregs in intrahepatic immunity is helpful to develop novel HCC treatment options.

## INTRODUCTION

Liver cancer is the third leading cause of cancer-related death worldwide with 8.3% of death ratio, following lung and colorectal cancers<sup>[1]</sup>. The most common type of primary liver cancer is hepatocellular carcinoma (HCC) and the second type is cholangiocarcinoma (CCA)<sup>[2]</sup>. Factors, including carcinogens (e.g., aflatoxin B1), infection of hepatitis viruses, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD), can induce HCC and promote HCC progression<sup>[3-5]</sup>. In addition, accompanying the increasing incidence of obesity and type 2 diabetes (T2D), NAFLD becomes an increasing factor that causes HCC worldwide<sup>[6, 7]</sup>.

Surgical resection is a curative treatment option for the early stage of HCC. However, most cases in HCC were found in the late stage. In addition, other minimally invasive local therapies, such as radiofrequency ablation (RFA) and microwave ablation (MWA), and systemic therapy, such as tyrosine kinase inhibitors, are treatment options for patients who are not suitable for surgery<sup>[8]</sup>. Furthermore, immunotherapy by targeting checkpoint inhibitors (e.g., anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies) shows benefits against advanced HCC in the clinic. A combination treatment by blocking both PD-L1 (e.g., atezolizumab) and vascular endothelial growth factor (VEGF) (e.g., bevacizumab) is one of the best first-line treatments for advanced HCC<sup>[9]</sup>. Other potential immunotherapy options including T cell-mediated therapy such as chimeric antigen receptor (CAR)-engineered T cells<sup>[10-12]</sup>,

peptide-based vaccines<sup>[13-15]</sup>, and microRNAs (miRNAs)-mediated therapies<sup>[16]</sup>, are undergoing investigations for HCC treatment.

Intrahepatic immunity including both innate and adaptive immune responses plays pivotal roles in the development and progression of HCC, especially for T cells<sup>[17]</sup>. Among them, the imbalance between effector CD4 and/or CD8 T cells and regulatory T cells (Tregs) induces immunotolerance and promotes HCC progression<sup>[18, 19]</sup>. Factors impacting the balance of effector T cells and Tregs include gut microbiota, transforming growth factor-beta (TGF- $\beta$ ), and treatments such as trans-arterial chemoembolization (TACE)<sup>[18-20]</sup>, etc. The expression of cytokines such as interleukin (IL)-2, IL-5, interferon (IFN)- $\gamma$  was increased with an increased ratio of cytotoxic T lymphocytes (CTLs)/Tregs with the treatment of Lenvatinib, a multiple kinase inhibitor, while the expression of T-cell immunoglobulin mucin-3 (Tim-3) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) was decreased on Treg cells<sup>[21]</sup>. Therefore, modulating the Treg frequency and the expression of related cytokines are critically important for anti-tumor immunotherapy.

In this review, functions of Tregs on HCC causing factors such as alcoholic liver disease (ALD), NAFLD, liver fibrosis, and cirrhosis are discussed. In addition, molecules mediated Treg functions and therapeutic options by targeting Tregs are summarized. Moreover, clinical trials by targeting Tregs to modulate immune response were analyzed.

## **TREGS IN CHRONIC LIVER DISEASE**

### ***Tregs in ALD***

As immunosuppressive cells, Tregs play a pivotal role in chronic liver diseases, including ALD. For example, chronic-binge alcohol exposure in C57BL/6 mice induced the reduction of Treg cells, but increased T helper 17 cells (Th17) cells and the production of interleukin (IL)-17<sup>[22]</sup>. Treatment with ginsenoside F2 can ameliorate ALD by increasing the frequency of Foxp3<sup>+</sup>Tregs and decreasing IL-17-producing Th17 cells compared to control groups<sup>[23]</sup>. However, the molecular mechanism of how Tregs

impact the progression of ALD except for modulation of liver inflammation remains unclear.

### *Tregs in NAFLD and NASH*

The balance Th17 cells/Tregs plays an essential role in metabolic diseases by regulating immune response and glucose and lipid metabolism<sup>[8]</sup>. The lower Treg (forkhead box P3<sup>+</sup>/FOXP3<sup>+</sup>) and higher Th17 cell (IL-17-producing cells) numbers were found in portal or periportal tract in livers of adult NAFLD patients, whereas more Tregs were shown in pediatric NAFLD patients<sup>[24]</sup>. In addition, severe liver inflammation was positively associated with intralobular expression of FOXP3 in pediatric patients but was positively associated with higher expression of IL-17 and lower expression of FOXP3 in adult patients, indicating the role of Tregs in NAFLD is age-dependent. Intrahepatic imbalance of Th17/Treg cells promotes the progression of NAFLD, accompanying higher expression of inflammatory cytokines such as IL-6, IL-17, and IL-23 in both serum and liver<sup>[25]</sup>. Feeding a high-fat diet (HFD) can impact the balance of Th17/Treg cells and Th1/Th2 cells of CD4 T cells in mesenteric lymph nodes (MLN). In addition, those CD4 T cells can potentially migrate into the liver to promote liver inflammation to result in NAFLD progression<sup>[26]</sup>. The effects of CD4 T cells in MLN on liver inflammation and fat accumulation can be ameliorated by administration of antibiotics and probiotics, indicating an important role of gut microbiota in NAFLD pathogenesis<sup>[26]</sup>.

Dywicki *et al.* showed intrahepatic Tregs were increased in high-fat high-carbohydrate (HF-HC) diet-induced NASH in BALB/c mice<sup>[27]</sup>. In addition, depletion of adaptive immunity aggravated HF-HC diet-induced NASH in recombination activating 1 (Rag)-knockout BALB/c mice. Although Tregs showed an anti-inflammation effect in ALD<sup>[23]</sup>, adoptive transfer of Tregs increased steatosis and serum level of alanine aminotransferase (ALT), indicating that Tregs enhance the progression of NAFLD<sup>[27]</sup>. Another study also showed that increasing Tregs in subcutaneous adipose tissue induced by adoptive transfer of Tregs from healthy C57BL/6J mice to high-fat high-

fructose diet (HFHFD)-fed mice increased hepatic steatosis during NAFLD development<sup>[28]</sup>.

Mechanistically, the formation of neutrophil extracellular traps (NETs) during NASH progression can induce Treg differentiation from naïve CD4 T cells, which is dependent on Toll-like receptor 4 (TLR-4) and involved in NASH-HCC progression<sup>[29]</sup>.

### *Tregs in liver fibrosis and cirrhosis*

Progression of chronic liver disease, including ALD and NAFLD, can promote the development of liver fibrosis and its advanced stage liver cirrhosis. However, there are no currently available therapies that can treat or reverse liver cirrhosis. Deng *et al.* reported that co-infusion with human amniotic mesenchymal stromal cells (hAMSCs) and Tregs can prevent mild liver fibrosis<sup>[30]</sup>. Tregs play a critical role in the secretion of hepatocyte growth factor (HGF) and cell differentiation of hAMSCs.

Furthermore, an imbalance of Th17 cells/Tregs was also shown in cirrhotic patients with hepatitis B virus (HBV) infection. The frequency of Tregs was reduced in peripheral blood, while the frequency of Th17 cells was increased, resulting in a decreased Treg/Th17 ratio as a potential diagnostic marker for decompensated liver cirrhosis<sup>[31]</sup>. Another study also showed that the frequencies of both Tregs and Th17 cells were increased in the blood of patients with HBV infection and cirrhotic livers but with a higher extent in Th17 cells, resulting in an increased ratio of Th17/Treg, compared to the control group<sup>[32]</sup>. In addition, the mRNA levels of proinflammatory cytokines IL-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$ , as well as the protein expression of nuclear factor  $\kappa$ B (NF- $\kappa$ B) in the liver were significantly increased in HBV-infected liver and cirrhotic liver compared to healthy controls. Another study also showed that HBV infection can induce IL-8/C-X-C motif chemokine receptor 1 (CXCR1)/TGF- $\beta$  signaling to provoke Treg polarization, resulting in suppression of anti-tumor immunity and enhance of HCC metastasis<sup>[33]</sup>. Moreover, the frequency of Tregs in blood and plasma levels of IL-35 were increased and positively related to viral load in HCV infected patients with cirrhosis and HCC<sup>[34]</sup>.

### *Tregs in HCC*

A meta-analysis showed that a higher infiltration of CD3 T cells, CD8 T cells, and natural killer (NK) cells was associated with better overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS). In contrast, a higher infiltration of Tregs and neutrophils indicated lower OS and DFS<sup>[35]</sup>. Another report also showed that an increase of Tregs or a decrease of M1 macrophages (proinflammatory phenotype) were associated with a poor prognosis of HCC patients<sup>[36]</sup>. CCR4<sup>+</sup>Tregs are predominant Tregs that are recruited in tumor tissue of HCC associated infection of hepatitis viruses, which is associated with HCC resistance to sorafenib treatment<sup>[37]</sup>. The frequency of CD127<sup>low</sup>CD25<sup>+</sup>CD4<sup>+</sup>Tregs was increased significantly in the peripheral venous blood of HCC patients compared to healthy controls<sup>[38]</sup>. In addition, the serum levels of TGF- $\beta$ 1 and IL-10 in HCC patients were positively associated with the Treg population in the blood, which were decreased post-operation and chemotherapy treatments. CCL5 expression on circulating tumor cells in HCC patients can attract Tregs to induce an immunosuppressive environment, one of the mechanisms for CTC escaping immune surveillance<sup>[39]</sup>.

The expression of immune checkpoint proteins in the HCC microenvironment impacts Tregs and antitumor immunity. PD-L1<sup>+</sup>neutrophils, Tregs, and neutrophil to lymphocyte ratio (NLR) were significantly increased in peripheral blood of patients with poorly differentiated HCC with a worse prognosis compared to that in patients with highly-moderately differentiated HCC<sup>[40]</sup>. Zhou *et al* reported that tumor-associated neutrophils (TANs) can induce the infiltration of the macrophages and Tregs from HCC mice or patients *via* producing C-C motif chemokine ligand 2 (CCL2) and CCL17, resulting in HCC progression and resistance to sorafenib<sup>[41]</sup>. CTLA-4 on Tregs in HCC impacts dendritic cell function by downregulating CD80/CD86 on dendritic cells (DCs)<sup>[42]</sup>. Therefore, blockade of CTLA-4 in HCC can improve DC-mediated anti-tumor immunity.

Treatment with tivozanib, a tyrosine kinase inhibitor, can suppress Tregs by inhibiting receptor tyrosine kinase c-Kit (CD117)/stem cell factor (SCF) axis and increased CD4<sup>+</sup>PD-1<sup>+</sup>T cells, resulting in a significant improvement in OS of HCC patients<sup>[43]</sup>.

Treatment with Lenvatinib also can inhibit IL-2 mediated Treg differentiation except for decreasing PD-L1 expression in HCC cells<sup>[44]</sup>. Overall, the balance between Tregs with other T cells plays a vital in liver diseases, including the initiation and progression of HCC (Figure 1).

Furthermore, alteration of intrahepatic immunity is associated with HCC prognosis and treatment (Figure 2). An increase of Tregs, Th2, and Th17 T cells, as well as M2 macrophages, is usually and positively associated with HCC progression in patients, whereas an abundance of CD8 T cells, Th1 T cells, and M1 macrophages is associated with HCC therapy and good prognosis for HCC patients<sup>[45]</sup>. Single-cell RNA sequencing technologies have been applied to investigate the immune landscape of HCC samples to illustrate the subtypes of immune cells in HCC and their gene expressing profiles, as well as immune cell interactions, such as DCs with Tregs or CD8 T cells<sup>[46]</sup>.

## **IMPORTANT MOLECULES MEDIATED TREG FUNCTION AND METABOLISM**

### ***HIF-1 $\alpha$***

Hypoxia-inducible transcription factors (HIFs) regulate cell metabolism, proliferation, and migration in low oxygen or hypoxic environment, as well as angiogenesis<sup>[47]</sup>. It has been reported that the expression of HIF-1 $\alpha$  was higher in HCC tissues compared to that in corresponding adjacent tissues. In addition, overexpression of hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ) was associated with poor outcomes of HCC in human patients<sup>[48]</sup>. Chronic intermittent hypoxia can promote NASH progression *via* regulating the balance of Th17/Treg by inducing the expression of HIF-1 $\alpha$ <sup>[49]</sup>.

### ***Gal-9***

Tregs can be subclassified into inflamed-tissue related memory Tregs (mTregs) and non-related resting Treg (rTregs). During HBV infection, mTregs were increased accompanying liver inflammation and liver injury evidenced by an increase of serum ALT level, but not rTregs<sup>[50]</sup>. The S-type lectin galectin-9 (Gal-9) was increased in the HBV-infected liver, contributing to T cell depletion and exhaustion by binding Tim-3<sup>[51]</sup>.

For example, activation of Gal-9/Tim-3 signaling in concanavalin A (Con A)-induced mouse hepatitis suppressed the induction of effector T (Teff) cells and the production of interferon (IFN)- $\gamma$ <sup>[52]</sup>. In addition, the Gal-9/Tim-3 signaling pathway plays an important role in the expansion of mTregs<sup>[50]</sup>.

### **GDF15**

The expression of growth differentiation factor 15 (GDF15) was positively related to the frequency of Tregs in HCC. GDF15 can promote the suppressive effect of natural Tregs via binding with its unrecognized receptor CD48 on T cells to inhibit the function of homology and U-box containing protein 1 (STUB1), which can degrade FOXP3<sup>[53]</sup>. Thus, neutralizing GDF15 by an antibody can eradicate HCC and enhance anti-tumor immunity.

### **microRNAs**

Hepatic expression of microRNA-195 (miR-195) was reduced in NAFLD development, accompanying an increased ratio of Th17/Treg ratio in the blood, as well as the expression IL-17, CD40, and TNF- $\alpha$  in rat liver<sup>[54]</sup>. Overexpression of miR-195 can maintain the balance of Th17/Treg to ameliorate NAFLD and liver inflammation. Many miRNAs can regulate Th17/Treg cell balance in NAFLD such as miR-29c via interacting with insulin-like growth factor binding protein 1/IGFBP1<sup>[55]</sup>. In addition, other microRNAs such as miR-155<sup>[56, 57]</sup>, miR-423-5p<sup>[58]</sup>, and miR-1246<sup>[59]</sup> play important roles in modulating the balance of Tregs with Th17 cells and their functions in liver disease.

### **TLRs**

Activation of Toll-like receptor (TLR) signaling pathway can suppress the effect of Tregs on adaptive immune response, which is in part dependent on microbial production-induced expression of IL-6<sup>[60]</sup>. TLR9-deficiency increased the frequency of Treg cells in the intestine, resulting in a decrease of IL-17 and IFN- $\gamma$  producing Teff cells<sup>[61]</sup>. The imbalance of Treg/Teff cells compromised immune response to oral infection, which can be reversed by reconstitution of gut flora DNA<sup>[61]</sup>. In addition, the antibiotic treatment caused gut microbiota dysbiosis and recapitulated TLR9 deficiency-induced impaired immune response.

## YAP

Yes-associated protein (YAP), a coactivator and a corepressor of the Hippo signaling pathway, plays a vital role in Tregs *in vivo* and *in vitro*<sup>[62]</sup>. Blocking YAP-mediated activation of activin can improve anti-tumor immunity *via* regulating TGF- $\beta$ /mothers against decapentaplegic homolog (SMAD)<sup>[62]</sup>. Similarly, blockage of TGF- $\beta$  signaling can compromise Treg function to improve anti-tumor immune response<sup>[63]</sup>, which may expand the population of quiescent Tregs, CD4<sup>+</sup>CD25-Foxp3<sup>+</sup>.

The above-mentioned molecules can modulate Treg metabolism and function as potential molecular targets for HCC treatment. In addition, modulation of these molecules can potentially recover the balance of Tregs with other tumor-infiltrating immune cells to activate anti-tumor immunity (Figure 3).

## TREATMENT OPTIONS

### *Modulation of microRNAs*

Administration of miR-26a can reduce the frequency of Tregs and the concentrations of alpha-fetoprotein (AFP), des-gamma carboxyprothrombin (DCP), and VEGF in Balb/c mice with diethylnitrosamine (DEN)-induced HCC<sup>[64]</sup>. The suppressive effects of miR-26a on HCC growth and angiogenesis are mediated by targeting IL-6/signal transducer and activator of transcription 3 (Stat3) signaling<sup>[65]</sup> and HGF/HGF receptor (HGFR/c-Met) signaling<sup>[66]</sup>, respectively. In addition, miR-26a inversely regulated the expression of F-box protein 11 (FBXO11), which was upregulated and played an oncogenic role in HCC<sup>[67]</sup>.

### *Adoptive transfer of cells*

Adoptive transfer of Tregs attenuated triptolide-induced liver injury, while depletion of Tregs showed the opposite effect, indicating that Tregs contribute to the progression of liver injury<sup>[68]</sup>. Another study showed that adoptive transfer of hepatic stellate cell (HSC)-stimulated Tregs can significantly decrease liver injury in mice with autoimmune hepatitis by inducing the balance of Treg/Th17 ratio<sup>[69]</sup>. In addition, the adoptive transfer of HSCs promoted the differentiation of Tregs and decreased Th17 cells,

resulting in amelioration of liver injury<sup>[70]</sup>. Deng *et al.* reported that co-infusion with hAMSCs and Tregs can prevent mild liver fibrosis<sup>[30]</sup>. Tregs play a critical role in the secretion of HGF and cell differentiation of hAMSCs.

### ***Modulation of gut microbiota***

Depletion of Tregs in the intestine caused an increase in the abundance of *Firmicutes* and intestinal inflammation<sup>[71]</sup>. Supplementation of *Lactobacillus rhamnosus* GG or its culture supernatant can ameliorate chronic alcohol-induced liver injury by reducing TNF- $\alpha$  expression *via* inhibition of TLR4- and TLR5-mediated hepatic inflammation<sup>[72]</sup>, as well as amelioration of intestinal barrier integrity and suppression of alcohol-induced endotoxemia<sup>[73]</sup>. In addition, the culture supernatant can balance the ratio of Treg and Th17 cells to reduce alcoholic-induced liver injury<sup>[22]</sup>.

Treatment with Prohep, a novel probiotic mixture, significantly inhibited the HCC growth compared to the control group, resulting in an abundance of beneficial bacteria, such as *Prevotella* and *Oscillibacter*<sup>[74]</sup>. This study also showed that probiotic treatment regulated T-cell differentiation in the gut by reducing Th17 polarization and increasing the differentiation of anti-inflammatory Treg cells.

### ***Blockade of immune checkpoints***

Dual anti-PD-1/VEGF receptor (VEGFR)-2 therapy increased CD8 T cell infiltration and activation, reduced Tregs and infiltration of CCR2<sup>+</sup> monocytes, as well as the phenotype of tumor-associated macrophages (the M1/M2 ratio) in HCC tissue<sup>[75]</sup>. Another study also showed that Treg-mediated inhibition of IFN- $\gamma$  production and cytotoxicity of CD8 T cells can be partially reduced by anti-PD-1 and anti-PD-L1 antibodies in HCC<sup>[76]</sup>.

Treg depletion-mediated by anti-CTLA-4 monoclonal antibody (clone 9H10) restored the function of tumor antigen-specific CD8 T cells, with a synergetic effect with anti-PD-1 treatment<sup>[77]</sup>.

### ***Other treatments***

CCR4 expression in Tregs accompanied with an increased expression of IL-10 and IL-35, resulting in suppression of CD8 T cells and HCC progression. Administration of a CCR4 antagonist or N-CCR4-Fc, a neutralizing pseudo-receptor that can block Tregs

accumulation in HCC, can enhance therapeutic efficacy to PD-1 blockade and sorafenib<sup>[37]</sup>. Treg depletion induced by anti-CCR4 antibody (mogamulizumab), in combination with anti-PD-1 antibody (nivolumab) showed antitumor activity and increased CD8<sup>+</sup> T cell infiltration<sup>[78]</sup>.

Treatment with resveratrol, a natural phenol, can inhibit H22 (a mouse HCC cell line)-induced orthotopic HCC tumor growth *via* decreasing the frequency of CD8<sup>+</sup>CD122<sup>+</sup>Tregs and M2-like macrophages in mice<sup>[79]</sup>.

Ren *et al.* reported that Tregs were further increased in HCC patients compared to healthy and cirrhosis controls, as well as in HCC patients with Barcelona clinic liver cancer (BCLC) stage C compared to that in HCC patients with BCLC stage B<sup>[80]</sup>. The authors also showed that treatment with microparticles-transarterial chemoembolization dramatically decreased Treg cell proportion at 1 to 2 wk post-treatment. Overall, the treatment options for HCC associated with Treg regulation were summarized in Table 1.

## CLINICAL TRIALS

Tregs display multiple roles in the development and progression of HCC. The ratio of Treg/Th17 cells in peripheral blood can be applied to monitor immune tolerance as immune markers in liver transplantation<sup>[81]</sup>. The balance of Treg/Th17 cells or other effector T cells is essential for suppressing autoimmune diseases and cancers<sup>[82]</sup>. Therefore, treatments including diverse immunomodulatory therapies can regulate Tregs to enhance the antitumor immune response. In Table 2, potential therapies in clinical trials were summarized. Treatments including infusion of Tregs<sup>[83-85]</sup> and mesenchymal stromal cells (MSCs)<sup>[86]</sup>, vaccines<sup>[87-89]</sup>, and kinase inhibitors<sup>[90]</sup>.

## CONCLUSION

Tregs modulate the intestinal and intrahepatic immune response, contributing critically important roles in the gut-liver axis. Functional changes of Tregs are involved in the pathogenesis of chronic liver diseases, such as ALD and NAFLD, causing factors for

HCC. Several important molecules investigated in recent studies are summarized and targeting them may potentially treat HCC by modulating Treg function and/or frequency. Clinical trials are undergoing to further explore the new treatments for HCC, which modulate the function of the frequency of Tregs. In the future, multi-omic analysis including metabolic and proteomic data for Treg metabolism and function during the progression of HCC is critical to illustrate the underlying mechanisms of Tregs in HCC pathogenesis and find out new therapeutic targets.

# Regulatory T cells and their associated factors in hepatocellular carcinoma development and therapy

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