Targeting Immune Cells in the Tumor Microenvironment of HCC: New Opportunities and Challenges

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Immune associated cells in the microenvironment have a significant impact on the development and progression of hepatocellular carcinoma (HCC) and have received more and more attention. Different types of immune-associated cells play different roles, including promoting/inhibiting HCC and several different types that are controversial. It is well known that immune escape of HCC has become a difficult problem in tumor therapy. Therefore, in recent years, a large number of studies have focused on the immune microenvironment of HCC, explored many mechanisms worth identifying tumor immunosuppression, and developed a variety of immunotherapy methods as targets, laying the foundation for the final victory in the fight against HCC. This paper reviews recent studies on the immune microenvironment of HCC that are more reliable and important, and provides a more comprehensive view of the investigation of the immune microenvironment of HCC and the development of more immunotherapeutic approaches based on the relevant summaries of different immune cells.

Keywords: HCC, TAM, NK cell, cancer immunotherapy, challenge, development

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for the sixth most common type of cancer and the second leading cause of death among all cancers (Ferlay et al., 2015). Due to changes in environmental factors, immunization and people’s lifestyle, the incidence of HCC and HCC-related mortality are increasing all over the world. The latest research indicates that HCC accounts for approximately 85% of patients diagnosed with liver cirrhosis. Its 5-year survival rate is only 18%, second only to pancreatic cancer (Asafo-Agyei and Samant, 2021). With the improvement of the treatment level for HCC, a variety of treatment options such as liver transplantation, surgical removal, systemic therapy and liver targeted therapy are constantly enhanced and created. At present, only surgical treatment is considered as a potential radical treatment for HCC. But only 15% of HCC patients have the opportunity to have surgery, most patients are found in the advanced stage (Roxburgh and Evans, 2008). Sorafenib is the only systemic medication approved by the FDA for advanced HCC. However, because of the overexpression of dihydropyrimine dehydrogenase, the multi-drug resistance gene MDR-1 and p-glycoprotein gene products, HCC is regarded a chemotherapy-resistant tumour, and how to execute effective chemotherapy is still a major difficulty (Soini et al., 1996; Jiang et al., 1997; Kato et al., 2001).
Seven essential characteristics of cancer have been identified as crosstalk between cells and immune cells, self-sufficiency of signals for growth, unrestricted replication potential, apoptosis avoidance, growth signals insensitivity and continuous angiogenesis and invasion/metastasis of tissue (Hanahan and Weinberg, 2000; Hanahan and Weinberg, 2011). Tumor cells, immune cells, stromal cells, endothelial cells, and cancer-related fibroblasts are all found in the tumor microenvironment (TME), according to current research. Malignant tumour cells can evade immune monitoring and kill, as well as impair the human body, via a range of intricate ways (Hanahan and Weinberg, 2011). Due to the limitations of traditional chemotherapy regimens in the treatment of HCC, a variety of immunotherapy methods for HCC have been developed. Immunotherapy mostly employs immune cells within or outside of the TME to specifically target and assault cancer cells, with the benefits of high specificity and low side effects (Yost et al., 2019). More crucially, thanks to advances in tools such as mass spectrometry and single-cell RNA sequencing, we can map immunological cells in TMEs at the single-cell level (Spitzer and Nolan, 2016; Zheng et al., 2017; Papalexi and Satija, 2018; Wang et al., 2019a). We outline the significance of tumor-associated immune cells in the HCC tumour microenvironment and highlight their relevance in HCC cancer immunotherapy in this study.

THE IMMUNE CELLS IN TME

Tumor-associated immune cells are broadly classified into two types: tumor-promoting immune cells and tumor-antagonistic immune cells. At different stages of tumour formation, these two types of cells play different functions and impact each other (Figure 1). Because the significance of tumor-associated B cells in tumour growth is debatable, we shall introduce B cells additionally.

TUMOR-ANTAGONIZING IMMUNE CELLS

Effector T Cells

Current studies suggest that CD8+ cytotoxic T cells (CTLs) are the main lymphocytes that kill cancer cells. When CD8+ T cells recognize antibodies on DC, CD80-CD86 and CD70 ligands on DC connect to CD27 and CD28 receptors on CD8+ T cells, and CD8+ T cells are modified to become cytotoxic effector CD8+ T cells (Tanaka et al., 1999; Farhood et al., 2019). Furthermore, CD4+ T cells can activate CD8+ T cells through CD40-CD40L interaction, and CD4+ T cells can produce IL-2 to enhance CD8+ T cell proliferation. CD4+ T cells are also important in the maturation of CD8+ T cells into memory cells (Bennett et al., 1997; Mackey et al., 1997; Bennett et al., 1998; Mackey et al., 1998;
TABLE 1 | The immune cells in TME: Effector T cells.

| Cells          | The research direction | Result                                                                 | Reference       |
|----------------|------------------------|------------------------------------------------------------------------|-----------------|
| CD8+ T cell    | The immune mechanism   | NanoMnSor enhances the efficacy of anti-PD-1 antibodies and whole cell cancer vaccine immunotherapy by reducing tumor invasion of hypoxia-induced tumor-associated macrophages, promoting macrophage polarization into an immune-stimulating M1 phenotype and increasing the number of CD86 cytotoxic T to reprogram the immunosuppressive TME. | Chang et al. (2020) |
| CD8+ T cell    | immunotherapy          | PVR1 upregulated by HCC cells stabilizes PVR on the cell surface, which interacts with the inhibitory molecule TIgIT of CD8 effector memory T cells. It is possible to develop PVR1/TIgIT inhibitors as well as anti-PD1 to treat HCC. | Chiu et al. (2020) |
| CD8+ T cell    | Prognostic marker      | PD1 or TIM3PD1 CD8 T cells were significantly associated with poor prognosis, and the latter were adjacent to PD-L1 tumor-associated macrophages. | Ma et al. (2019) |
| CD8+ T cell    | immunotherapy          | SFG2L2 promotes HCC growth by reducing DC activity and subsequent cytotoxicity of CD8 T cells, suggesting that SFG2L2 is a novel potential therapeutic target for HCC therapy. | Yang et al. (2019a) |
| CD6+ T cell    | The immune mechanism   | IL-33 inhibits the cytolytic and noncytolytic functions of CD8 T cells against non-viral hepatitis associated HCC, possibly inhibiting the expression of perforin. | Yang et al. (2019b) |
| CD8+ T cell    | The immune mechanism   | Suppression of the tumor immunosuppressive environment and immune escape is accompanied by proliferation of functional cytotoxic CD8 T cells as well as suppression of myeloid suppressor cells and regulatory T cells in the tumor environment. | Tao et al. (2019) |
| CD8+ T cell    | The immune mechanism   | A large number of TEM-1 positive (TEM-1 TAM) in the late stage of HCC development indirectly impair the cytotoxic function of CD8 T cells and induce the apoptosis of CD8 T cells. | Wu et al. (2019a) |
| CD8+ T cell    | immunotherapy          | The Δcatenin peptide vaccine stimulates the activation of cytotoxic T lymphocytes (CTL) and enhances the invasion of CD8+ T cells into the tumor. In addition, Δcatenin peptide vaccine can enhance the secretion of IFN-γ and the killing effect of T cells on tumor cells. | Huang et al. (2018) |
| CD6+ T cell    | The immune mechanism   | Stat3-blocked lysates of whole HCC cells stimulated activation of T and natural killer (NK) cells and enhanced cytotoxic CD8 T cell infiltration in tumor tissues. | Han et al. (2017) |
| CD8+ T cell    | The immune mechanism   | Antibody against CD274(PO-ligand 1 [PD-L1]), TIM3, or Lag3 increases CD8 and CD4 TIL proliferation and cytokine production in response to stimulation by polyclonal antigens or TAA. | Zhou et al. (2017) |
| CD8+ T cell    | immunotherapy          | Tremelimumab in combination with tumor ablation is a potential new therapy for patients with advanced HCC, resulting in the accumulation of CD8 T cells in tumors. Positive clinical activity was observed and may replace HCV viral load. | Duffy et al. (2017) |
| CD8+ T cell    | immunotherapy          | PD-L1 upregulation is mainly induced by pre-existing activated CD8α+ cytotoxic T cells in the HCC environment, rather than constitutively expressed by tumor cells, and is a favorable prognostic factor for HCC. | Xie et al. (2016) |
| CD8+ T cell    | The immune mechanism   | Expression of programmed death 1(PD-1) and programmed death ligand 1(PD-L1) correlated with CD8+ and CD8α+ cell density and clinical outcome. High density of internal and peripheral CD3+ and CD8+ T cells and corresponding immune scores were significantly associated with lower recurrence rates and prolonged RFS. | Gabrielson et al. (2016) |
| CD8+ T cell    | Prognostic marker      | Crosstalk of NK and CD8+ T cells in tumor microenvironment may benefit patient prognosis. The count of NK and CD8+ T cells infiltrating in CRC tumors may provide useful prognostic information | Sconocchia et al. (2014) |
| CD8+ T cell    | immunotherapy          | In the tumor microenvironment of sorafenib treated mice, tumor-specific effector T cells were upregulated, while the ratio of CD8+ T+ cells expressing PD-1 and regulatory T cells (Tregs) was reduced. | Chen et al. (2014) |
| CD8+ T cell    | The immune mechanism   | In HLA-A2 transgenic mice, the CD8+ T cells producing IFN-γ and the cytolytic activity in vivo were significantly increased. | Chen et al. (2012) |
| CD8+ T cell    | The immune mechanism   | As the disease progresses from LC to HCC, the frequency of circulating PD-1 (+) CD8+ T cells increases. Tumor-infiltrating CD8+ T cells showed a dramatic increase in PD-1 expression. In vitro, CD8+ T cells induced PD-1+ expression on HCC cells in an IFN-γ-dependent manner, thereby promoting APOPTOSIS of CD8+ T cells, while blocking PD-L1 reversed this effect. | Shi et al. (2011) |
| CD8+ T cell    | immunotherapy          | Strong TAA-specific CD8+ T cell response inhibited HCC recurrence. For patients with HCC following local therapy, induction of TAA-specific cytotoxic T lymphocytes should be considered with immunotherapy, such as peptide vaccine. | Hiroishi et al. (2010) |
| CD8+ T cell    | Prognostic marker      | Overexpression of HLA-G protein in HCC is an independent indicator of poor prognosis, especially in early disease. The combination of HLA-G expression and Tregs/CD8+ ratio increased the prognostic power of both variables. | Cai et al. (2009) |
| CD8+ T cell    | immunotherapy          | HCA661 peptides H110 and H346 are naturally processed in dendritic cells (DCs) and when applied to DCs, they are sufficient to induce autologous CD8+ T cells to initiate cytotoxic responses against HCA661+ human cancer cells. | Pang et al. (2007) |
| CD8+ T cell    | Prognostic marker      | The combination of low intratumoral Tregs with high intratumoral activated CD8+ cytotoxic cells (CTL) is the balance of CTL and is an independent prognostic factor for improved DFS and OS. | Gao et al. (2007) |
| CD8+ T cell    | Prognostic marker      | Increased CD4 (+) CD25 (+) Foxp3 (+) Treg may impair effector function of CD8+ T cells, promote disease progression, and represent a potential prognostic marker and therapeutic target in HBV-associated HCC patients. | Fu et al. (2007) |
| CD6+ T cell    | immunotherapy          | The functionally detectable presence of M3 (271) specific CD8+ T cells in HCC patients makes M3 (271) a potential target for immunotherapy in these patients. CD8+ T cells that respond to both NY-ESO-1 and MAG-A3 antigens provide a theoretical basis for the use of a bivalent vaccine in HCC patients with tumors expressing both antigens. | Zhang et al. (2007) |

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**Table 1** Prognostic markers and effects of cellular therapy in HCC.

| Cells | The research direction | Result | Reference |
|-------|------------------------|--------|-----------|
| CD8+ T cell | Prognostic marker | HCC patients showed significantly higher WT pS3-specific CD8+ T cell frequency and stronger WT pS3-specific CTL activity compared to healthy controls. Increased frequency and activity of P53 specific CD8+ T cells were associated with deletion of selective HLA-A2 alleles and decreased expression of co-stimulatory molecules in tumor cells. | Cicinnati et al. (2006) |
| CD8+ T cell | The immune mechanism | CD8+ CD25+ T cells in the peripheral region of HCC may play a key role in controlling the activity of CD8+ cytotoxic T cells, thus promoting the development of HCC. | Yang et al. (2006) |
| CD4+ T cell | The immune mechanism | The C/EBPa/miR-7 axis negatively regulates CD4+ T cell activation and function through MAPK4, thus orchestrating experimental AIH mice. | Zhao et al. (2020) |
| CD4+ T cell | The immune mechanism | In vivo treatment with MYC ASO without control ASO reduced proliferation, induced apoptosis, increased senescence, and remodeled the tumor microenvironment by recruiting CD4+ T cells. | Dhanasekaran et al. (2020) |
| CD4+ T cell | The immune mechanism | Tumor associated CD4/CD8 double positive T (DPT) cells were found to be rich in L region, with co-expression of PD-1/HLA-DR/ICOS/CD45RO, and showed high levels of IFN-γ, TNF-α, and -1 after PD stimulation. Enrichment of DPT and PD-1DPT in L region indicated a good prognosis. | Zheng et al. (2020a) |
| CD4+ T cell | The immune mechanism | The recruitment of cytotoxic cells, namely terminally differentiated CD4+ and CD8+ T cells (TEFF), is impaired in the tumor, and the effector memory CD4+ T cells are more attracted in this region. | Chaoul et al. (2020) |
| CD4+ T cell | The immune mechanism | Knockdown of DCRI expression in HCC significantly restored the immunity of CD4+ T cells. Inhibition of DOR3 expression may provide a novel immunotherapy approach to restore immunity in HCC patients. | Zhu et al. (2019) |
| CD4+ T cell | The immune mechanism | Activated CD4+ T cells from HCC stimulate macrophages to produce CX-C motif chemokine 10(CXCL10). CXCL10 binds to the CXC chemokine receptor 3 on B cells and signals them to inhibit the activation of BTLAPD-1 tumor cells. | Wei et al. (2019) |
| CD4+ T cell | The immune mechanism | In a study of mice with liver tumors, CXCR6 was found to mediate the removal of NKT cells and increased senescence, and remodeled the tumor microenvironment by recruiting CD4+ T cells from senescent liver cells. | Mossanen et al. (2019) |
| CD4+ T cell | Immunotherapy | Liver-specific MYC transgenic mice fed the MCD diet were induced. Blockage of CPT with the pharmacological inhibitor perhexiline reduced apoptosis of CD4+ T cells in the liver and inhibited tumor formation in HCC. These results provide useful information for the potential targeting of the CPT family to salvage intrahepatic CD4+ T cells and for immunotherapy to assist NAFLD-promoted HCC. | Brown et al. (2018) |
| CD4+ T cell | Immunotherapy | Tumor-infiltrating Ly6G MDSCs from orthotopic liver tumors treated with sorafenib significantly induced CD4+ T cells expressing IL-10 and TGF-β and down-regulated the cytotoxic activity of CD8 T cells. Antibody against CD274 (PD-ligand 1, PD-L1), TIM3, or LAG3 increases CD8 and CD4 TIL proliferation and cytokine production in response to stimulation by polyclonal antigens or TAA. In vitro treatment with MYC ASO without control ASO reduced proliferation, induced apoptosis, increased senescence, and remodeled the tumor microenvironment by recruiting CD4+ T cells. | Chang et al. (2018) |
| CD4+ T cell | The immune mechanism | In vitro treatment with MYC ASO without control ASO reduced proliferation, induced apoptosis, increased senescence, and remodeled the tumor microenvironment by recruiting CD4+ T cells. CD4+ T cells killed gene-independent CT26 cells and even homologous HEPA1-6 cells. In mice treated with DC/BNL + IL-12, a large number of CD4+ T cells and MHc class II positive macrophages infiltrated the tumor tissue. | Kaikita et al. (2012) |
| CD4+ T cell | Prognostic marker | The high expression of IL-17 and IL-17RE is a promising predictor of poor prognosis in HCC. The precursor capacity of the CD4+ T cells that produce IL-17 may be involved in cross-talk of different types of inflammatory/immune cells than in HCC. | Liao et al. (2013) |
| CD4+ T cell | The immune mechanism | CD25-Foxp3-T cells with a CD127-IL-10 phenotype can be induced in vitro from naive CD4+ T cells involving programmed cell death 1 ligand 1, immunoglobulin-like transcript 4, and human leukocyte antigen G. Tregs significantly increased the inhibition of CD8+ and CD4+ T cell proliferation and cytokine secretion, and increased numbers of circulating CD4+ CD25+ Foxp3+ Tregs and tumor-infiltrating Foxp3+ cells prior to cryoablation were associated with a higher risk of recurrence or progression in HCC patients after cryoablation. | Zhou et al. (2010) |
| CD4+ T cell | Immunotherapy | MDSC exerts its immunosuppressive function by inducing CD4+ CD25+ Foxp3+ regulatory T cells in co-cultured CD4+ T cells. | Hoesch et al. (2008) |
| CD4+ T cell | Immunotherapy | CD4+ T cells killed gene-independent CT26 cells and even homologous HEPA1-6 cells. In mice treated with DC/BNL + IL-12, a large number of CD4+ T cells and MHc class II positive macrophages infiltrated the tumor tissue. | Homma et al. (2005) |

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Schoenberger et al., 1998; Bourgeois et al., 2002; Cheng et al., 2002; Borst et al., 2018). CTL kills target cells through granular exocytosis and apoptotic induction mediated by Fasl ligand (FasL) in working state. CTL can also produce interferon- (IFN-) and tumour necrosis factor (TNF-) to cause cancer cell cytotoxicity (Farhood et al., 2019). Activation and regulation of CTL requires signals from T cell receptors (TCR) and immune checkpoints (Rogler et al., 2019). For example, cancer cells inhibit CTL activity through the expression of a ligand that binds to an inhibitory checkpoint, such as PD-L1 (Iwai et al., 2002). A significant number of studies have established the function of CD8+ T cells and CD4+ T cells in the formation and progression of HCC, including diagnosis/treatment/prognosis, and so on.

Chang et al.'s study confirmed that NanoMnSor improves the effectiveness of anti-PD-1 antibodies and whole-cell cancer vaccine immunotherapy by encouraging macrophage polarization to an immunostimulating M1 phenotype, decreasing hypoxica-induced tumor infiltration of tumor-associated macrophages, and raising the number of CD8 cytotoxic T cells in tumors, thereby reprogramming immunosuppressive TME (Chang et al., 2020). Xie et al.'s research proposed that PD-L1 overexpression is mostly triggered by pre-existing activated CD8+ cytotoxic T cells in the HCC environment, rather than being produced constitutively by tumor cells, and that it is a good prognostic factor for HCC (Xie et al., 2016). The frequency of circulating PD-1+ (+) CD8+ (+) T cells increases as the illness develops from LC to HCC. PD-1 expression was shown to be much higher in tumor-infiltrating CD8+ (+) T cells. In vitro, CD8+ (+) T cells promoted the production of PD-L1 on HCC cells in an IFN-dependent way, increasing CD8+ (+) T cell death, whereas inhibiting PD-L1 reversed this effect (Shi et al., 2011).

Both in vitro restimulation and in vivo depletion studies have indicated that CD4+ and CD8+ lymphocytes contribute to anticancer activity. ASPH activation resulted in considerable production of antigen-specific CD4+ T cells in PBMC from healthy volunteers and HCC patients (Shimoda et al., 2012). Lack of recovered CD19+, CD3+, CD4+, and especially CD8+ T cells is associated with poor survival in patients (Carr and Metes, 2012). Zhou et al.'s study revealed that antibodies against CD274 (PD-L1), LAG3, or TIM3 boost CD4+ and CD8+ T cell proliferation and cytokine secretion in response to polyclonal antigens or TAA stimulation (Zhou et al., 2017). More research results on the effect of Effector T cells in HCC are summarized in Table 1. It is clear that Effector T cells play a critical role in the immunological milieu of HCC. Many studies have shown that targeting these cells is effective in patients with HCC.

**NK Cells**

NK cells are an essential anti-tumor immune cell that primarily mediates immune surveillance of malignancies. It performs a similar function as CD8+ T cells: NK cells regulate the killing response of tumor cells by releasing perforin and granulein, triggering apoptosis in target cells. In addition, to improve their anticancer activity, NK cells can produce proinflammatory cytokines and chemokines (Voštoboinik et al., 2006; Guillerey et al., 2016; Habif et al., 2019). Existing studies have confirmed the value of NK cells in the development, targeted therapy, prognosis of HCC. Sprinzl et al.'s research confirmed that Sorafenib can promote the pro-inflammatory response of tumor-associated macrophages in HCC, and then activate the anti-tumor NK cell response through the cytokine and NF-κB pathway (Sprinzl et al., 2013). Senescence monitoring necessitates the recruitment and maturation of CCR2 myeloid cells, and CCR2 deficiency promotes HCC growth. Conversely, HCC cells suppress the maturation of recruited myeloid progenitors, which promotes mice HCC growth and worsens prognosis and survival in human HCC patients via NK cell inhibition (Egger et al., 2016). Kohga et al. ’s revealed that natural killer (NK) cells had stronger cytolytic activity on ADAM9KD-HCC cells than on control cells, and that this cytotoxicity is enhanced by the MICA/B and NK group 2, D pathways. Sorafenib treatment resulted in a decrease in ADAM9 expression in HCC cells, an increase in membrane-bound MICA expression, and a decrease in the quantity of soluble MICA. Sorafenib increased HCC cell NK sensitivity by boosting the expression of membrane-bound MICA (Kohga et al., 2010a). Table 2 summarizes current research on NK cells in HCC, confirming the importance of NK cells in immune escape and anti-HCC therapy.

**Dendritic cells**

DC cells, as specialized antigen-presenting cells in the human body, can present antigens to T cells and produce costimulatory signals for T cell activation. According to the current study, mature DC cells can penetrate tumor cells and limit tumor incidence and progression. Under many severe conditions, this inhibition effect will be avoided by tumors through certain means. Therefore, targeting at DC cells, some studies have reported its role in the occurrence, development, immunotherapy, diagnosis and prognosis of HCC. For
TABLE 2 | The immune cells in TME: NK cells.

| Cells          | The research direction | Result                                                                                       | Reference                        |
|----------------|------------------------|---------------------------------------------------------------------------------------------|-----------------------------------|
| NK cells       | immuno+therapy         | Sorafenib can promote the pro-inflammatory response of tumor-associated macrophages in HCC, and then activate the anti-tumor NK cell response through the cytokine and NF-κB pathway. | Sprinzl et al. (2013)             |
| NK cells       | The immune mechanism   | NK cell activator Poly (I:C) promotes HCC in Hbs-Tg mice. Poly (I:C) induces liver inflammation and liver cell damage in Hbs-Tg mice. The increase of hepatocyte EMT depends on the presence of NK cells in Hbs-Tg mice. IFN-γ derived from NK cells plays a key role in the development of HCC in Hbs-Tg mice. | Chen et al. (2019)                |
| NK cells       | The immune mechanism   | The phenotype of peripheral blood NK cells was biased towards the defect/fatigue immune pattern, and the frequency of cells expressing Nkp30 and member D of natural killer group 2 decreased, and the proportion of cells expressing T cell immunoglobulin and mucin domain increased. In addition, nkp30-positive NK cells have reduced expression of NCR3 immunostimulated splicing variants and increased expression of inhibitory variants, leading to NKP30-mediated loss of function in patients with advanced tumors. | Mantovani et al. (2019)           |
| NK cells       | Prognostic marker      | Blocking the CD96 CD155 interaction restores NK cell immunoreactivity to tumor by reversing NK cell depletion or TGF-β1 reversing NK cell depletion, suggesting that CD96 may have a therapeutic role in HCC. | Sun et al. (2019a)                |
| NK cells       | The immune mechanism   | The cytotoxicity of NK cells in patients with HCC is reduced. MDSCs inhibit NK cell cytotoxicity and IFN-γ release. MDSCs inhibit NK cells depending on cell contact. MDSCs inhibit NK cells for a long time. MDSCs use Nkp30 receptor to inhibit NK cell function. | Hage et al. (2019)               |
| NK cells       | The immune mechanism   | Leptin can significantly inhibit human HCC. This effect is mediated by inducing the proliferation and activation of natural killer cells and directly inhibiting tumor growth. The decreased NK expression of inhibitory CIS and the overexpression of anti-proliferative STAT2 and SOCS1 proteins in HCC lines may emphasize the anticancer effect of leptin. | Qin et al. (2020)                |
| NK cells       | The immune mechanism   | Smoking is associated with a decrease in the frequency of natural killer (NK) cells in the peripheral blood, which is characterized by a reduction in NK function through systemic immunology. The combination of smoking and lowering the frequency of NK cells further increases the likelihood of viral load and ALT ≥ 80 U/L. | Wang et al. (2019b)              |
| NK cells       | The immune mechanism   | NKT and CD4+ T cells promote the elimination of senescent liver cells to prevent the occurrence of HCC, and this process requires CXCR6. CXCR6 inhibits the occurrence of HCC by promoting natural killer T and CD4+ T cell-dependent senescence control. | Mossansen et al. (2019)           |
| NK cells       | The immune mechanism   | Using CAR transduced T cells and NK cells that recognize the surface marker CD147 (also known as Basigin), various malignant HCC cell lines were effectively killed in vitro, as well as HCC tumors in transplanted and patient-derived mouse models of transplanted tumors. | Tseng et al. (2020)               |
| NK cells       | The immune mechanism   | The liver gene delivery of high IL-15 makes CD8 T cells and NK cells proliferate in large quantities, resulting in the accumulation of CD8 T cells in the body (over 40 days), especially in the liver. Hyper-IL-15 therapy has significant therapeutic effects on established liver metastases and even autologous HCC induced by DEN. These effects can be depleted by CD8 T cells instead of NK cells. | Cheng et al. (2014)               |
| NK cells       | The immune mechanism   | The cytolytic activity of natural killer (NK) cells on ADAM9KD-HCC cells is higher than that on control cells, and the enhancement of this cytolytic activity depends on the MICA/B and Nkp30, and the metabolic pathways. Sorafenib treatment resulted in a decrease in the expression of ADAM9 in HCC cells, an increase in the expression of membrane-bound MICA and a decrease in the level of soluble MICA. The addition of sorafenib enhanced the NK sensitivity of HCC cells by increasing the expression of membrane-bound MICA. | Kohga et al. (2010a)              |
| NK cells       | The immune mechanism   | ADAM9 protease plays a key role in the shedding of MHC class I related chain A (MICA) which regulates the sensitivity of tumor cells to natural killer cells (NK). The expression of ADAM9 in CD313si-PLC/PRF/5 cells and CD133si-Huh7 cells decreased, membrane-bound MICA increased, and soluble MICA production decreased. CD313si-PLC/PRF/5 cells and CD133si-Huh7 cells are both sensitive to NK activity, which depends on the expression level of membrane-bound MICA, while HCC cells expressing CD133 are not. | Kohga et al. (2010b)              |
| NK cells       | The immune mechanism   | CD8 T cells and NKT cells promote NASH and HCC by interacting with hepatocytes, but not myeloid cells. NKT cells mainly cause steatosis by secreting light, and CD8 T cells and NKT cells synergistically induce | Wolf et al. (2014)                |

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example, In mice, combining DC vaccination and PD-L1 inhibitor treatment can result in longer overall life, reduced tumor volume, and increased tumor cell apoptosis. As a new therapy method for HCC, combined treatment with DC vaccination and PD-L1 inhibitor may offer promising results (Teng et al., 2020). Ali et al. ’s research clarified that the combination of PEI or RFTA with active antigen-specific immunotherapy using DCS is a promising approach to induce a sustained anti-tumor immune response aimed at reducing tumor recurrence and metastasis in patients with HCC. Table 3 summarizes the current role of DC cells in HCC.

M1-Polarized Macrophages

Another important type of immune cell in TME is macrophages derived from circulating monocytes, which can generally be divided into M2 polarization and M1 polarization (Figure 2). M1-polarized macrophages, for example, can create pro-inflammatory cytokines and reactive oxygen species/nitrogen to prevent the formation and progression of malignancies (Aras and Zaidi, 2017). There are limited investigations on the function of M1-polarized macrophages in HCC at the moment. Studies have shown that M1-polarized macrophages in the S3 subclass in HCC increased, and the prognosis was good. Memory B cells, Total B cells, M1 macrophages and T follicle helper cells, were linked with strong total immune cell infiltration into HCC, whereas resting mast cells, neutrophils, and NK cells were associated with poor infiltration (Rohr-Udilova et al., 2018). Table 4 summarizes the current role of M1-polarized macrophages in HCC.

| Cells         | The research direction | Result                                                                                     | Reference                        |
|---------------|------------------------|--------------------------------------------------------------------------------------------|----------------------------------|
| NK cells      | The immune mechanism   | liver damage. Hepatocyte LTβR and typical NF-κB signals promote the transformation of NASH to HCC, indicating that different molecular mechanisms determine the development of NASH and HCC. | Lim et al. (2019)                |
| NK cells      | The immune mechanism   | In-depth studies of the immune landscape show that regulatory T cells(T) and CD6 resident memory T cells(T) are enriched in hcv-related HCC, while Tim-3CD8 T cells and CD244 natural killer cells are in non-virus-related HCC in the enrichment. | Eggert et al. (2016)             |
| NK cells      | The immune mechanism   | Senescence monitoring requires the recruitment and maturation of CCR2 bone marrow cells, while CCR2 ablation induces HCC growth. In contrast, HCC cells inhibit the maturation of recruited myeloid precursors, which promote mouse HCC growth and deteriorate the prognosis and survival of human HCC patients by inhibiting NK cells. | Chen et al. (2010)               |
| NK cells      | The immune mechanism   | β-glucosylceramide alleviates immunologically incongruent disease by altering the plasticity of NKT cells. Inhibitors of β-glucosylceramide activate NKT cells and promote the recruitment of NKT cells. | Zigmund et al. (2007)            |
| NK cells      | The immune mechanism   | Proliferating immune cells, mainly NK cells and T cells, were present in the patient’s long-lived tumor and consisted only of tumor cells lacking proliferation in the region. The density of NK cells and CD8+ T cells was positively correlated with tumor cell apoptosis and negative proliferation. | Schmitz et al. (2001)            |
| NK cells      | The immune mechanism   | GS-9620 treatment is associated with a reversible increase in serum liver enzymes and thrombocytopenia, and induction of intrahepatic CD8+ T cells, NK cells, B cells, and interferon response transcriptional signaling. | Schmitz et al. (2001)            |
| NK cells      | The immune mechanism   | Fibrosis is a way to enhance the occurrence of HCC. Changes in fibrosis also regulate the activity of inflammatory cells in the liver and reduce natural killing, which is generally helpful for tumors to monitor the activity of natural killer T cells. These pathways work in conjunction with inflammatory signals, including telomerase activation and the release of reactive oxygen species, ultimately leading to cancer. | Zhang and Friedman, (2012)       |
| NK cells      | The immune mechanism   | AdCMVMCD40I therapy can induce strong lymphocyte infiltration in tumor tissues and increase the apoptosis of malignant cells. The observed anti-tumor effect is mediated by CD6+ T cells and is related to increased serum levels of interleukin (IL)-12 and enhanced natural killer (NK) activity. | Barajas et al. (2001)            |
| NK cells      | The immune mechanism   | The activation of β-catenin in hepatocytes can change the liver microenvironment and lead to the specific targeting of iNKT cells. The activation of β-catenin in hepatocytes triggers the pro-inflammatory process related to the activation of NF-κB. In the process of liver inflammation induced by β-catenin, iNKT cells showed anti-inflammatory properties. In HCC induced by β-catenin, iNKTs and LECT2 are the key cellular and molecular effectors to control tumor progression. | Barajas et al. (2001)            |
| NK cells      | The immune mechanism   | AdCMVMIL-12 can activate natural killer cells (NK) and inhibit angiogenesis. | Barajas et al. (2001)            |
| NK cells      | The immune mechanism   | Gene transfer of angiostatin inhibited tumor angiogenesis and enhanced NK cell infiltration, while B7H3 therapy activated CD6+ and NK cells and increased their infiltration into the tumor, and enhanced circulating IFN-γ levels. | Schmitz et al. (2001)            |

TUMOR-PROMOTING IMMUNE CELLS

In the immune microenvironment of HCC, some cells could promote the occurrence and development of HCC, and we will review them one by one.

Regulatory T cells(Tregs)

Tregs play a vital role in immunological homeostasis and immune self-tolerance, and they can express the CD4+ marker and the Foxp3 marker (Samstein et al., 2012). Foxp3+ Treg acts as a switch for all levels of immune response, and its effects appear to be two-sided. First, Treg can inhibit harmful immune responses and thus inhibit the occurrence of autoimmune diseases (Berod...
### Table 3: The immune cells in TME: Dendritic cells.

| Cells                      | The research direction | Result                                                                 | Reference                        |
|----------------------------|------------------------|------------------------------------------------------------------------|----------------------------------|
| Dendritic cells            | Immunotherapy          | The combination of DC vaccine and PD-L1 inhibitor resulted in longer overall survival, smaller tumor size, and higher tumor cell apoptosis rate in mice. The combination of DC vaccine and PD-L1 inhibitor may have broad prospects as a new therapeutic strategy for HCC. | Teng et al. (2020)               |
| Dendritic cells            | The immune mechanism   | XCL1-GPC3 cells chemically attract murine CD11c+ dendritic cells (DCs) and human CD11c+ DCs, and promote their IL-12 production. | Chen et al. (2020)               |
| Dendritic cells            | The immune mechanism   | A more severe reduction in basal OCR was observed in tumor-derived DCs exposed to AFP due to down-regulation of cytochrome C oxidase. The expression of PSC1-α in circulating medullary DC in HCC patients was decreased, and the ability to stimulate the function of antigen-specific effector was impaired, indicating the negative effect of AFP on DC metabolism. | Santos et al. (2019)             |
| Dendritic cells            | The immune mechanism   | The use of nifurazine and DC-loaded TCL significantly increased the survival rate, inhibited tumor growth and promoted anti-tumor immune response in HCC mice implanted in situ. | Hu et al. (2017)                 |
| Dendritic cells            | Immunotherapy          | Overexpression of IL-12 induced by adenovirus vector can effectively immunize DC. Intratumor but not systemic injection of activated IL-12-DC is essential for effective tumor regression. Improved immunotherapy with IL-12-DC represents a promising approach for the treatment of HCC. | Vogt et al. (2014)               |
| Dendritic cells            | Immunotherapy          | β-2G activated mouse liver NKT cells and enhanced the anti-tumor activity of PAD-HBsAg-DC. β-2G may act as an effective innate immune enhancer to enhance the antitumor effect of PAD-HBsAg-DC vaccine. | Long et al. (2013)               |
| Dendritic cells            | Immunotherapy          | Camroy may play an important role in the development and progression of HCC through recruitment of DC and NK cells. | Lin et al. (2011)                |
| Dendritic cells            | The immune mechanism   | Electroportation of GPC-3 mRNA is an effective method for antigen-carrying monocytes to generate DCs because they produce functional GPC-3 reactive T cells in vitro. | O’Beirne et al. (2010)           |
| Dendritic cells            | The immune mechanism   | Immature DCs(MDCs) derived from human monocytes were fully mature after effective phagocytosis of dying cells, and showed significant proliferation and cytotoxicity to HLA-matched HEPG (2) cells in autologous peripheral blood monocyte (PBMC). | Xing et al. (2009)               |
| Dendritic cells            | The immune mechanism   | Secondary lymphoid tissue chemokines (SLC) are strongly expressed in secondary lymphoid organs. It has the ability to promote dendritic cell (DC) and T cell chemotaxis, making it a promising candidate for cancer therapy. | Lian et al. (2007)               |
| Dendritic cells            | Immunotherapy          | Ad5/HAVF- transduced DCs activate high frequencies of Th1 CD4 responses to AFP in healthy donors and AFP positive HCC patients. Importantly, when activated by adenovirus-engineered DC, the cytokine expression profile of CD4+ T cells was biased towards the production of interleukin-2 and interferon-γ, which has therapeutic implications for vaccination work. | Emodikomova et al. (2007)        |
| Dendritic cells            | Immunotherapy          | Dendritic cells transfected with total HCC mRNA stimulated an antigen-specific cytotoxic T cell response capable of recognizing and killing autologous tumor cells in vitro. | Peng et al. (2006)               |
| Dendritic cells            | The immune mechanism   | Impairment of MDCs produced by IL-12 may result in impaired stimulation of naive T cells, suggesting that targeted IL-12 therapy may enhance tumor-specific immune responses in patients with HCC. | Ormandy et al. (2006)            |
| Dendritic cells            | Immunotherapy          | The combination of PEI or RFTA with active antigen-specific immunotherapy using DCs is a promising approach to induce a sustained anti-tumor immune response aimed at reducing tumor recurrence and metastasis in patients with HCC. | Ali et al. (2005)                |
| Dendritic cells            | The immune mechanism   | The phenotypic and functional deficits of PBMC-derived DCs in LC and HCC patients may play a key role in HBV infection and HCC immune escape. After tumor is stimulated by antigen, DC function can be enhanced in LC patients. | Wong et al. (2005)               |
| Dendritic cells            | Immunotherapy          | Ad5-HBsAg-transduced DCs stimulated a strong cytotoxic T lymphocyte (CTL) response to HBsAg-expressing tumor cells and protected mice from lethal tumor attack. | Ritter et al. (2004)             |
| Dendritic cells            | The immune mechanism   | At concentrations up to 20 μg/mL, AFP did not alter the in vitro generation, maturation and T cell stimulation of DC. Higher AFP concentration (>20 μg/mL) led to phenotypic changes in DC without impairing its ability to stimulate CD4+ T cells. Independent of serum AFP levels, the frequency and function of DC and AFP-specific T cells did not decrease in HCC patients. | Liu et al. (2001)                |
| Dendritic cells            | Immunotherapy          | Autologous DCs containing the HCA587 protein can induce specific T cell responses in healthy individuals by in vitro stimulation, and HCA587 is a good candidate for the development of a protein-based therapeutic DC tumor vaccine for the treatment of HCC patients. | Li et al. (2004)                 |
| Dendritic cells            | Immunotherapy          | DCs transfected with Mage-1 gene can induce higher cytotoxicity of SMMC7721 in vitro, suggesting that this transgenic DC may have the potential to induce specific antitumor activity and be used as a novel HCC vaccine. | Liu et al. (2001)                |
| Dendritic cells            | The immune mechanism   | Decline in DC function and normal T cell response were observed in HBV-infected HCC patients, suggesting that the low function of DC is related to the pathogenesis of HBV or HCV-infected HCC. | Kakumu et al. (2000)             |
et al., 2012). Second, Treg suppresses protective immune responses against invading pathogens or tumors, leading to further progression of the disease (Sakaguchi et al., 2010). How does Treg play a role in tumors, including how does Treg infiltrate and metastasize to tumor sites or how does Treg help tumors evade immune monitoring, has become a hot research topic in recent years. Many ideas have been put forward. Tregs were found in much higher numbers in HCC patients than in healthy controls. In addition, patients with high Treg(III) levels after TACE had a significantly lower progression-free survival than patients with low Treg(III) levels after TACE (Park et al., 2020). Other studies have shown that tumor Treg upregulated the expression of the glucocorticoid-induced tumor necrosis factor receptor (GITR). Treatment with soluble GITR ligand (GITRL) reduced inhibition caused by activated tumor infiltrating Treg and restored CD4+ CD25-T cell proliferation and cytokine production. (Pedroza-Gonzalez et al., 2013). In addition to that, the proportion of Tregs cells in HCC patients was significantly higher than in healthy and cirrhosis controls, and was related to various clinical indicators of HCC patients. In HCC patients with BCLC stage C, the proportion of Treg cells was more pronounced than in BCLC stage B patients. One to 2 weeks after surgery, the fraction of Treg cells was much lower than before GSMS-TACE. Three to 5 weeks following surgery, the proportion of Treg cells continued to decline (Ren et al., 2021).

Table 5 summarizes the most credible studies related to the role of Treg in HCC.

Myeloid-Derived Suppressor cells
MDSC is thought to be a cancer-promoting immune cell in the HCC tumor microenvironment and was discovered a decade ago (Gabrilovich et al., 2007). MDSC is divided into granulocyte or multinuclear MDSC(PMN MDSC) and mononuclear MDSC(M-MDSC) (Veglia et al., 2018). MDSCs enhance angiogenesis by producing vascular endothelial growth factor (VEGF), actuator 2 and MMP9. They can also cause cancer cells to migrate to endothelial cells and encourage metastasis (Zhou et al., 2018a). MDSC also suppresses T cell activity by secreting immunosuppressive cytokines, inducible nitric oxide synthase, and argininase (Gabrilovich et al., 2012; Gabrilovich, 2017). MDSCs can have a dual influence on immune cells via distinct methods. B cells, T cells, DCs and NK cells, are all inhibited by

![FIGURE 2] M1/M2 model of macrophage activation. M1 cells exert an inflammatory phenotype and are involved in killing bacteria, viruses and tumor cells, while M2 cells are involved in killing encapsulated parasites, immunosuppression, angiogenesis, etc.

| Cells                      | The research direction | Result                                                                 | Reference                          |
|----------------------------|------------------------|------------------------------------------------------------------------|-------------------------------------|
| M1-polarized macrophages   | The immune mechanism   | The number of M1-polarized macrophages in the S3 subclass in HCC was increased, and the prognosis was good. Strong total immune cell infiltration into HCC was associated with total B cells, memory B cells, T follicle helper cells, and M1 macrophages, while weak infiltration was associated with resting NK cells, neutrophils, and resting mast cells. | Rohr-Udilova et al. (2018)          |
| M1-polarized macrophages   | The immune mechanism   | Conditionalized media from M1 macrophages promoted HCC cell migration and induced activation of NF-κB and FAK signal transduction. Activation of Bay 11-7,802 and NF-κB and FAK pathways eliminated HCC cell induced migration, suggesting that M1-like TAM has a metastatic role in HCC. | Wang et al. (2014)                  |
TABLE 5 | Tumor-promoting immune cells: Regulatory T cells.

| Cells       | The research direction | Result                                                                 | Reference                  |
|-------------|------------------------|------------------------------------------------------------------------|----------------------------|
| Treg        | immunotherapy          | The proportion of Treg cells in BCLC stage C HCC patients was higher than that in BCLC Stage B patients, and the proportion of Treg cells was significantly lower than that before GMS-TACE 1–2 weeks after surgery. The percentage of Treg cells continued to decrease 3–5 weeks after surgery. Tumor progression is associated with the deep depletion of tumor antigen-specific CD8 T cells and the accumulation of PD-1 CD8 T cells and Treg cells. | Ren et al. (2021)          |
| Treg        | The immune mechanism   | At a non-cytotoxic concentration, resveratrol inhibited differentiation of CD8CD122 Treg from CD8CD122 T cells. | Tipton et al. (2011)       |
| Treg        | The immune mechanism   | The baseline reduction in the number of FOXP3 Tregs, MDSCs, and exhausted T cells was significantly greater after tivozanib treatment. In addition, a larger increase in CD4 T cells: Treg ratio after tivozanib treatment compared with sorafenib was associated with a significant improvement in OS. | Zhang et al. (2020)        |
| Treg        | The immune mechanism   | Lower CD8 T cell density and higher Foxp3 Tregs and immune checkpoint strength in intrahepatic cholangiocarcinoma (ICC) components compared to HCC components may indicate a stronger immune escape capability of ICC. | Li et al. (2020a)          |
| Treg        | Prognostic marker      | The frequency of Tregs was significantly higher in HCC patients than in healthy controls. In addition, patients with high Treg (III) after TACE had a significantly reduced progression-free survival compared to patients with low Treg (II) after TACE. | Park et al. (2020)         |
| Treg        | The immune mechanism   | Regulatory CD4/CD25/Foxp3 T cells (Tregs) were activated by transcriptional reprogramming of HCC parent cells in Macroph2A1 KD conditioned medium. Loss of Macroph2A1 in HCC cells drives proliferation and avoidance of immune surveillance by cancer stem cells. | Lo Re et al. (2020)        |
| Treg        | The immune mechanism   | Treg-induced inhibition of IFN-γ secretion is partially prevented by neutralizing PD-1 and PD-L1 antibodies in HCC patients. In HCC, peripheral Tregs upregulate checkpoint inhibitors and promote systemic immune dysfunction and antitumor activity through several inhibitory pathways, presumably contributing to the development of tumors at a young age. | Langhans et al. (2019)     |
| Treg        | Prognostic marker      | Patients with an increased T-effector/Treg ratio before treatment showed significant improvement in OS. Overexpression of IncRNA FENDRR and down-regulated miR-423-5p reduced cell proliferation and tumorigenicity, and promoted apoptosis of HCC cells, thereby regulating Treg-mediated immune escape of HCC. | Kalathil et al. (2019)     |
| Treg        | The immune mechanism   | The hypoxic environment induces tumor immunosuppression by attracting TREM-1 TAMs of CCR6. Foxp3 Treg, and TREM-1 TAMs make HCC resistant to PD-L1 therapy | Wu et al. (2019a)          |
| Treg        | The immune mechanism   | After sorafenib alone and in combination, plasma Smet was elevated and TTP and OS shortening were associated with increased Tregs and CD86 natural killer (NK) cells. | Goyal et al. (2019)        |
| Treg        | immunotherapy          | Sunitinib treatment induces an anti-tumor immune response by significantly reducing Treg frequency, TGF-β and IL-10 production by Treg, and protecting TAC CD8 T cells from HCC infection. | Liu et al. (2017)          |
| Treg        | The immune mechanism   | Newly produced STAT3-blocked whole-cell HCC vaccines reduced production of Treg as well as production of TGF-β and IL-10. | Han et al. (2017)          |
| Treg        | The immune mechanism   | LNC-EGFR specifically binds to EGFR and prevents its interaction with c-erbB, which inhibits the expression of c-met and is ubiquitinated by c-CBL, which stabilizes and enhances the activation of its own and its downstream AP-1/MAPK axis, thus causing EGFR expression. LNC-EGFR has been associated with immunosuppressive status and cancer by promoting Treg cell differentiation. | Jiang et al. (2017b)       |
| Treg        | The immune mechanism   | Overexpression and activation of YAP-1 in HCC T cells can promote differentiation of Treg through enhanced transcription of TGFβR2, thereby inducing immunosuppression. | Fan et al. (2017)          |
| Treg        | Prognostic marker      | CXCL10/CXCR3 signals were upregulated after liver graft injury, directly inducing the mobilization and recruitment of Tregs during transplantation, and further promoting the recurrence of HCC after transplantation. | Li et al. (2016)           |
| Treg        | The immune mechanism   | After treatment with sorafenib, the ratio of CD4CD127PD-1 T effector cells to CD4Foxp3PD-1 Treg was significantly increased. The increased frequency of CD4CD127 T effector cells in posttreated samples was significantly correlated with OS. | Kalathil et al. (2016)     |
| Treg        | immunotherapy          | Sunitinib-mediated tumoricidal effect, Treg inhibition and antibody-mediated PD-1 blocking synergistic effect can effectively inhibit tumor growth and activate anti-tumor immunity. | Li et al. (2017)           |
| Treg        | The immune mechanism   | The secretion of cancerous TGF-β may increase Tregs, while TGF-β1 knockdown may impair immunosuppression in the tumor microenvironment by decreasing Tregs. | Wang et al. (2016)         |
| Treg        | The immune mechanism   | Intra-tumor combination of SLC and anti-CD25 mAb is an effective method for the treatment of HCC, which is related to the change of tumor microenvironment and the systemic optimization percentage of Treg, CD8 T cells and CD4 T cells in peripheral immune organs. | Chen et al. (2013)         |
| Treg        | immunotherapy          | Sorafenib treatment can reduce the number of Treg by inhibiting the proliferation of Treg and inducing its apoptosis. In addition, sorafenib inhibits the function of Tregs, characterized by reduced expression of functionally important Treg-related molecules and impaired inhibition. Sorafenib treatment alleviated non-cellular autonomous inhibition of the tumor microenvironment mediated by Treg, leading to an effective anti-tumor immune response. | Chen et al. (2014)         |
| Treg        | immunotherapy          | The subpharmacological doses of sorafenib had different effects on T cell subsets, selectively increasing T eff cell activation while blocking Treg function. | Cabrera et al. (2013)      |

(Continued on following page)
MDSCs. MDSCs, on the other hand, can stimulate Th17 cells, Tregs, and TAMs, as well as tumor angiogenesis and metastasis (Figure 3). There has been a great deal of research on the processes through which MDSC supports the advancement of HCC, and many therapeutic pathways have been developed for MDSC as a target of HCC. For example, myeloid-derived suppressor cells (MDSCs) are drawn to the tumor microenvironment by PIWIL1-overexpressed HCC cells. MDSCs consumption reduced the proliferation and growth of PIWIL1-overexpressed HCC tumors. Complement C3 stimulates HCC cell secretion via PIWIL1 and mediates the contact between HCC cells and MDSC via p38 MAPK activation in MD38, and then

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**TABLE 5** (Continued): Tumor-promoting immune cells: Regulatory T cells.

| Cells | The research direction | Result | Reference |
|-------|------------------------|--------|-----------|
| Treg  | The immune mechanism   | Tumor Treg upregulated glucocorticoid-induced tumor necrosis factor receptor (GITR) expression. Treatment with soluble GITR ligand (GITRL) induced a reduction of inhibition mediated by activated tumor infiltrating Treg and restored the proliferation and cytokine production of CD4⁺ CD25⁻ T cells. | Pedroza-Gonzalez et al. (2013) |
| Treg  | The prognosis          | Elevated FOXP3 (+) Tregs may represent a prognostic marker in patients with early HCC. The natural history of CHB influences the density of tumor infiltrate Treg in patients with chronic hepatitis B virus infection. | Wang et al. (2012) |
| Treg  | The immune mechanism   | The increased frequency of CD45Ro⁺ subsets in CD4⁺ CD25(HIGH) Tregs in HCC patients may cooperate with the establishment of an immunosuppressive environment that induces tolerance of plasmocyte like DCs, thereby promoting the development of HCC. | Takata et al. (2011) |
| Treg  | The immune mechanism   | The tumor-associated MVARPHI may trigger an increase in the number of Foxp3 (+) Treg populations in tumors, thereby promoting the development of HCC. | Zhou et al. (2009) |

**Figure 3** The mechanism of MDSC-mediated immunosuppression. MDSC inhibits the functions of DC, T cells, B cells and NK cells by secreting various cytokines, while promoting the functions of Th17, Treg, TAMs cells, and can promote angiogenesis and metastasis.
| Cells         | The research direction | Result                                                                 | References |
|--------------|------------------------|------------------------------------------------------------------------|------------|
| MDSCs        | The immune mechanism   | The heterozygous loss of SPTBN1 significantly upregulated the liver expressions of IL-1α, IL-1β, and IL-6, and increased the proportion of myeloid inhibitory cells (MDSCs) and CD4CD25Foxp3 regulatory T cells (Foxp3Treg) in liver, which promoted the occurrence of HCC in DDC-fed mice. | Lin et al. (2021) |
| MDSCs        | The immune mechanism   | MDSCs contribute to tumor progression under psychological stress, chronic binding stress significantly promotes the growth of HCC, and MDSCs are mobilized from bone marrow to spleen and tumor sites. Also, the β-adrenergic signaling cascade plays a key role in the mobilization and recruitment of MDSC under chronic confinement stress. | Cao et al. (2021) |
| MDSCs        | Immunotherapy          | Icaritin blocks MDSC production by blocking the attenuation of EMH, thereby inhibiting the immunosuppressive effect of the tumor, thereby triggering an anti-tumor immune response. Therefore, Icaritin can be used as a new adjuvant or even an independent therapeutic agent for the effective treatment of HCC. | Tao et al. (2021) |
| MDSCs        | Immunotherapy          | PIWIL1 overexpressed HCC cells attract myeloid suppressor cells (MDSCs) to the tumor microenvironment. MDSCs consumption reduced the proliferation and growth of HCC tumors overexpressed by PIWIL1. Complement C3 induces the secretion of HCC cells through PIWIL1, mediates the interaction between HCC cells and MDSC by activating the T9P8 MAPK signal in MD38, and then initiates the expression of the immunosuppressive cytokine IL10. | Wang et al. (2021a) |
| MDSCs        | Immunotherapy          | After tivozanib treatment, the baseline number or frequency of FOXP3treg, MDSC, and exhausted T cells decreased significantly more. This may help identify patients who may benefit from c-kit/SCF antagonism and provide guidance for improving the efficacy of tivozanib in combination with immunotherapy. | Kalathil et al. (2020) |
| MDSCs        | The immune mechanism   | CD8+ T cells, MDSCs, and M2 macrophages were particularly increased in the tumorigenic liver of NCOA 5 + male mice, NCOA5 deficiency promotes a unique hepatic tumorigenic microenvironment through p21WAF1/CDP1 overexpression, which metformin reverses. | Williams et al. (2020) |
| MDSCs        | Immunotherapy/The immune mechanism | HSC promoted migration of MDSC through the SDF-1/CXCR4 axis. Pretreatment of MDSC with CXCR4 inhibitors or injection of SDF-1 knockout HSC inhibited migration of MDSC to the spleen and liver of tumor-bearing mice. | Xu et al. (2019) |
| MDSCs        | Prognostic marker      | Patients with an increased T-effector/Treg ratio before treatment showed significant improvement in OS. ERK + FLT-3+ Treg and MDSCs were significantly reduced after sorafenib treatment. An increase in baseline Flt-3+ p-ERK + MDSC was associated with a patient survival benefit. Conclusion High baseline CD4+ T effector/Treg ratio may be an important biomarker for prognosis in HCC. | Kalathil et al. (2019) |
| MDSCs        | Immunotherapy          | CCR2 antagonists inhibited the infiltration of TAM and MDSC and delayed tumor growth in tumors of mice expressing Aibb and Aibb. Mechanically, upregulation of Aibb in HCC inhibits the global abundance of H3K27me3 and reduces the presence of H3K27me3 on the chemokine Ccl2 promoter by interacting with the multicomb repressor complex 2(PRC2), thus recruiting large amounts of TAM and MDSC. | Wang et al. (2019c) |
| MDSCs        | Immunotherapy          | Activated HSC induces mononuclear intrinsic p38 MAPK signaling, which triggers enhancer reprogramming for M-MDSC development and immunosuppression. Treatment with p38 MAPK inhibitors eliminated HSC-M-MDSC crosstalk to prevent HCC growth. Combined with l-BET 762 suppressed patient-derived M-MDSC, combined with anti-PD-L1 therapy synergically enhanced TIL, resulting in tumor eradication and prolonged survival in a fibrotic HCC mouse model. | Liu et al. (2020b) |
| MDSCs        | The immune mechanism   | RIP3 knockdown results in an increase in MDSCs and a decrease in interferon-α (IFN-α) positivity of tumor-infiltrating lymphocytes (CD8) differentiated into 8 positive (CD8) cells in HCC tissue, thus promoting immune escape and HCC growth in immunologically competent mice. | Li et al. (2019b) |
| MDSCs        | The immune mechanism   | By down-regulating the expression of IDO1, the HS donor induced T effector cells and inhibited MDSCs, and effectively restricted the tumor development of H22 HCC tumor-bearing mice. | Yang et al. (2019c) |
| MDSCs        | The immune mechanism   | March-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAM) from the tumor microenvironment contribute to the suppression of the CD8 T cell response. | Liu et al. (2018a) |
| MDSCs        | Immunotherapy          | Adoptive transfer of CIK to tumor-bearing mice induced an increase in inflammatory mediators (e.g., CX3CL1, IL-13) and tumor-infiltrating MDSC in the tumor microenvironment, and MDSCs effectively inhibited the cytotoxic activity of CIKs in vitro. In contrast, treatment with PDES inhibitors reversed MDSC inhibition by Ang1 and NOx, while systemic treatment with PDES inhibitors prevented MDSC accumulation in the tumor microenvironment after CIK cell treatment and increased its anti-tumor efficacy. | Yu et al. (2019b) |
| MDSCs        | The immune mechanism   | RTIL-12 significantly reduced the accumulation of tumor-infiltrating myeloid suppressor cells (MDSC) and its inhibitory function by reducing the production of reactive oxygen species | Wu et al. (2018) |
| MDSCs        | Immunotherapy          | Tumor-infiltrating Ly6G MDSCs from orthotopic liver tumors treated with sorafenib significantly induced CD4+ T cells expressing IL-10 and TGF-β and down-regulated the cytotoxic activity of CD8 T cells. IL-6 protects Ly6G MDSC against sorafenib induced cell death in vitro. The combination of anti-Ly6G antibody or anti-IL-6 antibody and sorafenib significantly reduced the cell proportion of Ly6G MDSCs in orthotopic liver tumors, enhanced the proliferation of T cells, and synergically improved the therapeutic effect of sorafenib. | Chang et al. (2018) |
| MDSCs        | The immune mechanism   | Tumor-infiltrating CD11BDC33HLA-DR MDSCs in HCC patients can effectively inhibit autologous CD8 T cell proliferation, Concordant overexpression of CCR7 and MDSC markers (CD11b/CD33) (Continued on following page) | Zhou et al. (2018b) |
initiates the expression of immunosuppressive cytokine IL10. PIWI1, which is expressed by tumor cells, could be a viable target for the development of new HCC treatments (Wang et al., 2021a). Tumor-infiltrating LY6G MDSCs from orthotopic liver tumors treated with sorafenib dramatically increased CD4 T cells expressing IL-10 and TGF-and decreased CD8 T cell cytotoxicity. In vitro, IL-6 protects LY6G MDSC from sorafenib-induced cell death. Combining sorafenib and anti-IL-6 antibody or anti-LY6G antibody dramatically decreased the cell proportion of LY6G MDSCs in orthotopic liver tumors, synergistically boosted sorafenib’s therapeutic efficacy and increased T cell proliferation (Chang et al., 2018). Icaritin blocks MDSC production by blocking the attenuation of EMH, thereby inhibiting the immunosuppressive effect of the tumor, thereby triggering an anti-tumor immune response. Therefore, Icaritin can be used as a new adjuvant or even as an independent therapeutic agent for the effective treatment of HCC (Tao et al., 2021). In Table 6, we show the relevant role of MDSC in HCC immune microenvironment in recent years.

**Cancer-Associated fibroblasts**

CAF is not an immune cell, but it plays an important role in the tumor microenvironment, so we will introduce it in detail here. CAF exists as a prominent component of the tumor stroma between various inflammatory cells and components in the tumor microenvironment (Kalluri, 2016). As a result, CAF possesses functions that normal fibroblasts do not. A vast number of prior studies have demonstrated that CAF plays a critical function in changing the tumor microenvironment and driving the development of a variety of cancers (Jiang et al., 2017a; Zhao et al., 2017a; Deng et al., 2017; Pistore et al., 2017). CAF is also significant in HCC. Many studies have revealed the great role of CAF in the pathogenesis, progression, prognosis, treatment and other aspects of HCC. CAF-derived cardiotonutrient-like cytokine 1 (CLCF1) has been found in studies to stimulate the release of TGF-β and CXCL6 in tumor cells, consequently increasing tumor stem cell development in HCC-TME (Song et al., 2021). Other research have found that CCN2, EMA, and FAP expression may be involved in the activation of CAF in HCC, resulting in aggressive behavior. The substantial association between EMA-expressing tumor cells and FAP-expressing CAF, as well as their topographical proximity, suggests that there may be interplay between tumor epithelial and stromal cells in the HCC tumor microenvironment (Kim et al., 2014). Table 7 summarizes the current role of CAF in HCC.

**M2-Polarized Macrophages**

M2 polarized macrophages, as opposed to M1 polarized macrophages, have anti-inflammatory and pro-tumor actions (Figure 4). M2 macrophages are further differentiated into M2a, M2b, M2c, and M2d subsets. Th2 cytokines such as IL-13 and IL-4 can trigger macrophage transformation to the M2A phenotype, whereas TLR and immune complex activation induces M2B macrophages, the M2C subtype polarized by IL-10 (Hao et al., 2012; Sica and Mantovani, 2012). Despite the fact that there have been few research on M2-polarized macrophages in HCC, the function of them in the occurrence and development of HCC has been confirmed. According to several studies, arsenite raises miR-15b levels and causes M2 polarization in THP-1 cells. Increased miR-15b in Evs transfer from arsenite-treated THP-1 (AS-THP-1) cells to HCC cells via miR-15b. By targeting LATS1, it can reduce Hippo pathway activation while still accelerating the invasion and metastasis of growing HCC cells (Li et al., 2021). The potential therapeutic potential of M2 polarized macrophages has also been pointed out that Tumor cell-derived Wnt ligands induce M2-like polarization of TAM via traditional Wnt/-catenin signaling, resulting in tumor migration, development, immunosuppression and metastasis in HCC (Yang et al., 2018a). We summarize the current relevant research progress in Table 8.

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**Table 6** (Continued) Tumor-promoting immune cells: Myeloid-derived suppressor cells.

| Cells       | The research direction                      | Result                                                                 | References               |
|-------------|--------------------------------------------|-----------------------------------------------------------------------|--------------------------|
| MDSCs       | The immune mechanism                       | was positively associated with poorer survival. Hepatocyte CCRK stimulated the immunosuppressive CD11B/CD33/HLA-DR MDSC amplification of human peripheral blood mononuclear cells by up-regulating IL-6. | Chiu et al. (2017)        |
| MDSCs       | Immunotherapy                              | In HCC, hypoxia induces the expression of ENTPD2 on cancer cells, leading to an increase in extracellular 5'-AMP, which in turn promotes MDSC maintenance by preventing its differentiation. | Lin et al. (2017)         |
| MDSCs       | The immune mechanism                       | The tumor suppressive effects of chemerin were associated with metastasis of tumor-infiltrating immune cells from myeloid suppressor cells (MDSC) to interferon-y T cells and decreased tumor angiogenesis. | Deng et al. (2017)        |
| MDSCs       | The immune mechanism                       | TAF-derived cytokines (such as IL-6 and SDF-1A) can induce MDSC generation and activation, and then weaken the human anti-tumor immune response, thus creating favorable conditions for the development of HCC. | Mizukoshi et al. (2016)   |
| MDSCs       | Immunotherapy                              | The frequency of MDSC before treatment is a prognostic factor for HAIC prevention of HCC. | Arihara et al. (2013)     |
| MDSCs       | Immunotherapy                              | The frequency of MDSC increased significantly in HCC patients. It is associated with tumor progression, but not with liver fibrosis or inflammation. | Hoescht et al. (2009)     |
TABLE 7 | Tumor-promoting immune cells: cancer-associated fibroblasts.

| Cells          | The research direction | Result                                                                 | Reference                  |
|----------------|------------------------|------------------------------------------------------------------------|----------------------------|
| CAF            | The immune mechanism   | Sulf2 secreted by HCC cells induces the differentiation of HSC into CAF through the TGFβ1/Smad3 signaling pathway. | Wang et al. (2021b)        |
| CAF            | Immunotherapy          | CNP inhibits the HCC promotion of CAF by inhibiting several HCC-promoting cytokines secreted by CAF expressing GPR168. Further studies have shown that the combination of CNP and existing anticancer agents has some potential in the treatment of intractable HCC associated with the activation of CAF. | Yamanaka et al. (2021)    |
| CAF            | The immune mechanism   | CAF-derived cytokines enhance the progression and metastasis of HCC by activating the circRNA-miRNA-miRNA axis in tumor cells. | Liu et al. (2021)          |
| CAF            | The immune mechanism   | In HCC-TME, CAF-derived cardiooctonutrient-like cytokine 1 (CLCF1) increases the secretion of CXCL6 and TGF-β in tumor cells, thereby promoting tumor stem cell growth. | Song et al. (2021)         |
| CAF            | Immunotherapy          | Coptidine blocked the secretion of CAF exosome CIRCCCT3 and significantly inhibited tumor growth of HepG2 cells in immunodeficient mice. | Lv et al. (2020)           |
| CAF            | The immune mechanism   | MIR-150-3p was significantly reduced in CAFs-derived exosomes and inhibited HCC migration and invasion. MIR-150-3p was transferred from MIR-150-3p transfected CAF to HCC cells via exosomes and eliminated HCC migration and invasion. | Yugawa et al. (2021)       |
| CAF            | The immune mechanism   | IL-6 and HGF are key EMT-stimulating cytokines secreted by H-CAF. | Jia et al. (2020)          |
| CAF            | The immune mechanism   | The proportion of CAFs was positively correlated with the expression of CD73 in HCC cells. The c-Met and MEK-ERK1/2 pathways are activated by HGF from CAF, which upregulates CD73 expression in HCC cells. | Peng et al. (2020)         |
| CAF            | Immunotherapy          | Endothelial sialic acid protein expressed by CAF is the main regulator of macrophage recruitment and polarization, and inhibition of endothelial sialic acid protein inhibition is a potential therapeutic strategy for HCC. | Yang et al. (2020)         |
| CAF            | Prognostic marker      | CAFs can produce pGFP-LGF, which is associated with tumor angiogenesis markers and predicts poor prognosis in HCC patients. | Liu et al. (2020c)         |
| CAF            | Immunotherapy          | CAFs can promote the dryness and metastasis of HCC cells, and blocking autophagy can significantly reduce the enhanced dryness of CAFs, suggesting that targeting HCC autophagy may be an effective strategy for the treatment of HCC. | Zhao et al. (2019)         |
| CAF            | The immune mechanism   | LXRα agonists limit TGFβ-dependent CAF differentiation and may limit the growth of primary HCC. | Morin et al. (2019)        |
| CAF            | Immunotherapy          | RVD1 inhibits the stem cell characterization of CAF-induced EMT and HCC cells by inhibiting the secretion of COMP. | Sun et al. (2019b)         |
| CAF            | The immune mechanism   | Endogenous and exogenous BMP4 activates liver fibroblasts, acquires the ability to secrete cytokines, and enhances the aggressiveness of HCC cells. | Mano et al. (2019)         |
| CAF            | The immune mechanism   | CAFs promote self-renewal, chemotherapy resistance, metastasis and tumorigenicity of CD24 HCC cells. CAFs secreted HGF and IL6 promote the dryness of CD24 HCC cells by phosphorylation of STAT3. | Li et al. (2019c)          |
| CAF            | The immune mechanism   | HCC-CAFs regulate the survival, activation, and function of neutrophils in HCC through the IL6-STAT3-PDL1 signaling cascade. | Cheng et al. (2018)        |
| CAF            | The immune mechanism   | IL-6 secreted by CAF promotes stem-cell-like properties in HCC cells by enhancing STAT3/Notch signaling. | Xiong et al. (2018)        |
| CAF            | The immune mechanism   | CAF-induced Notch3 expression is responsible for the activation of LSD1 in CSC, thereby promoting its self-renewal in HCC. | Liu et al. (2018b)         |
| CAF            | The immune mechanism   | CAF-mediated tumor progression in HCC is associated with the deletion of anti-tumor miR-320a in CAF exosomes. | Zhang et al. (2017)        |
| CAF            | The immune mechanism   | MIR-101 eliminated SDF1 signal transduction cells by inhibiting the expression of SDF1 in CAF and inhibiting the expression of VE-cadherin in tumors. | Yang et al. (2016)         |
| CAF            | The immune mechanism   | CCL2; CCL5, CCL7 and CXCL16 secreted by CAF promote HCC metastasis through synergistic activation of Hh1 and TGF-β pathways in HCC cells. | Liu et al. (2016)          |
| CAF            | Immunotherapy          | Targeting the CAF-derived, HGF-mediated c-Met/FRA1/Hey1 cascade may be a therapeutic strategy for the treatment of HCC. | Lau et al. (2016)          |
| CAF            | The immune mechanism   | When stimulated, CAF shows the potential to differentiate into adipocytes, osteoblasts, and pancreatic cells. When co-cultured with human HCC cell lines, CAF upregulated the expression of TGFβ1 and FAP genes in HuH-7 and JHH-6, thus having the ability to enter the circulation. | Sukowati et al. (2015)     |
| CAF            | The immune mechanism   | The expression of CCN2, EMA and FAP may be involved in the activation of CAF in HCC, leading to aggressive behavior. The significant correlation between tumor cells expressing EMA and CAF expressing FAP and their terrain proximity suggests that there may be cross-talk between tumor epithelial cells and stromal cells in the HCC tumor microenvironment. | Kim et al. (2014)          |

THE CONTROVERSIAL IMMUNE CELL TYPE IN CANCER: B CELLS

One type of immune cells that cannot be ignored in the HCC tumor microenvironment is B cells. According to the current relevant studies, it is not clear whether B cells are “good” or “bad.” Some studies have reported that B cells promote HCC, while others have reported the opposite effect. B cells, on the one hand, release cytokines that comport with CTL activity and serve as potent antigen-presenting cells (APCs). On the other hand, they may be tumorigenic due to the production of cytokines that attract MDSC and promote angiogenesis (de Visser et al., 2005; Tsou et al., 2016). Studies have shown that CCL20 derived from tumor cells interacts with CD19CD5 B cells overexpressed by CCR6 to promote the development of HCC, possibly through enhanced angiogenesis (He et al., 2017). Liu et al. ’s study...
confirmed that Selective recruitment of CXCR3 (+) B cells bridges the pro-inflammatory interleukin-17 response and the polarization of tumorigenic macrophages in the tumor environment, and blocking the migration or function of CXCR3+ B cells may help to overcome HCC (Liu et al., 2015). Therefore, B cells are involved in both the development and inhibition of HCC. Table 9 highlights the most recent reliable research on the involvement of B cells in HCC.

CONCLUSIONS AND PERSPECTIVES

With the development of single-cell sequencing and other technologies, we have the opportunity to further explore TME. Immunotherapy, a new tumor treatment method, also has a better and broader application prospect. However, at present, it is still too early for immunotherapy to replace traditional chemotherapeutic therapy, and there is still a long way to go in the process of clinical application. However, immunotherapy can be regarded as a good alternative therapy for patients with chemotherapy resistance. As mentioned in this paper, immunotherapies for tumor suppressor related immune cells, such as effect DCs, as well as tumor promoting immune cells, such as MDSC/Treg, are being developed one after another.

Compared with traditional chemotherapy, immunotherapy has many advantages. For example, immunotherapy has fewer overall side effects than chemotherapy and, once effective, may lead to long-term survival and even clinical cure. In addition,
immunotherapy can be used as an important anti-tumor adjuvant therapy in addition to chemotherapy, radiotherapy and surgery. Appropriate immunotherapy can kill the tiny residual tumor cells after chemotherapy or some tumor cells resistant to chemotherapy. Immunotherapy should be considered for patients who are intolerant to chemotherapy or have extensive metastasis and cannot undergo surgery, radiotherapy or chemotherapy (Yang, 2015).

At present, the mainstream immunotherapy mainly includes CAR T therapy/immune checkpoint inhibitor therapy (PD-1, PD-L1, etc.)/tumor vaccine. CAR-T is the T cells, biological engineering, when the cancer has an immune deficiency, immune surveillance, give play to the role of the case, through the biological engineering to determine the targets of leukemia, it specifically chimeric in T cells, to attack the leukemia cells, the effect is significant, but easy to appear "storm" cells, serious and even cause death (Feins et al., 2019). Immune checkpoint inhibitor therapy has the advantage of long-term survival and relatively small adverse reactions. This therapy activates tumor-specific immune cells in the body by removing or attenuating the negative regulatory factors of immunoreactive cells, but it is not suitable for all patients. The higher the mutation load, the better the treatment response. Therefore, biomarkers should be used to screen the dominant population. The most common predictive indicators of PD-1/PD-L1 immune checkpoint inhibitors are microsatellite instability, PD-L1 and tumor mutation load (Pinato et al., 2019). The treatment of cancer vaccines is still incomplete.

Immunotherapy is not the end of tumor therapy; on the contrary, tumor immunotherapy represented by immune checkpoints has just opened a new chapter in tumor therapy. Combined with the basic and characteristics of immunotherapy,
with the deepening of human understanding of tumors, tumors as a chronic disease that can be cured are no longer so far out of reach.

AUTHOR CONTRIBUTIONS

The manuscript had three first authors who made equal contributions to the project. XH, GS, and YZ were responsible for collecting information and design reviews of relevant studies. XK and DR are responsible for drawing the pictures. In addition, there are three corresponding authors in this manuscript. WT, JS, and XW contributed to the interpretation, editing and critical revision of the manuscript.

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FUNDING

We are grateful for the grants from the National Natural Science Key Foundation of China (Grant No. 31930020) and National Natural Science Foundation of China (Grant No. 81771716).

ACKNOWLEDGMENTS

We would like to express our sincere thanks to Magdalens Klink, the author of the book “Interaction of immune and cancer cells.” Our pictures have been partially changed and repainted on the basis of this book. At the same time, this book has also given us a lot of writing inspiration.
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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