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Immune microenvironment and therapeutic progress of recurrent hepatocellular carcinoma after liver transplantation

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ABSTRACT

HCC is a highly lethal tumor, and orthotopic liver transplantation, as one of the radical treatment methods for HCC, has opened-up a new therapeutic approach for the treatment of primary liver cancer. However, tumor recurrence after liver transplantation is the main reason that affects the long-term survival of recipients. At present, the application of ICIs has brought dawn to patients with refractory HCC. However, because of the special immune tolerance state created by long-term oral immunosuppressants in patients with HCC after liver transplantation, the current focus is how to regulate the immune balance of such patients and simultaneously maximize the anti-tumor effect. This article reviews the relationship between liver cancer and immunity, immune tolerance of liver transplantation, immune microenvironment after liver transplantation for HCC, and the application of immunotherapy in the recurrence of liver transplantation for HCC.

Introduction

HCC is the fifth most common cancer in the world and the second leading cause of cancer death [1]. In 2020, there were 910,000 new cases of HCC worldwide, of which 410,000 were in China, accounting for more than 45%. In 2020, there were 830,000 deaths from HCC worldwide, including 390,000 deaths from HCC in China. The conventional treatment of HCC mainly includes surgical resection, radiotherapy, chemotherapy, and interventional therapy. Because 85%-90% of patients of HCC are accompanied by liver cirrhosis, poor liver function and multicentric tumor growth, although surgical resection is the preferred treatment for patients of HCC, patients often cannot tolerate a wide range of liver resection. Furthermore patients undergoing surgical treatment are often accompanied with recurrence [2]. Therefore, the low resection rate and the high recurrence rate after treatment are the main reasons for the poor therapeutic effect of HCC.

In 1963, the advent of liver transplantation opened up a new therapeutic idea for the treatment of HCC. Because liver transplantation can remove all the diseased liver, regional lymph nodes and, and adjacent blood vessels with tumor invasion, and at the same time of radical resection of liver cancer, liver transplantation also solves the problem of simultaneous portal hypertension. Thus, liver transplantation has a more promising application prospect compared with conventional treatment methods for HCC. Clinical statistics in recent years have shown that the 5-year survival rate of liver transplantation recipients with HCC is $< 50\%$, and postoperative recurrence and metastasis are the main reasons that affect the long-term survival of recipients [3]. At present, ICIs represented by PD-1/PD-L1 inhibitors or CTLA-4 have achieved remarkable curative effect in the treatment of advanced HCC [4–6]. Nevertheless, many controversies exist regarding whether ICIs can be used for the recurrence of HCC after transplantation. Because immunosuppressive drugs are routinely used in patients after liver transplantation, acute rejection may occur when immunosuppressive drugs and ICIs are used at the same time. Therefore, how to balance the

Abbreviations: HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death-1; PD-L1, programmed cell death-Ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; NPCs, non-parenchymal cells; KC, kupffer cells; LSEC, hepatic sinusoidal endothelial cells; DCs, dendritic cells; IFN-γ, interferon-γ; TGF-β1, transforming growth factor-β1; Tregs, regulatory T cells; PI3K, phosphatidylinositol-3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; ERK, extracellular regulated protein kinase; GVHD, graft-versus-host disease.

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use of these two drugs is one of the current research priorities.

Relationship between HCC and immunity

The liver is the largest digestive gland in the human body. It receives double infusion from the hepatic artery and the hepatic portal vein, and the blood supply is very rich [7]. The liver is not only involved in the synthesis, transformation and decomposition of proteins, carbohydrates, lipids and vitamins in the body, but also in the transformation and detoxification of hormones, drugs and other substances. In addition, the liver has a very strong relationship with immunity. The normal human liver is composed of liver parenchymal cells and NPCs, which are the first line of defense against the external environment [8]. NPCs, including KC, LSEC, DCs and hepatic stellate cells, play important roles in liver pathology [9,10]. The liver is also the largest phagocytic system of reticuloendothelial cells in the human body. The normal human liver contains approximately 10^{10} lymphocytes, which are widely distributed in the liver parenchyma and portal area, most of which are T lymphocytes (63%), followed by natural killer cells (31%) and B lymphocytes (6%). These cells build the powerful immune function of the liver, and it is the coexistence of various immune-related cells in the liver that makes the liver an "immune-privileged" organ.

Most of HCCs are developed on the basis of chronic hepatitis; thus, HCC is a kind of tumor that is highly related to inflammation. An imbalance of immune cells in liver tumor microenvironment, impairment of immune cell function and antigen presentation, and activation of multiple inhibitory pathways lead to immune tolerance and immune escape. Myeloid cells, including monocytes/macrophages, DCs and neutrophils, are the most abundant nucleated immune cells in the human body, which are essential for the maintenance of liver immune homeostasis. Heterogeneous myeloid cell populations with immunosuppressive activity, such as myeloid-derived suppressor cells, are greatly expanded under pathological conditions. In addition, the molecular typing of HCC based on the liver immune microenvironment has gradually become the basis for guiding precise treatment. Sia et al. [11] analyzed the gene expression profiles of 956 HCC patients and found that nearly 25% of HCC patients were molecularly characterized by high infiltration of immune cells, expression of PD-1/PD-L1, active IFN-γ signaling, and a lack of CTNNB1 mutation. According to immune characteristics, HCC is further divided into immune-activated and -depleted subtypes. The immune-activated subtype often shows over-expression of IFN-γ and CD8A, and the overall survival rate is high. The immune-depleted subtype is characterized by the expression of immunosuppressive genes, which is regulated by TGF-β1. The high expression of PD-1/PD-L1 in the immune-depleted subtype may benefit from ICI therapy. In addition, approximately 25% of HCCs are immunoprivileged, which is characterized by CTNNB1 mutation, T-cell deficiency, and PTK2 over-expression, and a lack of response to ICI therapy. The remaining 50% of HCCs are between the immune and immune exempt type, and belong to the immune intermediate type. According to the PD-1 expression level of liver cancer samples, Kim et al. [12] divided invasive CD8 + T cell populations into high PD-1 subsets, medium PD-1 subsets and PD-1 negative subsets. High PD-1 subsets are associated with more aggressive tumor biological characteristics and a poor prognosis. Infiltrating CD8 + T cells in the high PD-1 subsets represent more severe features associated with T cell exhaustion compared with the medium PD-1 and PD-1-negative subsets.

Liver transplantation and immune tolerance

Rejection refers to the process of attack, destruction and elimination of graft by transplant recipient, including antibody- and cell-mediated rejection. T cell-mediated cellular immune responses have a key role in rejection [13]. The host APC binds the epitope peptide fragments to the MHC by ingesting and processing foreign antigens. When the MHC binds to the T cell receptor, the MHC can transmit signals to the interior of T cells through direct recognition and indirect recognition, thereby activating T cells. T cells also play important roles in the development of transplantation immune tolerance. T cells are not only stimulated by the first signal, but also affected by costimulatory molecules. Co-stimulatory molecules are divided into positive stimulatory signals (CD27-H7, CD40-CD154) and negative stimulatory signals (CTLA-4, PD-1/PD-L1, OPG, DcR3). When the former is dominant, T cells proliferate and activate into effector T cells to improve immune activity. When the latter is dominant, immune tolerance is formed. The PD-1/PD-L1 pathway is an important negative regulatory pathway of immune response. Most studies have shown that CTLA-4 and PD-1 have important roles in the formation and maintenance of transplantation immune tolerance [14–17]. Morita et al. [18] showed in animal experiments that blocking the PD-1/PD-L1 pathway or knocking down PD-L1 lead to infiltration of graft immune cells, hemorrhage, and necrosis, and eventually death of recipient mice in a mouse transplantation model. Furthermore, Chen et al. [19] showed that PD-1 inhibits both T and B cells, whereas CTLA-4 has a relatively stronger inhibitory effect on the production of high-adherent T cells. T and B cells have complementary and synergistic roles in the formation of immune tolerance.

Compared to other solid organs, the liver is less prone to rejection and requires a lower intensity of immunosuppression.The liver is a special immuneprivileged organ. Unlike other organs, the liver has two blood supply systems(arterial and portal vein). The portal vein system receives the blood return from the gastrointestinal tract to ensure the immune tolerance of the liver to antigens from the gastrointestinal tract. In addition, the formation of microchimeras, the induction of cell death by activation of lymphocyte, activation of immature DCs and Tregs have all been shown to contribute to the induction of immune tolerance in transplanted livers. Studies have demonstrated that LSECs play important roles in the development of immune tolerance after liver transplantation [10]. LSECs accounts for approximately 70% of NPCs, participates in the pathological process of most liver diseases, and play important roles in the occurrence and development of liver diseases. LSECs mainly work by anti-inflammatory, endocytic clearance in the capillaries of sinusoids, secretion of pro-angiogenic signaling factors, repair of liver injury, immunomodulation and induction of immune tolerance of T lymphocytes. Unlike professional APCs, LSECs can present antigens to CD4+/CD8+ T cells and prevent naive CD4+ T cells from differentiating into helper T cells by synthesizing immunosuppressive factors such as interleukin-10 and TGF-β, and induce naive CD4+ T cells to become Tregs, which suppress T cell activity, thereby achieving immune tolerance formation after liver transplantation. In contrast, when LSECs are presented to naive CD8+ T cells, LSECs induce activation and proliferation of naïve CD8+ T cells into an immunotolerance phenotype, leading to loss of cytokine expression, lack of specific cytotoxicity, and dissemination of tumor cells in the liver [20–22]. In addition, studies have shown that KCs also have roles in immune tolerance. Gong et al. [23] showed that KCs highly expressing PD-L1 could maintain the immune response to a certain extent. Moreover, KCs induce T cell apoptosis through the Fas/FasL pathway, and then maintain immune tolerance of transplanted liver [24] (Fig. 1).

Immune microenvironment after liver transplantation for HCC

As mentioned above, both CTLA-4 and PD-1 have roles in transplantation immune tolerance. CTLA-4 mainly has a role in the induction phase of immune tolerance, while the PD-1/PD-L1 pathway has a role in the maintenance phase of immune tolerance. After T cell activation, the expression of CTLA-4 on the cell membrane is upregulated, which inhibits T cell function through a variety of mechanisms, including competitive binding with B7-CD28, and at the same time inducing T cell cycle termination to maintain immune homeostasis and induce immune tolerance [17]. The binding of PD-1 to PD-L1 blocks the activation of pathways such as PI3K / Akt / mTOR and Ras / MAPK / ERK, which can inhibit the differentiation of effector T cells and reduce their functions,

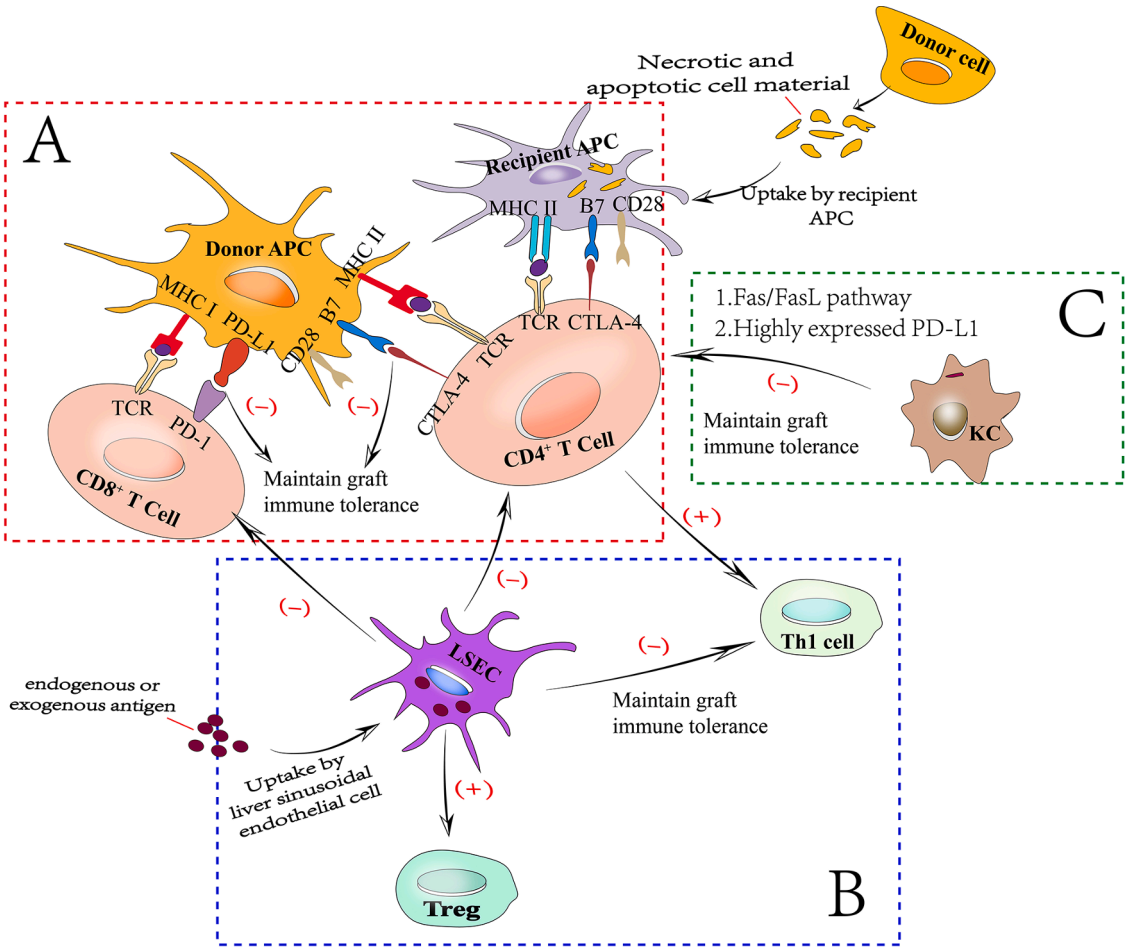

Fig. 1. *T cells mediate the mechanism of immune tolerance in transplanted liver.* **A.** Donor APCs or antigen-presented recipient APCs present antigens to CD4+/CD8+ T cells, which inhibit T lymphocyte activity through CTLA-4/B7 and PD-1/PD-L1 pathways. **B.** LSEC presents antigen to CD4+/CD8+ T cells, which prompts them to synthesize IL-10 and TGF-β, thereby preventing the differentiation of naive CD4+ T cells into T helper 1 cells, and inducing CD4+ T cells to become Treg and CD8+ T cells to activate and proliferate into an immune tolerance phenotype, which inhibiting T cell activity. **C.** KC cells induce T cell apoptosis through the Fas/FasL pathway. The three pathways together lead to the incapacitation of CD8+ T cells and CD4+ T cells to maintain immune tolerance. APC, antigen presenting cell; CTLA4, cytotoxic T-lymphocyte-associated protein 4; PD1, programmed cell death 1; PD-L1, programmed death-ligand 1; LSEC, hepatic sinusoidal endothelial cells; IL-10, interleukin-10; TGF-β, transforming growth factor-β; Treg, regulatory T cells; KC, kupffer cell.

resulting in the incapacitation of CD8 + T cells and CD4 + T cells [25–27] (Fig. 2). Liu et al. [28] confirmed that the number of CD4 + T cells and CD8 + T cells in peripheral blood of recipients with acute rejection was significantly lower than that of recipients with immune tolerance after liver transplantation, while the number of CD8 + T cells and CD4 + T cells infiltrated around the liver was significantly increased. CD152 and PD-1 expression on CD8 + T cells and CD4 + T cells were also reduced. De Leon et al. [29] reported that PD-L1 expression was detected in five graft biopsies and no rejection occurred in three patients who were PD-L1-negative, and rejection occurred in two patients with 30% (liver cancer) and 25% (melanoma) expression of PD-L1. Thus, PD-1 expression may have an important role in maintaining immune tolerance in liver transplantation.

Tumor immunotherapy is to strengthen the surveillance and killing ability of the body's immune system and correct the imbalance of the immune microenvironment, thus killing tumor cells. At present, PD-1/PD-L1 inhibitors and CTLA-4 inhibitors are commonly used in the immunotherapy of HCC. It has been shown that the anti-tumor effect of PD-1/PD-L1 inhibitors were superior to CTLA-4 inhibitors. However, after liver transplantation patients required immunosuppressive drugs. When immunosuppressive drugs and ICI therapy are used at the same time, acute rejection may occur. Therefore, it is necessary to clarify whether the immune tolerance of transplanted organs and tumor immune escape are PD-1 dependent or dependent on other molecules, thus enabling specific selection of ICI therapy to maximize the immunotherapeutic effect and avoid inducing acute rejection [30].

Application of immunotherapy in HCC recurrence after liver transplantation

To enhance the anti-tumor effect, the dosage of immunosuppressive agents is usually reduced when ICIs are administered to the recipients with recurrence after liver transplantation, but this further increases the risk of rejection. Previous studies have shown that the incidence of acute rejection in patients with tumor recurrence after liver transplantation for HCC was approximately 35% [31]. In addition, the adverse reactions of ICI after liver transplantation can be manifested as abdominal pain, high fever, jaundice, diarrhea and abnormal liver enzymes. The most serious complication is irreversible fulminant hepatic failure, which leads to graft failure [32]. Therefore, most studies suggest that the use of ICIs should be used with caution in patients with tumor recurrence after liver transplantation.

With the precise regulation of transplantation immune tolerance and the further exploration of tumor-specific immunity, the use of ICIs in transplantation patients (Table 1) is on the rise, but most transplantation patients have a poor prognosis and obvious adverse reactions [29,

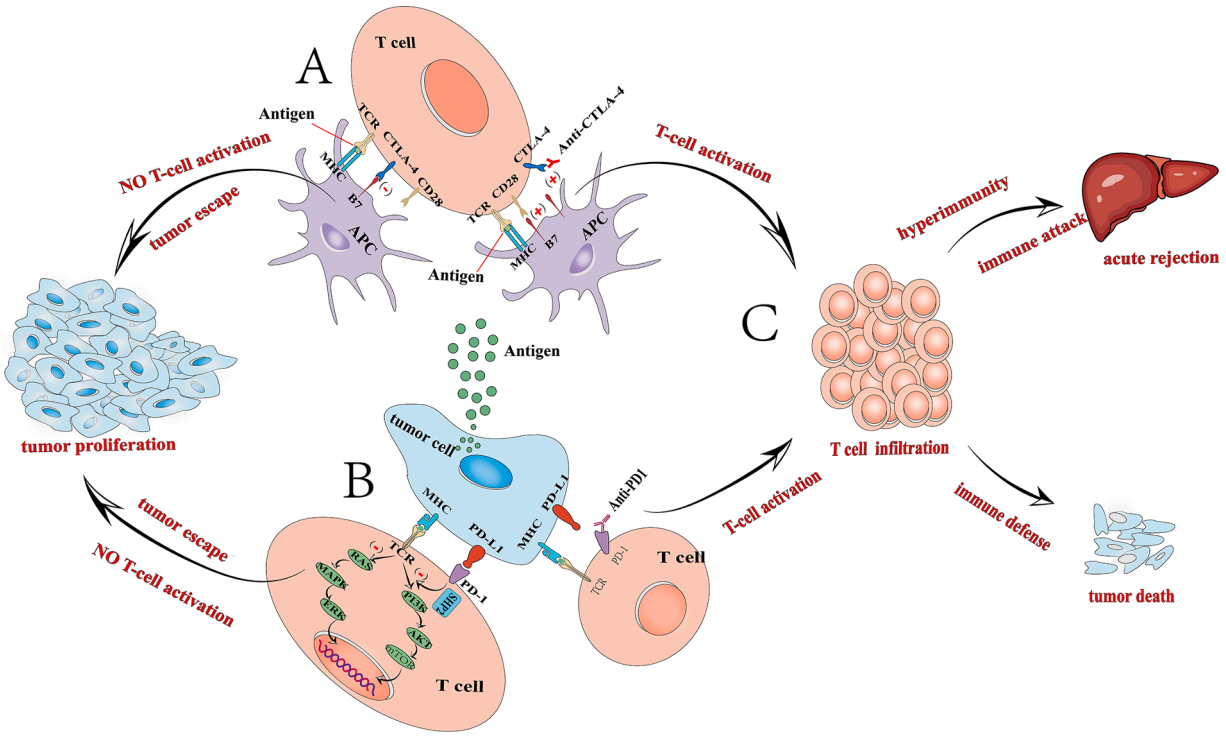

Fig. 2. *The mechanism of immune checkpoint in tumor immune escape.* **A.** After tumor antigen presentation, CTLA-4 on APC surface competitively binds to ligand B7 of CD28, inducing T cell cycle termination and antagonizing T cell function. **B.** The binding of PD-1 on APC surface to PD-L1 on tumor surface blocked the activation of PI3K/AKT/mTOR and RAS/MAPK/ERK pathways, inhibited the differentiation of effector T cells and resulted in the deactivation of CD8 + T cells and CD4 + T cells. The two pathways work together to promote the escape of tumor cells, tumor cells proliferation, infiltration and invasion of the body organs. **C.** CTLA-4 and PD-1 inhibitors specifically bind to CTLA-4 and PD-L1 receptors, which promote the activation and proliferation of inactivated T cells, and kill tumor cells. CTLA4, cytotoxic T-lymphocyte-associated protein 4; APC, antigen presenting cell; PD1, programmed cell death 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; ERK, extracellular regulated protein kinase.

32-37]. Varkaris et al. [33] reported a patient with HCC complicated by liver cirrhosis recurred after liver transplantation. After using sorafenib and capecitabine, and radiotherapy, the tumor progressed again after a period of stable disease. Following treatment with pembrolizumab did not cause any obvious rejection, but the tumor progressed rapidly. The recipient died 3 months later. Al Jarroudi et al. [35] reported a case of HCC recurrence after liver transplantation in a patient with multiple HCCs. The patient received sorafenib as the first-line treatment and six cycles of gemcitabine and oxaliplatin, but the disease progressed. The patient then received salvage therapy with nivolumab (240 mg every 2 weeks). As a result, the patient developed irreversible acute rejection and eventually died.

Although most of the clinical data show that the prognosis of the patients with recurrent or metastatic HCC after liver transplantation was poor after ICI therapy, there are some successful cases [38–40]. Amjad et al. [38] reported a case of HCC with viral hepatitis C and cirrhosis who underwent liver transplantation after treatment for hepatitis C. One year later, the tumor recurred with multiple metastases. Immunohistochemistry showed that PD-L1 was positive. After 6 months of subsequent treatment with nivolumab, the liver lesions and all metastatic lesions were necrotic or disappeared, and the effect was significant. As of the publication of this report (24 months after diagnosis of disseminated liver cancer), magnetic resonance imaging, bone scan or positron emission tomography has shown no evidence of recurrence. In 2018, Rammohan et al. reported a case of HCC patient after living donor liver transplantation, which was found to have lung metastasis 3 years after operation. After 1 year of sorafenib-targeted therapy, the disease progressed, and then combined with pembrolizumab, the lung metastasis disappeared completely after 10 cycles. Up to the time of the report, the patient had survived for 10 months without tumor and there was no rejection [39]. In 2017, De Toni et al. reported a case of HCC patient after liver transplantation, which was treated with microwave ablation combined with transcatheter arterial chemoembolization for HCC recurrence, resection of adrenal metastases, and immunotherapy with nivolumab on the basis of low dose immunosuppressants. The survival time was more than 10 months, and no rejection was observed [40]. Among the cases that can be evaluated at present, this patient had the longest survival time of patients with recurrence of HCC after liver transplantation who were treated with ICI. These case reports inform us that it is possible to use anti-tumor immunotherapy for patients with HCC recurrence after transplantation.

However, the choice of ICI drug type and dose is the focus of current attention. Preclinical models confirm that CTLA-4 contributes to the induction of graft tolerance but not to the maintenance of graft tolerance, which may indicate that patients treated with CTLA-4 inhibitors have a lower propensity to develop graft rejection [41]. Friend et al. [34] demonstrated that anti-PD-1 antibodies lead to increased GVHD compared with anti-CTLA-4, and that combination therapy with these two antibodies resulted in more severe GVHD than anti-PD-1 antibody alone. The expression of PD-L1 is another key factor in evaluating the choice of ICI drugs. A meta-analysis by Zhang et al. included a total of 41 patients undergoing liver transplantation [42]. Of these, 56.1% had HCC recurrence, and 87.8% received anti-PD-1 therapy. Ten patients responded to immunotherapy. The incidence of transplant rejection was 31.7%, and six cases died secondary to transplant rejection. Transplant rejection occurred in half of the recipients with positive PD-L1 staining (4/8), suggesting a correlation between positive PD-L1 staining and rejection. Munker et al. [43] reported that PD-L1 staining was positive in the liver biopsies of 3 recipients who had acute rejection after the initiation of ICI treatment, while it was negative in 4 recipients who

Table 1
Clinical characteristics of immunotherapy in recipients with recurrence and metastasis after liver transplantation for hepatocellular carcinoma.

References	Age (y)/ Sex	Years from LT to ICI	IS therapy before ICI	Antitumor therapy before ICI	IS therapy during ICI	ICI / No.doses/ cycle	PD-1/PD-L1 staining	Tumor response	Overall outcome	Rejection	Survival/ death time after ICI
DeLeon TT [29]	56/ M	2.7	Tacrolimus	Sorafenib	N/A	Nivolumab / N/A/ 3 ×	10% tumor expression of PD-L1	N/A	PD	No	Alive at 1.2 mo
	55/ M	7.8	Sirolimus+MMF	Sorafenib	N/A	Nivolumab / N/A/ 4 ×	PD-L1 (-)	N/A	PD	No	Alive at 1.1 mo
	34/F	3.7	Tacrolimus	Sorafenib	N/A	Nivolumab / N/A/ 5 ×	PD-L1 (-)	N/A	PD	No	Alive at 1.3 mo
	63/ M	1.2	Tacrolimus	Sorafenib	N/A	Nivolumab / N/A/ 2 ×	N/A	N/A	OF	No	Alive at 0.3 mo
	68/ M	1.1	Sirolimus	Sorafenib	N/A	Nivolumab / N/A/ 2 ×	allograft expression of PD-L1	N/A	OF	Yes	Death at 0.9 mo
Gassmann D [32]	53/F	2	Everolimus +MMF	Sorafenib	Everolimus +MMF	Nivolumab / 3mg/ kg/1 ×	N/A	N/A	OF	Yes	Death at 25 d
Varkaris A [33]	70/ M	8	Tacrolimus	Sorafenib;Capecitabine+external bean radiation	Low-dose (50%) of Tacrolimus	Pembrolizumab / 2mg/kg/1 ×	N/A	No response	PD	No	Death at 3 mo
Friend BD [34]	14/ M	3	Tacrolimus	Sorafenib; gemcitabine+oxaliplatin; capecitabine	Tacrolimus	Nivolumab / N/A/ 1 ×	PD-1 (+) PD-L1 (+)	N/A	OF	Yes	Death at 4 wk
	20/ M	4	Sirolimus	Sorafenib; Capecitabine	Sirolimus	Nivolumab / N/A/ 2 ×	PD-1 (+) PD-L1 (+)	N/A	OF	Yes	Death at 5 wk
Al Jarroudi O [35]	70/ M	3.1	Tacrolimus	Sorafenib; gemcitabine+oxaliplatin	Tacrolimus	Nivolumab / 240mg/1 ×	N/A	N/A	PD	Yes	Death at 4 mo
	62/F	2.8	Tacrolimus	Sorafenib;Regorafenib; fluorouracil+oxaliplatin	Tacrolimusd	Nivolumab / 240mg/5 ×	N/A	N/A	PD	No	Alive at 10 wk①
	66/ M	4.8	Tacrolimus	Sorafeni;Regorafenib; gemcitabine+oxaliplatin	Tacrolimus	Nivolumab / N/A/ 6 ×	N/A	Partial response	PD after Dissociated response (3 month)	No	Alive at 6 mo
Anugwom C [36]	62/ M	1.2	Tacrolimus	Sorafenib; Carboplatin + Gemcitabine; Folinic acid + Fluorouracil + Oxaliplatin	N/A	Nivolumab / N/A/ 1 ×	PD-L1 (-)	N/A	OF	Yes	Death at 2 mo
Zhuang L [37]	54/ M	2.5	Tacrolimus	Sorafenib; mFolfox-6; Gemcitabine	Tacrolimu	Nivolumab / N/A/ 31 ×	N/A	N/A	PD	No	Death at 20 mo
Amjad W [38]	62/F	1.3	Tacrolimus+MMF	TACE	Tacrolimus+MMF	Nivolumab / N/A/ N/A	PD-L1 (+)	complete response	CR	No	Alive at 20 mo①
Rammohan A [39]	57/ M	4.3	Tacrolimus+MMF+ Steroids	Sorafenib	Low-dose of Tacrolimus+ mTOR inhibitors+MMF+ Steroids	Pembrolizumab / 200mg/10 ×	N/A	complete response	CR	No	Alive at 10 mo①
De Toni EN [40]	41/ M	1	Tacrolimus	TACE+ microwave ablation	Low-dose of Tacrolimus	Nivolumab / 3mg/ kg/15 ×	N/A	Partial response	PD After Dissociated response (7 months)	No	Alive at 10 mo

Note: ① The recipients are still following up when the article is submitted. LT liver transplantation, IS immunosuppressive, ICI immune checkpoint inhibitor, PD-1 programmed death-1, PD-L1 programmed death ligand-1, PD progressive disease, OF organ failure, CR complete remission, N/A not available, MMF, mycophenolate mofetil, TACE Transarterial chemoembolization

never had rejection, suggesting that the expression level of PD-L1 in the liver graft may be related to the occurrence of acute rejection. The detection of PD-1/PD-L1 by liver biopsy has guiding value for the use of ICI. Another study pooled 39 solid organ transplant recipients, of whom 16 developed rejection after ICI and 5 underwent PD-L1 testing, of whom 4 were PD-1/PD-L1 positive. The results suggested that PD-L1 expression level could predict not only the response rate of PD-1/PD-L1 inhibitor, but also the incidence of rejection [44]. Therefore, there is a current view that before initiating ICI therapy, a biopsy of the transplanted liver is recommended, and if PD-L1 is positive, treatment with CTLA-4 inhibitor may be considered. In terms of drug dose selection, studies have shown that the PD-1 receptor on the surface of peripheral T cells can be completely occupied when the dose of nivolumab is $\geq$ 0.3 mg/kg [45]. In the KEYNOTE-010 non-small cell lung cancer study, dose reduction of nivolumab to 2 mg/kg did not significantly shorten overall survival compared to 10 mg/kg [46]. In theory, the application of low-dose ICI can reduce the occurrence of acute rejection to a certain extent for such groups of patients with recurrence after liver transplantation. Therefore, the use of low-dose ICI may be a promising treatment for this population.

In addition, long-term use of immunosuppressants in liver transplant patients may determine tumor recurrence. A reduction of immune defense function leads to the imbalance of CD8 lymphocyte and Tregs, which is the main reason for the increased recurrence after liver transplantation [15,16]. In addition, immunosuppressants may stimulate the growth of tumor cells and accelerate the occurrence of tumor [47]. Therefore, the selection of immunosuppressants for HCC recurrence after liver transplantation should not be neglected. In patients who relapse after transplantation, the dose of immunosuppressants is usually reduced before starting ICIs treatment to avoid potential interference of immunosuppressants with the antitumor effects of ICIs. It has been reported that replacing tacrolimus with mTOR inhibitors, such as rapamycin in combination with lowdose glucocorticoids during PD-1 inhibitor therapy, can reduce the risk of rejection [48–50]. Previous clinical studies have shown that compared to recipients using calcineurin inhibitors, recipients using mTOR inhibitors have a significantly lower rate of postoperative tumor recurrence, and systemic therapy with mTOR inhibitor combined with sorafenib in patients with HCC recurrence after liver transplantation can achieve a certain degree of survival benefit [51,52]. mTOR inhibitors can also increase antitumor efficacy when combined with with PD-1 inhibitors. Li et al. [53] showed that the binding of PD-1 to the downstream effectors of mTOR, eukaryotic initiation factor 4E, and ribosomal protein S6, promotes phosphorylation. Some researchers, however, believe that although mTOR inhibitors reduce the rate of recurrence and mortality to some extent, the difference is not statistically significant, and the overall survival of the recipients did not improve significantly. Zhou et al. and Jeng et al. showed that sirolimus or everolimus combination with low dose tacrolimus was well-tolerated and effective in reducing relapse [54,55]. Current research suggests that mTOR inhibitors may be more effective in some liver transplantation recipients with overactivation of the mTOR pathway.

Outlook

With the development of immunotherapy for HCC, ICI drugs have been used in the treatment of HCC recurrence after liver transplantation. Because many signaling molecules and pathways, such as CTLA-4 and PD-1/PD-L1, are involved in the formation of immune tolerance in liver transplantation, the study of the immune microenvironment in HCC and liver transplantation is the focus of current research. Current clinical practice has shown that ICIs, although prolonging the survival of recipients with recurrent HCC after liver transplantation, also carry the risk of inducing fatal acute rejection. Therefore, liver function and rejection should be closely observed during treatment, and in the event of severe rejection, intensive immunosuppressive regimens or application of plasma exchange to remove ICIs in the circulation are required to preserve graft function. With the deepening of the concept of transplantation oncology and the maturity of multidisciplinary team cooperation, it is believed that immunotherapy will play a greater role in the field of liver transplantation for HCC in the future.

Ethical statement

Not applicable.

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Personal contribution

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Author statement

XJ and XTM wrote the manuscript. DZ inquired information. LY revised the manuscript. NM revised the manuscript and provided the funds. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interests.

Availability of data and materials

The references supporting the conclusions of this article is included within the article.

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Not applicable.

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