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Role of Intrahepatic Regional Immunity in Post-Transplant Cancer Recurrence

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ABSTRACT

Hepatic malignancy is a major indication for liver transplantation; however, post-transplant cancer recurrence is an emerging clinical challenge affecting long-term outcomes. Pre-transplant tumor biology, staging, and post-transplant immunosuppression regimens have been elucidated as risk factors for recurrent liver cancer. However, increasing evidence indicates that hepatic ischemia and reperfusion (IR) injury to allografts are crucial to providing a favorable immunologic microenvironment for cancer cell invasiveness and metastasis after liver transplantation. The association of severe graft injury in marginal grafts, such as small-for-size or fatty grafts, with lower recurrence-free survival rates in living donor liver transplantations, substantiates the correlation between hepatic IR injury and cancer recurrence. IR has been demonstrated to trigger intrahepatic immunological microenvironment remodeling, including pro-inflammatory responses exacerbating graft injury and anti-inflammatory responses promoting tissue repair. However, the role of regional immunity in post-transplant cancer recurrence is not comprehensively understood. This review describes the up-to-date evidence of the intrahepatic humoral microenvironment and regional regulatory immunological microenvironment induced by IR injury, as well as their roles in cancer recurrence after liver transplantation. A comprehensive understanding of regional immunity will provide novel precise diagnostic, therapeutic, and prognostic strategies for post-transplant cancer recurrence.

1. Introduction

Liver transplantation is the most effective treatment for various end-stage liver diseases, including decompensated liver cirrhosis, acute liver failure, hepatic malignancy, and metabolic disease. Among these, hepatic malignancy is one of the major indications for liver transplantation and accounts for over 20% of all cases of liver transplantation [1]. Rigorous selection criteria are applied to best benefit cancer patients, as well as for the justice of patients on the waiting list [2]. Over the past decades, the five-year overall survival (OS) rate of hepatocellular carcinoma (HCC) recipients has increased to 70%–80% after liver transplantation [3,4]. However, the emerging clinical challenge of post-transplant cancer recurrence severely dampens the benefits for patients.

Circulating tumor cells are a source of cancer recurrence. An allograft subjected to ischemia and reperfusion (IR) during liver transplantation also provides a suitable environment for this pathogenesis. IR injury in grafts has been demonstrated to aid circulating tumor cell homing, adhesion, migration, and growth [5], especially in marginal grafts experiencing more severe IR injury [6]. The immunosuppressive status of the recipient creates a favorable microenvironment for cancer recurrence. Graft injury also renders the uniquely tolerant organ more susceptible to immunosuppression [7]. In addition to routine immunosuppressants, patients may have a high chance of recurrence because they lack a sufficient anti-tumor immune response [8,9]. Thus, elucidating the mechanisms of allograft IR injury and the balance between tolerance and anti-tumor immunity is essential to develop prophylactics and therapeutics for post-transplant cancer recurrence. This review will focus on hepatic regional immunity and microenvironment alteration during liver transplantation and their role in post-transplant cancer recurrence.

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2. Intrahepatic microenvironment of regional immunity in liver transplantation

2.1. Humoral microenvironment

Hepatic IR has a significant impact on the humoral microenvironmental, which leads to allograft injury as well as regional immunological homeostasis disturbance. Immediately after reperfusion, transient portal hypertension causes intrahepatic microcirculation dysfunction, directly injuring liver sinusoidal endothelial cells (LSECs) [6]. Microcirculation dysfunction presents as congestion in the sinusoid and collapse of the Disse space, and it may become more severe when vasodilation and vasocontraction factor imbalances occur due to expression changes. It is reported that within 1 h of reperfusion, endothelin-1 (ET-1) messenger RNA (mRNA) levels increase by 161%, whereas endothelial nitric oxide synthase (eNOS) expression decreases significantly and is accompanied by reduced production of nitric oxide in the blood of the portal vein and inferior vena cava [6]. These changes may further contribute to intrahepatic microcirculation dysfunction and cause prolonged parenchymal ischemia. In addition, oxidative stress due to overwhelming oxygenation immediately after reperfusion can directly damage hepatocytes and LSECs. Together with these direct and indirect influences, heat shock protein 70 and heme oxygenase-1 expression decrease in parenchymal and non-parenchymal liver cells, resulting in hepatocyte metabolic dysfunction and LSEC oxidative stress, as shown by hepatocyte mitochondrial swelling and LSEC necrosis [6]. Injured hepatocytes release various damage-associated molecule patterns (DAMPs), which act as part of the innate immune response by releasing cytokines and adhesive molecules [10].

2.2. Cellular microenvironment

The activation of residential and circulating innate immune cells participates in the inflammatory response after hepatic IR injury and consequently shapes the microenvironment as well as intrahepatic regional immunity. Residential macrophage (Kupffer cell) and recruited polymorphonuclear (PMN) cell activation is the initial activity. They recognize DAMPs (high-mobility group protein 1, heat shock proteins, DNA, RNA, etc.) released from injured hepatocytes and LSECs through pattern recognition receptors (PRRs) on the cell surface, and are activated to synthesize and secrete cytokines, chemokines, adhesive, and co-stimulatory molecules, which recruit more innate immune cells to injured sites, causing inflammation [11]. Our study shows that the acute-phase inflammatory reaction peaks between 2 h to 24 h after reperfusion, displaying increased interleukin (IL)-6, IL-15, and tumor necrosis factor (TNF)-α, C–X–C motif chemokine ligand 10 (CXCL10), and C–C motif chemokine ligand 2 (CCL2) [6]. New evidence demonstrates that in marginal grafts, the inflammatory response is even more augmented; this can be explained by changes in several molecular signaling pathways, including an increase in lipocalin-2, aldose reductase, repressor activator protein 1, nod-like receptor protein 3, CXCL10, and CXCL2, as well as the migration and activation of macrophages and neutrophils [12–15]. Circulating and bone marrow-derived myeloid-derived suppressor cells (MDSCs), mesenchymal stromal cells (MSCs), and dendritic cells (DCs) are also recruited to allografts via chemokines. In addition, hepatic stellate cells (HSCs) are activated through IR-triggered Wnt4 signaling [16,17]. These recruited and activated innate immune cells release abundant cytokines and chemokines, such as TNF, IL-1β, IL-6, IL-10, IL-12, reactive oxygen species (ROS), CXCL10, CCL2, CXCL8, and so on, to form a unique, slightly tolerant microenvironment [18]. They provide a chaotic microenvironment for acute phase graft injury, as well as for circulating tumor cell adhesion, migration, and proliferation. They can also activate effector T (T_{eff}) cells and regulatory T (T_{reg}) cells, creating a dynamic environment for either rejection or tolerance [19].

The dynamics between T_{eff} and T_{reg} cells are regulated by cytokine networks. IL-2 is a pivotal cytokine that maintains balance [20,21]. Upon activation by antigen-presenting cells (APCs), $CD4^+$ T cells are primarily activated and release proportional IL-2, which is essential for T_{reg} cell proliferation and function [22]. The ligation of IL-2 to its receptor, IL-2Rα (CD25), on T_{reg} cells depends on the differentiation status of $CD4^+$ T_{eff} cells, which must be intermediately differentiated rather than fully activated [23]. Otherwise, the effect of IL-2 is exerted on T_{eff} cells themselves rather than on T_{reg} cells [24]. This cytokine support from T_{eff} cells is extrapolated to ameliorate acute inflammation [25]. However, T_{reg} cells exert a suppressive effect on T_{eff} cell differentiation. This suppressive effect is either through inhibitory cytokines such as IL-10, transforming growth factor (TGF)-β, and IL-35, or by cellular interaction via APCs such as DCs and alternatively activated macrophages (M2) [26–30]. Alternatively, T_{eff} cells could also resist suppression by inhibiting T_{reg} cell differentiation. This resilience of T_{eff} cells can be achieved via IL-6-mediated T_{reg} cell instability, Fas ligand (FasL)-mediated T_{reg} cell death, or by directly antagonizing TGF-β via interferon (IFN)-γ [31–33]. Thus, in the liver transplant setting, an increased ratio of T_{eff}/T_{reg} will result in acute rejection, whereas a decreased ratio leads to uncontrolled infection in the acute phase or cancer recurrence in the late phase. In clinical studies, an elevated ratio of T_{eff}/T_{reg} favored tumor development in breast cancer, ovarian cancer, non-small cell lung cancer (NSCLC), and HCC [34–38]. Novel immunotherapy strategies for cancer are aimed towards rebalancing this ratio. However, due to endogenous tolerance and operative immunosuppression, the dynamics of T_{eff} and T_{reg} cells in post-transplant cancer recurrence require detailed investigation.

3. Regional humoral microenvironment favoring tumor cell homing and proliferation

The educated microenvironment caused by acute phase IR injury can not only recruit circulating tumor cells as "seed" to intrahepatic adhesion and migration, but it also provides "soil," favoring tumor cell survival and proliferation [39]. A higher expression of the chemokine CXCL10 has been identified in injured liver grafts, which is associated with the upregulated expression of its receptor—C–X–C motif chemokine receptor 3 (CXCR3)—in tumor cells. Our group demonstrated that CXCL10 intragraft expression was elevated threefold at 2 h after reperfusion, whereas its concentration in plasma increased only twofold [40]. CXCR3 expression in HCC is also two-fold higher than in non-tumor adjacent tissue [40]. Our animal model further shows that intragraft CXCL10 upregulation can last for seven days after liver transplantation and is always associated with higher expression of CXCR3 in tumor tissue. Thus, this chemokine and receptor-paired upregulation promote circulating tumor cell homing in the allograft. In addition, a disrupted microvascular barrier caused by LSEC injury during transient portal hypertension results in tumor cell invasion. HSC activation facilitates the adhesion and migration of tumor cells into the injured site [41]. IR also elicits a hypoxic and ROS-overwhelming milieu, in which cancer cells can survive because of their distinct aerobic glycolysis ability [42]. Our animal model of hepatic IR injury showed a significant decrease in glutathione peroxidase 3 (GPx3) in both liver tissue and blood, which hampered the elimination of ROS and accelerated tumor cell proliferation [43]. This study also demonstrated that GPx3 downregulation can promote tumor invasiveness directly by activating the c-Jun N-terminal kinase (JNK)-c-Jun-matrix metalloproteinase (MMP) 2 pathway [43].

Intratumoral angiogenesis is also enhanced after liver transplantation in allografts. In an animal model, higher expression of Rho kinase (ROCK) and vascular endothelial growth factor (VEGF) was found to be associated with tumor angiogenesis [44]. Upregulated CXCL10 can also directly increase the expression of ROCK and VEGF. In both clinical and animal liver transplant models, our study showed that in accordance with higher CXCL10 levels in the liver and plasma, a two-fold increase in CXCR3 expression on the surface of endothelial progenitor cells (EPCs) was found [40]. EPCs can migrate into the tumor and differentiate into endothelial cells of the intratumoral vessel, and this effect is dependent on the expression level of CXCL10. Furthermore, we also found that CXCL10 itself can promote cancer cell survival by activating an anti-apoptotic mechanism through activating transcription factor 6 (ATF6)/78 kilodalton glucose-regulated protein (Grp78) signaling activation [45]. These recent findings suggest that the altered humoral microenvironment caused by IR in liver transplantation provides the tumor with favorable soil for recurrence.

4. Regional immunological microenvironment favoring cancer recurrence

As discussed above, the pro-inflammatory microenvironment created by IR injury after liver transplantation mobilizes circulating or bone marrow-derived macrophages, neutrophils, DCs, B cells, T cells, MDSCs, and MSCs to allografts (Fig. 1). In synchronization with the pro-inflammatory response resulting in effector B and T cell activation, the regulatory immunological microenvironment is also initiated, which favors tumor recurrence [46].

4.1. Tumor-associated macrophage (TAM)

Residential or circulating macrophages can be classified into the subsets of conventional macrophages (M1) and M2 based on their distinct surface markers [47]. M2 have the potential to inhibit pro-inflammatory cytokine secretion from M1 and promote wound healing after hepatic IR injury [48]. TAMs exhibit the M2 phenotype but are closely correlated with malignancy, invasiveness, and metastasis, as well as recurrence [49,50]. Our group explored the association of M2 and TAMs with HCC occurrence and the underlying mechanism. In a rat orthotopic liver transplantation model, we observed a peak increase in intragraft and intratumoral TAMs at 2–3 weeks after reperfusion. This study also showed a significantly increased expression of CXCL10, which can recruit TAMs and promote angiogenesis by increasing granulocyte–macrophage (GM)–cancer stem cells (CSC), IL-2, monocyte chemoattractant protein 1 (MCP-1), and VEGF expression [44]. Moreover, another study indicated that higher $CD163^+$ M2 accumulation in HCC patients is an independent risk factor for poor five-year overall and recurrence-free survival [51]. $CD163^+$ M2 behave like TAMs in the promotion of tumor invasiveness by secreting CCL22 to enhance epithelial–mesenchymal transition (EMT) via Snail activation. A more specific subset of M2 macrophage—regulatory macrophages has been proposed in the liver transplantation setting. These macrophages secrete IL-10 but do not express arginase 1 and not activated by signal transducer and activator of transcription 6 (STAT6) signaling [52]. Regulatory macrophages, however, have immune tolerance because they inhibit T_{eff} cell activation and proliferation, as well as inducing T_{reg} cell generation [53]. However, the clinical

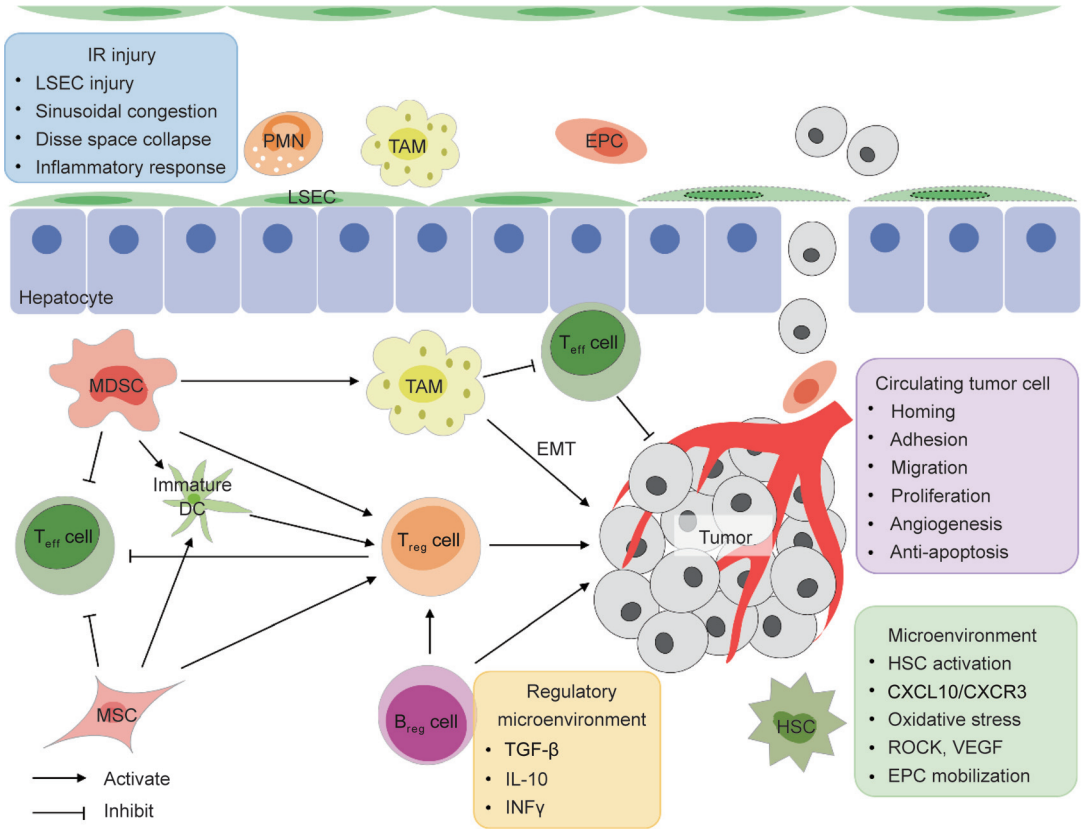

Fig. 1. Intrahepatic humoral and cellular immunological regulation promotes post-transplant cancer recurrence. TAM: tumor-associated macrophage; EMT: epithelial–mesenchymal transition; B_{reg}: regulatory B.

association of this regulatory macrophage with post-transplant cancer recurrence has not yet been determined.

4.2. Dendritic cell

DCs are the most effective APC in adaptive immunity. Both myeloid DCs and plasmacytoid DCs (pDCs) have been reported to be involved in tolerance and tumor progression. In a pediatric liver transplant study, higher pDC levels in immunosuppressed patients were found to be associated with lower immunosuppression [54]. Higher intratumoral pDC levels have also been identified as a prognostic factor for HCC recurrence after tumor resection [55]. In addition, higher expression levels of programmed death-ligand 1 (PD-L1) and CD86 on pDCs were found to be associated with a higher number of $CD4^+CD25^{hi}FOXP3^+$ T_{reg} (CD: cluster of differentiation; FOXP3: forkhead box P3) cells when immunosuppression is withdrawn [56]. Thus, these findings suggest that DCs with a higher expression of PD-L1 and CD86 could be key players in post-transplant tumor recurrence because they induce T_{reg} cell generation.

4.3. MDSC and MSC

MDSCs and bone marrow-derived MSCs are largely recruited and accumulated in allografts subjected to IR injury by pro-inflammatory cytokines [57,58]. They inhibit the inflammatory cascade and maintain microenvironment homeostasis for tissue repair and regeneration. MDSCs can suppress T_{eff} cell, B cell, and natural killer (NK) cell activity, and induce T_{reg} cell differentiation in the presence of IL-10 and IFN-γ [59–61]. Our recent study indicated a positive correlation between circulating and intrahepatic $CD33^+CD13^+CD34^+$ monocytic MDSCs with post-transplant HCC recurrence, especially in a small-for-size allograft scenario [57]. The mobilization of circulating MDSCs to the intrahepatic microenvironment depended on the elevated expression of Toll-like receptor 4 (TLR4) induced by higher expression of CXCL10 in the allograft. In addition, activated MDSCs can also interact with DCs and macrophages to promote alternatively activated macrophage differentiation and immature DC maintenance [62]. MSCs that migrated into the injured allograft showed a similar effect on the immunosuppressive microenvironment as MDSCs, but with a different mechanism involving TGF-β and prostaglandin E2 (PGE2) [63,64]. The modified immune microenvironment secretes a large amount of IL-10, favoring immune escape by tumor cells, but direct evidence is needed.

4.4. Regulatory B (B_{reg}) cell

Many subsets of B_{reg} cells have been identified in humans and mice [65]. However, they all have the common feature of IL-10 secretion, which maintains immune regulation during cancer or injury [66]. A study investigating B_{reg} cells in HCC progression indicated an accumulation of $CD19^+CD24^{hi}CD38^{hi}$ B cells at the tumor margin which was associated with more aggressive tumor behavior and a higher recurrence rate [67]. A higher number of circulating B_{reg} cells is also associated with advanced HCC staging and venous infiltration. This study further demonstrates the possible mechanism by which $CD19^+CD24^{hi}CD38^{hi}$ B cells promote tumor progression by direct interaction with cancer cells through CD40/CD154 signaling activation. The most common action of B_{reg} cells in immune regulation is the induction of $CD4^+$ T cell differentiation into T_{reg} cells [66]. The function and detailed role of B_{reg} cells in post-transplant cancer recurrence remain unclear.

4.5. Regulatory T cell

A limited number of studies have reported the role of T_{reg} cells in post-transplant liver cancer recurrence. Many subsets of T cells have a regulatory function, but thymus-derived and induced $CD4^+CD25^+FOXP3^+$ T_{reg} cells are the major regulatory cells [7]. One study reported that the detection of $FOXP3^+$ T_{reg} cells in HCC explant tissue was associated with vascular invasion, but not with post-transplant recurrence [68]. However, a more recent study including 131 HCC cases following liver transplantation or curative resection indicated that in addition to advanced cancer staging, a higher ratio of FOXP3/CD3 T cells in HCC tissue is associated with decreased recurrence-free survival [69]. These findings suggest that the intratumoral presence of T_{reg} cells predicts a poor prognosis of cancer recurrence after liver transplantation. However, the underlying mechanisms, including T_{reg} differentiation, induction, recruitment, and function during post-transplant cancer recurrence, as well as its prognostic role, remained unsolved until recently. Our study of 257 liver recipients with HCC found a positive correlation between circulating $CD4^+CD25^+FOXP3^+$ T_{reg} cell population and HCC recurrence rate [70]. The higher expression of intrahepatic TLR4, CXCL10, and its receptor CXCR3 is also associated with an increase in T_{reg} cells, especially in liver transplants using a small-for-size graft. In an animal experiment, we demonstrated that CXCL10/CXCR3 signaling is essential for intragraft T_{reg} cell mobilization and accumulation, which favors late-phase HCC recurrence after IR injury. More importantly, the correlation between circulating T_{reg} cell increase and post-transplant cancer recurrence implies that its prognostic role can be easily achieved by liquid biopsy.

5. Clinical implications

The specific intragraft immunological microenvironment provides critical information for the prediction, diagnosis, and treatment of cancer recurrence after liver transplantation. Biomarkers and immunotherapy regimens used in treating primary liver cancer could also be applied for tackling recurrent cancer, however, the disparity in the immune microenvironments is a cause for concern [71]. Because of the immunosuppressive regimen post-transplant, the compromised immunological microenvironment allows tumor cells to escape surveillance. Therefore, most immunological biomarkers for predicting or diagnosing recurrence are not present. Additionally, current immunotherapy strategies targeting relapsed tumor cells have the potential to induce allograft rejection. The identification of potential biomarkers and therapeutic targets related to the immune microenvironment is needed to increase the precise prediction and prevention of post-transplant cancer recurrence.

5.1. Biomarkers for predicting cancer recurrence

5.1.1. Vascular endothelial growth factor

Angiogenesis is vital for tumor growth; otherwise, the tumor size will be limited to less than 1–2 mm [72]. VEGF is the key regulator of intratumoral neovascularization, and its upregulation is associated with small-for-size graft injury and post-transplant cancer recurrence [39,44]. Therefore, it is possible to use circulating or intrahepatic VEGF levels to predict cancer recurrence. Duda et al. [73] reported on the application of VEGF-associated circulating biomarkers for outcome prediction in the setting of liver transplantation for HCC within the Milan criteria. Increased plasma VEGF and decreased soluble VEGF receptor (sVEGFR1) were found to decrease the odds of disease-free survival (hazard ratio = 1.45 and 0.64, respectively). Hence, the addition of VEGF to the current

prognostic criteria would improve the accuracy of post-transplant cancer recurrence prediction. Indeed, VEGF pathway inhibitors may be used for recurrent HCC treatment [74,75].

5.1.2. CXCL10

CXCL10 was recently identified as a chemokine that recruits regulatory immune cells for the tolerant microenvironment remodeling. Higher expression of both circulating and intrahepatic CXCL10 was found to be associated with recruitment of T_{reg} cells and MDSCs into the graft, as well as mobilization of EPCs for neovascularization [40,57,70]. Interestingly, the plasma level of CXCL10 was similar to the intrahepatic expression level, implying the feasibility of liquid biopsy for interpreting the regional intrahepatic immunologic microenvironment [40].

5.1.3. C-reactive protein (CRP)

CRP has recently gained attention for its predictive value in HCC recurrence. CRP is responsive to IL-1 and IL-6 secretion but is a highly sensitive inflammatory biomarker [76,77]. Although nonspecific, the value of CRP in predicting post-transplant cancer recurrence has been validated in several studies. Both liver transplant recipients from live donors and deceased donors with higher CRP levels before or immediately after operation were correlated with worse OS and disease-free survival [78–81]. In addition, high CRP levels are closely related to progressive tumor biology, such as vascular invasion, tumor size, and number. However, the correlation was only found to be significant in HCC beyond the Milan criteria. Nevertheless, easily accessible CRP levels may be used as a surveillance tool after liver transplantation.

5.1.4. Neutrophil-lymphocyte ratio (NLR)

In addition to molecular biomarkers, the use of immune cells as an indicator of post-transplant cancer recurrence has been proposed. Traditional pre-transplant prediction models for cancer recurrence, including the Milan criteria and University of California San Francisco (UCSF) criteria, only contain risk factors for tumor staging. More detailed models, such as the Risk Estimation of Tumor Recurrence after Transplant (RETREAT) score that includes more contributors such as alpha fetoprotein (AFP) and microvascular invasion on explant in addition to the Milan criteria, show better prediction performance. Most recently, the Model of Recurrence after Liver Transplantation (MORAL) score incorporated the immunological factor—NLR for outcome prediction, which showed better precision than the RETREAT score (c-statistic 0.91 vs 0.82) [82]. The inclusion of immunological parameters in the risk-prediction model reflects the immunological essence of tumor recurrence, especially within the milieu of complex regional immunity, but further validation in the relevant clinical cohorts is warranted.

5.2. Immunotherapy for post-transplant cancer recurrence

5.2.1. Targeted immunotherapy

Current immunotherapy mostly targets T-cell inactivation via checkpoint inhibition [83–85]. PD-1/PD-L1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors have been extensively used in many clinical trials designed for advanced HCC and showed significant superiority for progression-free or OS compared with sorafenib regimens [86–89]. However, immune checkpoint inhibitors (ICIs) for post-transplant recurrent HCC are rare because of the complications in balancing the anti-tumor immune response and allograft rejection. To date, there are only case reports on the use of checkpoint inhibitors for cancer that recurred after liver transplantation. In the 14 cases reported, the median progression-free survival duration after the use of ICIs was only 1.3 months, and the median OS duration was only 1.1 months [90–96]. The major causes of the 11 deaths in these patients were graft rejection (5/11, 45.4%) or disease progression and multiorgan failure (6/11, 54.5%) [97,98]. Notably, the application of the CTLA-4 inhibitor ipilimumab in two patients with recurrent melanoma showed no graft rejection or immune-related side effects [91,95]. This may be due to the expression of CTLA-4 in both T_{eff} and T_{reg} cells. In the absence of more evidence involving a high volume of patients in a post-transplant setting and new regimens containing ICIs, immunotherapy for recurrent cancer after liver transplantation should be avoided.

5.2.2. Cell therapy

The limitations of ICIs for treating recurrent cancer in the liver-transplant setting are the systemic medication and the non-specific reactivation of T_{eff} cells. Therefore, enhancing the regional intrahepatic immune response for tumor-specific antigens or the tumor microenvironment would theoretically increase the efficacy and reduce the side effects of allograft rejection.

Chimeric antigen receptor (CAR) T cells are the most popular cell therapy for killing tumors. This approach extracts T cells from healthy patients and engineers them with CARs targeting tumor-specific antigens [99]. The technique allows the recognition of tumor cells without responding to non-tumor cells, thereby decreasing the side effects of allograft rejection. However, to date, the regimen has rarely been reported and is only seen in some preclinical studies for treating HCC without liver transplantation [100]. The development of CAR T cell therapy was hindered by the common side effects of severe cytokine release syndrome [101]. Another type of adoptive cell therapy using T-cell receptor (TCR)-modified T cells showed promising results in liver transplant patients with cancer recurrence. In this study, TCR modified T cells were engineered to recognize hepatitis B virus (HBV)-specific antigens for treating HBV-related HCC recurrence and showed effective outcomes for widespread extrahepatic recurrent lesions [102,103]. This encouraging result implies that the key to successfully treating post-transplant recurrent cancer by adoptive immune cell therapy is finding the tumor-specific antigen, and this only required a small number of cells and did not induce cytokine release syndrome. In addition, cytokine-induced cell therapy, in which donor-derived NK cells induced by IL-2 were infused to prevent post-transplant tumor recurrence, showed no HCC recurrence at the two-year follow-up [104]. However, this was only a single-arm pilot study, and evidence should be further explored in a larger cohort. Interestingly, our recent study using engineered MSCs carrying highly expressed GPx3 showed a killing effect on cancer in an orthotopic liver cancer mouse model [105]. Specifically, the delivery was unique as it utilized a magnet-driven micro-scale biomaterial for transporting the MSCs to the targeted area [105,106]. This would ensure precise regional intrahepatic microenvironment remodeling and eliminate potential adverse effects in normal liver tissues. In total, adoptive cell therapy is the most effective way to treat recurrent cancer after liver transplantation. With the increasingly intricate design of the therapeutic immune cell itself or the delivery system, this approach shows a bright future.

6. Conclusions

Post-transplant cancer recurrence has become an emerging clinical challenge, but an undetermined underlying mechanism hinders the development of effective therapeutics. Recipient immunological microenvironment alteration after liver transplantation plays a critical role in cancer development. The regional hepatic immunological microenvironment is largely induced by IR injury, which favors cancer recurrence after liver transplantation. The humoral microenvironment shapes the graft to benefit cancer

invasiveness and metastasis by promoting tumor cell adhesion, migration, proliferation, and intratumoral angiogenesis. In addition, the regulatory, innate, and adaptive immune responses, including TAMs, DCs, MDSCs, MSCs, and T_{reg} cells, also educate the microenvironment to favor tumor cell growth and immune escape. The updated regional immunological findings in liver transplantation implicate new therapeutics targeting the intragraft immunological microenvironment and provide a potential prognostic tool for late-phase cancer recurrence.

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Compliance with ethics guidelines

Jiang Liu, Chung Mau Lo, and Kwan Man declare that they have no conflict of interest or financial conflicts to disclose.

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