The Impact of Liver Graft Injury on Cancer Recurrence Posttransplantation

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Abstract: Liver transplantation is the most effective treatment for selected patients with hepatocellular carcinoma. However, cancer recurrence, posttransplantation, remains to be the critical issue that affects the long-term outcome of hepatocellular carcinoma recipients. In addition to tumor biology itself, increasing evidence demonstrates that acute-phase liver graft injury is a result of hepatic ischemia reperfusion injury (which is an inevitable consequence during liver transplantation) and may promote cancer recurrence at late phase posttransplantation. The liver grafts from living donors, donors after cardiac death, and steatotic donors have been considered as promising sources of organs for liver transplantation and are associated with high incidence of liver graft injury. The acute-phase liver graft injury will trigger a series of inflammatory cascades, which may not only activate the cell signaling pathways regulating the tumor cell invasion and migration but also mobilize the circulating progenitor and immune cells to facilitate tumor recurrence and metastasis. The injured liver graft may also provide the favorable microenvironment for tumor cell growth, migration, and invasion through the disturbance of microcirculatory barrier function, induction of hypoxia and angiogenesis. This review aims to summarize the latest findings about the role and mechanisms of liver graft injury resulted from hepatic ischemia reperfusion injury on tumor recurrence posttransplantation, both in clinical and animal cohorts.

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Liver transplantation is the first curative treatment for the selected recipients with hepatocellular carcinoma (HCC). It offers significant higher long-term survival prospects compared with other surgical treatments, such as liver resection or local ablation.[1,2] With the accumulation of liver transplantation for HCC patients, tumor recurrence posttransplantation has become a critical issue affecting the long-term outcome of liver transplantation.[3] Because of the different selection criteria, the posttransplant tumor recurrent rates are varied from center to center.[4] In general, the posttransplant cancer recurrence and metastasis are significantly correlated with vascular invasion, tumor differentiation, tumor size, and stage.[5,6] In addition to liver tumor biology itself, both clinical and animal studies have shown that hepatic ischemia reperfusion (I/R) injury promotes tumor recurrence after liver transplantation.[7,8] Hepatic I/R injury, an inevitable consequence during liver transplantation, usually occurs during cold preservation of liver graft and subsequent warm reperfusion after implantation into the recipient.[9] Hepatic I/R injury can contribute to primary liver graft dysfunction or nonfunction and lead to a higher incidence of acute and chronic rejection.[10-13] This review aims to provide the latest updates regarding the role and mechanism of hepatic I/R injury on tumor recurrence after liver transplantation.

Liver Graft I/R Injury Promotes Tumor Recurrence Posttransplantation: Clinical Evidences

Increasing clinical evidence shows that graft I/R injury promotes tumor recurrence after liver transplantation. The degree of liver graft injury was reported to be determined by the time duration of cold and warm ischemia during liver transplantation, which was significantly correlated with peak

transaminase levels within 1 week after liver transplantation.[8] Patients with warm ischemia time (WIT) of more than 50 minutes showed significantly higher aspartate aminotransferase level compared with those with WIT of 30 minutes or less. Furthermore, ALT and aspartate aminotransferase levels were significantly higher in the patients with cold ischemia times (CITs) of more than 10 hours than the patients with CIT of less than 4 hours. Prolonged CIT and WIT were significantly associated with increased HCC recurrent rates and considered as independent risk factors for HCC recurrence postliver transplantation.[8,14] Nagai et al[8] showed that 1- and 3-year recurrent rates posttransplantation were 3.5% and 8% for CIT of less than 4 hours, respectively, and 15.5% and 25.9% for CIT of more than 10 hours, respectively. Consistently, 1- and 3-year recurrent rates were 7.4% and 13% for WIT of 30 minutes or less, respectively, and 17.2% and 23.5% for WIT of more than 50 minutes, respectively.[8] Kornberg et al[14] also confirmed that extended ischemia time duration increased the risk of HCC recurrence after liver transplantation. In this study, a total of 103 liver transplant patients with HCC were included, and 24 patients (23.3 %) developed tumor recurrence after liver transplantation. Mean durations of CIT (468.0 vs 375.5 minutes) and WIT (58.4 vs 45.7 minutes) were significantly longer in patients with tumor recurrence compared with those without recurrence. Recurrence-free survival rates at 1- and 3-year postliver transplantation were 97.2% and 92.8%, respectively, in WIT of 50 minutes or less, whereas it significantly decreased to 61.4% and 42 %, respectively, in WIT of more than 50 minutes. On the other hand, the therapy targeting hepatic I/R injury effectively reduced the risk of early HCC recurrence after liver transplantation.[15] Kornberg et al[14] reported that treating hepatic I/R injury with prostaglandin E1 significantly increased the 3- and 5-year recurrence-free survival rates from 65.3% and 63.1% to 87.9% and 85.7%, respectively. Furthermore, Orci et al[16] showed that donor WIT (>19 minutes) was associated with HCC recurrence both in a univariable analysis and multivariable analysis.

The Effect of Graft Type on Tumor Recurrence After Liver Transplantation

The success of liver transplantation has significantly increased the demand for the liver graft. However, donor organ shortage has become the biggest challenge of liver transplantation.[17] To decrease the gap between the demand and availability of donors, the use of marginal grafts has become more liberal. Living donors, donation after cardiac death (DCD), and steatotic donors have been considered as promising sources of organs for liver transplantation.[18,19] However, increasing evidences showed that these grafts are associated with higher incidence of acute-phase liver graft injury.

Living Donor Liver Transplantation

Living donor liver transplantation (LDLT) has been developed as an alternative choice to overcome the critical shortage of liver grafts from deceased donors and decreased the drop-off of cancer patients.[2] However, the liver graft from living donors are usually small for size for the recipient and are associated with a higher incidence of acute-phase liver graft injury.[20] The effect of LDLT on tumor recurrence posttransplantation remains controversial.[21] Compared with deceased donor liver transplants (DDLTs), HCC patients who received LDLT had higher tumor recurrence and inferior survival rate posttransplantation.[22-25] In the Adult to Adult Living Donor Liver Transplantation Cohort Study of United States, the researchers reported that the unadjusted 5-year tumor recurrence rate in LDLT patients was higher than that in DDLT patients (38% vs 11%). After adjustment for tumor characteristics, HCC recurrence rate remained higher in LDLT patients compared with DDLT patients.[24] This is consistent with the result of LDLT for liver cancer patients from Hong Kong.[26] However, comparable results of HCC recurrence and outcome between LDLT and DDLT patients were also reported in eastern and western countries.[27-29]

Liver Transplantation with DCD

In recent years, DCD has been adapted for expanding the donor pool.[30] DCD refers to the recovery of organs from a donor who has experienced circulatory arrest after withdrawal of life-sustaining medical interventions. Compared with liver grafts from donors after brain death (DBD), DCD liver grafts were associated with longer WIT, increased risk of graft failure, inferior outcomes, and higher tumor recurrence.[13,16,31-34] A meta-analysis using 11 studies reported that DCD recipients experienced worse 1-year patient and graft survival, higher rates of biliary complications, and ischemic cholangiopathy when compared with DBD recipients.[31] Orci et al[16] reported that recipients of organs from DCD donors with prolonged warm ischemia had higher HCC recurrence rates after liver transplantation. A study using the data from the Scientific Registry of Transplant Recipients showed that patients transplanted with DCD graft have lower 5-year survival (55.9%) compared with the recipients with DBD graft (63.8%).[35] However, the effect of the use of DCD on tumor recurrence posttransplantation for HCC remains controversial. Some reports showed similar outcomes between DCD and DBD.[36,37] A recent report using the data from Scientific Registry of Transplant Recipients showed that HCC recurrences in DBD and DCD group were 12.1% and 12.3%, respectively.[38] Furthermore, Khorsandi et al[36] reported that DCD has no influence on cancer-related survival after liver transplantation for HCC.

Steatotic Graft

In recent years, hepatic steatosis has become the most common liver disorder, which is caused by a variety of etiologies such as diabetes, obesity, and alcohol consumption.[39] Twenty-six percent of potential donors for liver transplantation received a diagnosis of hepatic steatosis.[40,41] More evidences showed that steatotic grafts are more prone to hepatic I/R injury after liver transplantation.[42,43] Importantly, the consequences of transplantation using fatty liver graft largely depend on the degree of steatosis.[44-46]

It has been confirmed that severe steatosis (>60%) is related to higher incidence of primary nonfunction, inferior allograft survival after liver transplantation.[47-49] Orci et al[16] showed that severe graft steatosis was linked to an increased risk of HCC recurrence after liver transplantation in their large clinical cohort with 3007 patients. Whether liver graft with moderate steatosis has similar outcome compared with normal graft is still controversial.[44,45] Nevertheless, the graft

with mild steatosis is believed to have no adverse effect on the outcomes of liver transplantation.[48,50]

Mechanisms of Hepatic I/R Injury Promoting Tumor Recurrence Posttransplantation

Several evidences have proposed a number of mechanisms of hepatic I/R injury promoting tumor recurrence[7,51-54] (Figure 1). The inflammatory response resulted from hepatic I/R injury not only makes the liver microenvironment favorable for tumor cell growth, migration, and invasion through the disturbance of microcirculatory barrier function, induction of hypoxia, and angiogenesis but also makes the tumor cells more aggressive by directly activating tumor cell migration and invasion pathways. In addition, acute-phase liver graft injury also directly induces the circulatory progenitor cells and immune cells mobilization and recruitment to liver graft, hence further promoting the late phase tumor recurrence postliver transplantation.

Microvascular Dysfunction, Hypoxia, and Angiogenesis Induced by Hepatic I/R Injury Produces a Favorable Environment for Liver Tumor Recurrence

During hepatic I/R injury, endothelial cell swelling, as well as a local imbalance of vasoconstrictors and vasodilators together with neutrophils infiltration, leads to microcirculatory disturbances.[55,56] Microvascular dysfunction plays a crucial role in promoting tumor outgrowth or metastasis.[57,58] Hepatic sinusoids lose their integrity because of the lining cell disruption resulting from hemodynamic force during I/R.[20] It not only is the major cause of acute-phase liver graft injury but also may facilitate tumor cell dissemination at late phase. Furthermore, infiltrated lymphocytes can induce hepatocytes apoptosis through stimulation of Fas signaling, which may alter liver tissue structure and facilitate tumor outgrowth.[59] van der Bilt et al[51] also demonstrated that hepatic I/R injury accelerates tumor growth predominantly surrounding necrotic parenchyma. Moreover, restoration of ischemia-induced microcirculation disturbance by treatment with L-arginine decreases the outgrowth of micrometastasis.[57]

Ischemia and microcirculatory disturbances are the main causes inducing hypoxia during hepatic I/R injury. Hypoxia contributes to I/R-accelerated tumor growth and metastasis through several distinct pathways. In response to liver tissue hypoxia, the transcription factor hypoxia-inducible factor (HIF-1α) stabilizes.[57,60] HIF-1α is a strong promoter of tumor cell proliferation, anaerobic metabolism, migration, and angiogenesis.[61-63] van der Bilt et al[57] demonstrated that I/R injury accelerates tumor growth that occurred in the areas of hypoxia, which is associated with increased liver parenchymal HIF-1α expression. The destabilization of HIF-1α by 17-dimethylaminoethylamino-17-demethoxygeldanamycin can attenuate hepatic I/R injury–stimulated tumor growth.[57] Furthermore, hypoxia also stimulates tumor cell proliferation and tumor angiogenesis by inducing the secretion of growth factors and angiogenic factors, such as vascular endothelial growth factor (VEGF).[64,65] VEGF, as a major angiogenic factor, is upregulated in ischemic liver by multiple factors including hypoxia and inflammatory cytokines and chemokines. VEGF plays a pivotal role in tumor growth by improving tumor angiogenesis.[66] Masood et al[66] reported that either inhibition of VEGF expression or prevention of VEGF binding to VEGFR suppresses the growth of VEGFR expressing tumor cell lines.

Inflammatory Response Results From I/R Injury Educates Tumor Cells to Be More Aggressive by Triggering Cell Adhesion, Migration, and Invasion Signaling

More evidence shows that I/R injury is a typical inflammatory response involving a complex web of interactions between various cellular (macrophages/neutrophils) and humoral contributors (cytokines/chemokines).[12,67] During hepatic I/R injury, activated macrophages contribute to the
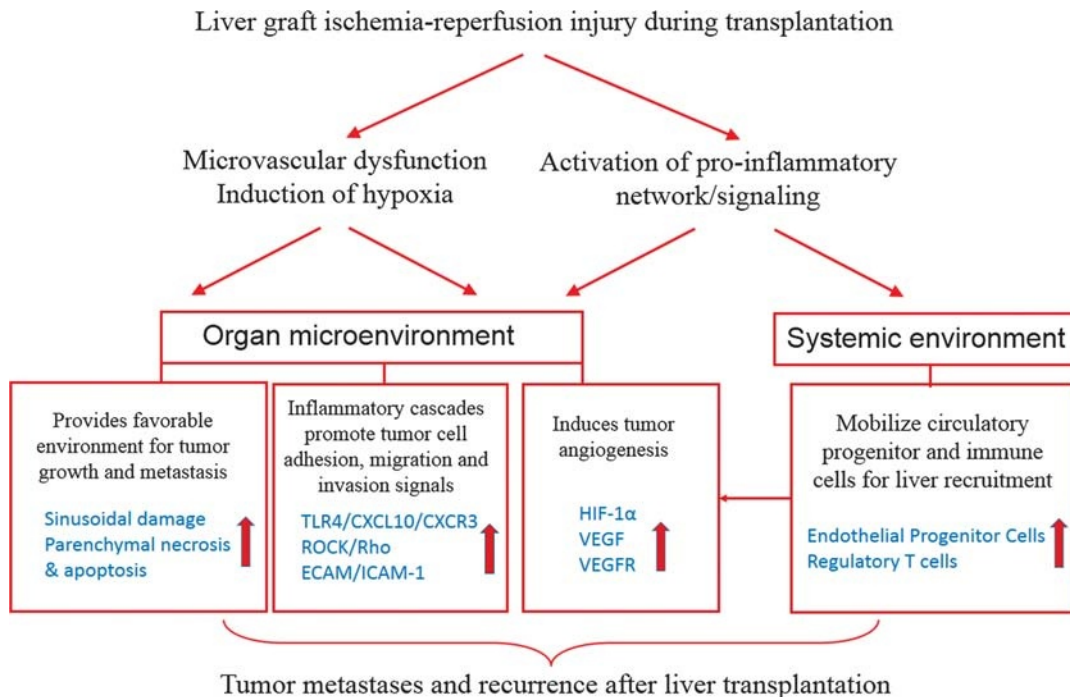

FIGURE 1. Acute-phase liver graft injury promotes late-phase tumor recurrence posttransplantation.

generation of a host of proteins associated with inflammatory responses and secretion of proinflammatory cytokines/chemokines.[67,68] Except to directly damage hepatocyte, these inflammatory cytokines/chemokines can also activate and recruit more circulating neutrophils into in the liver. After neutrophils transmigrate to the liver, inflammatory factors, reactive oxygen species, and proteases are active, which are able to directly cause hepatocellular injury and aggravate the inflammatory response.[69,70]

Hepatic I/R stimulates the expressions of many proinflammatory cytokines such as tumor necrosis factor α and interleukin 1, which can markedly upregulate the expressions of adhesion molecules such as E-selectin and intercellular adhesion molecule 1 in endothelial cells.[71] E-selectin and intercellular adhesion molecule 1 have been reported to play critical roles in tumor cell adhesion and growth.[72,73] E-selectin and intercellular adhesion molecule 1 induces the metastasis of tumor cells not only by facilitating the adhesion of cancer cells to endothelial cells[74-76] but also by promoting the capture of leukocytes rolling along the vascular endothelium.[77,78] Kurata et al[79] showed that the inhibition of tumor necrosis α–induced expression of E-selectin by antithrombin reduces I/R-induced hepatic metastasis of colon cancer cells.

In addition to facilitating cell adhesion, hepatic I/R injury also promotes tumor growth and metastasis through activating cell migration and invasion pathways.[7] Our animal experiments demonstrated that the Rho family (Rac1, rho-associated protein kinase, and Cdc42) is overexpressed in the tumor tissues from rats undergoing hepatic I/R injury and major hepatectomy. The upregulation of Rho signaling is also associated with the invasive tumor growth pattern and remarkable local and distant metastatic features.[7] Consistently, overexpression or activation of Rho signaling pathways may also induce tumor cell migration, invasion, and progression, significantly.[80,81] Rho-associated kinase inhibitor can suppress the cancer cell migration, thereby reducing tumor recurrence after liver transplantation.[82] Chemokines are critical mediators involved in the process of I/R injury and induction of cancer cell invasive potentials.[83-85] We showed that C-X-C motif chemokine ligand 10 (CXCL10) is not only upregulated in small-for-size graft at the early phase after liver transplantation but also overexpressed in tumor tissue developed from small-for-size grafts at the late-phase posttransplantation.[54] CXCL10 may not only affect the tumor microenvironment by increasing the intragraft macrophage infiltration but also directly stimulate the invasive properties of the tumor cell itself.[54] Furthermore, matrix metalloproteinases (MMPs) have been shown to be crucial in promoting tumor invasiveness and metastasis by allowing the initial migration and seeding of tumor cells.[86,87] Nicoud et al[88] demonstrated that MMP-9 is upregulated after I/R injury and promotes the outgrowth of colorectal carcinoma micrometastasis. The inhibition and silence of MMP-9 may reverse the I/R-induced tumor growth and metastasis.

Graft I/R Injury Mobilizes Circulatory Progenitor and Immune Cells to Facilitate Tumor Recurrence Posttransplantation

Endothelial progenitor cells (EPCs), a subtype of progenitor cells in postnatal bone marrow, can migrate to the peripheral circulation under physical and pathological conditions and differentiate into mature endothelial cells.[89,90] Increasing evidences indicated that EPCs play an important role in tumor growth through facilitating early-stage tumor vascularization and controlling tumor angiogenic switch of tumor metastasis transition.[91-93] Circulating EPCs are higher in the patients with advanced HCC. It may act as a potential prognostic surrogate marker in HCC patients.[94,95] We have demonstrated that CXCL10/C-X-C motif chemokine receptor 3 (CXCR3) signaling, which was upregulated by acute-phase liver graft injury, mobilizes circulatory EPCs into liver graft, hence promoting tumor growth and recurrence after liver transplantation.[53] Patients with small-for-size liver grafts had significantly higher HCC recurrence, which is associated with more circulating EPCs and higher expression of intragraft and circulatory CXCL10. The knockout of CXCL10/CXCR3 signaling significantly reduces the mobilization of EPCs after liver I/R injury. Furthermore, both EPCs injection and CXCL10 treatment can directly enhance the orthotopic liver tumor growth, angiogenesis, and metastasis in a nude mice liver tumor model. These results indicated that CXCL10/CXCR3 signaling can directly mobilize circulatory EPCs posttransplantation and thereby promote tumor angiogenesis. Lim et al[96] also reported that hepatic I/R injury leads to the mobilization of bone marrow–derived EPCs and increases tumor growth by enhancing angiogenesis in mouse model of colorectal liver metastasis. Targeting at EPCs with antiangiogenic drugs may enhance the sensitivity of tumors in response to chemotherapeutics.[97] We also showed that FTY720, an immune modulator, suppresses liver tumor recurrence and metastasis through attenuating hepatic I/R injury and reducing the number of circulating EPCs.[98]

Furthermore, a number of evidence has demonstrated that regulatory T cells (Treg cells) can promote tumor growth and metastasis. Treg cells play important roles in maintaining immune tolerance and preventing allograft rejection.[99,100] However, this negative regulatory activity can also suppress the host immune surveillance function, thereby promote tumor growth and progress.[101] We recently demonstrated that posttransplant inflammatory responses mobilize more circulatory Treg cells, which promote late-phase tumor recurrence posttransplantation.[52] More circulating Treg cells, together with higher expression of CXCL10/CXCR3, can be detected in the recipients with small-for-size liver graft and tumor recurrence. In mouse model, the knockout of CXCL10 significantly decreases hepatic recruitment of CXCR3+ Treg cells after hepatic I/R injury. Moreover, the knockout of CXCL10 and depletion of Treg cells may directly inhibit tumor recurrence after hepatic I/R injury.

In summary, liver transplantation is an effective treatment for the selected HCC patients. However, tumor recurrence posttransplantation remains to be the major obstacle for achieving long-term survival of the liver cancer recipients. Obviously, the mechanism of graft injury accelerating tumor growth and recurrence is multifactorial. Posttransplant tumor recurrence and metastatic properties are not only determined by the biological behavior of cancer cells but also because of the recruitment of circulatory progenitor cells and immunoregulatory cells during liver transplantation. The inflammatory microenvironment may play critical roles on orchestrating cancer cells together with immune cells to facilitate tumor recurrence posttransplantation. An updated and improved understanding of liver I/R injury and tumor recurrence will facilitate to develop new therapeutic measures, not only for attenuating early phase liver graft injury

but also for preventing late-phase tumor recurrence after liver transplantation.

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