Dig Dis Sci (2014) 59:2058–2068
DOI 10.1007/s10620-014-3182-7

REVIEW

The Role of Hepatic Ischemia–Reperfusion Injury and Liver Parenchymal Quality on Cancer Recurrence

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Received: 13 March 2014 / Accepted: 20 April 2014 / Published online: 3 May 2014

Abstract Hepatic ischemia/reperfusion (I/R) injury is a common clinical challenge. Despite accumulating evidence regarding its mechanisms and potential therapeutic approaches, hepatic I/R is still a leading cause of organ dysfunction, morbidity, and resource utilization, especially in those patients with underlying parenchymal abnormalities. In the oncological setting, there are growing concerns regarding the deleterious impact of I/R injury on the risk of post-surgical tumor recurrence. This review aims at giving the last updates regarding the role of hepatic I/R and liver parenchymal quality injury in the setting of oncological liver surgery, using a "bench-to-bedside" approach. Relevant medical literature was identified by searching PubMed and hand scanning of the reference lists of articles considered for inclusion. Numerous preclinical models have depicted the impact of I/R injury and hepatic parenchymal quality (steatosis, age) on increased cancer growth in the injured liver. Putative pathophysiological mechanisms linking I/R injury and liver cancer recurrence include an increased implantation of circulating cancer cells in the ischemic liver and the upregulation of proliferation and angiogenic factors following the ischemic insult. Although limited, there is growing clinical evidence that I/R injury and liver quality are associated with the risk of post-surgical cancer recurrence. In conclusion, on top of its harmful early impact on organ function, I/R injury is linked to increased tumor growth. Therapeutic strategies tackling I/R injury could not only improve post-surgical organ function, but also allow a reduction in the risk of cancer recurrence.

Keywords Ischemia–reperfusion injury · Liver steatosis · Hepatocellular carcinoma · Hepatectomy · Liver transplantation

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Introduction

Ischemia–reperfusion (I/R) injury is a process whereby parenchymal damage caused by blood flow deprivation is accentuated upon organ reperfusion. I/R injury is a common clinical challenge, as it arises in various clinical scenarios such as cerebrovascular disease [1], circulatory shock [2], cardiovascular [3] and liver surgery [4], and transplantation medicine [5, 6]. I/R injury, through the liberation of radical oxygen species and the activation of inflammatory pathways, induces cellular injury and microcirculatory damage, which translate to organ dysfunction, morbidity, and increased health care costs [7, 8]. In

the liver, I/R injury is at the source of poor outcomes after surgical procedures such as hepatectomy and liver transplantation [7].

Lowering intraoperative blood loss during hepatectomy is a crucial factor determining the success of liver resection, as surgical bleeding and transfusion are associated with poor outcomes in both the short- and long term [9–11]. Thus, liver surgeons have the option to apply vascular inflow control procedures and sometimes total vascular exclusion to reduce intraoperative bleeding. The major drawback of such strategies is that they can induce I/R injury to the residual liver parenchyma [4, 12]. In liver transplantation, tissue damage at reperfusion is mostly correlated with warm and cold ischemia times and leads in turn to poor graft function [13] and biliary complications [14, 15].

In addition to the direct I/R-mediated harmful effect on the liver parenchyma, underlying organ physiology and the presence of pre-established tissue lesions (e.g., steatosis) interact with I/R injury [16]. Hepatic steatosis increases susceptibility of the liver to I/R injury through microcirculatory dysfunction caused by sinusoid compression by lipid droplets [17–19] and reduced cellular energy stock and cell membrane disruption via I/R-mediated lipid peroxidation [20]. Moreover, aged livers also appear to be less tolerant to I/R injury [21]. This is particularly relevant to the transplantation setting, where the use of marginal donors, such as (macro-) steatotic graft or livers from older donors, has been shown to be associated with poorer outcomes after liver transplantation [22, 23].

Besides jeopardizing patients' outcome in the early postoperative period, there are growing concerns surrounding the role of hepatic I/R injury and surgical trauma in the oncological setting. Surgical manipulation of the liver induces the release of cancer cells in the blood stream, which could in turn engraft into the remnant liver or into the newly transplanted liver graft and constitute the source of tumor recurrence [24, 25]. I/R injury induces the expression of cytokines, growth factors, and adhesion molecules that have been repeatedly reported to foster tumor growth [26–28]. The aim of this review was to give the last updates regarding the role of hepatic I/R injury with regard to oncological outcomes, focusing on experimental models used to assess this issue, clinical evidence, and potential therapeutic strategies aimed at reducing the risk of I/R-mediated post-surgical tumor recurrence. Both the settings of liver resection and transplantation will be explored.

Methods

The design of the current manuscript consists of a narrative (non-systematic) review. Of note, systematic reviews of experimental studies are feasible [29] and may help answer a specific research question. Despite such a design would have been a possibility, the multiple settings and research questions (liver resection: pedicle vs. no pedicle clamping, hemi-vascular occlusion, therapeutic strategies; liver transplantation: donation after cardiac death, small-for-size) that were aimed to be addressed here fostered us to undertake a narrative review. A literature search was performed in Medline, using the following keywords: ischemia–reperfusion, steatosis, small-for-size, liver cancer, hepatocellular carcinoma, colorectal metastases, colon adenocarcinoma, and tumor growth. Only studies written English and published in peer-reviewed journals were considered for inclusion. Studies were categorized according to their research design (experimental, clinical retrospective, and clinical prospective). Study eligibility for inclusion was based on their ability to provide composite insight into the link between liver parenchyma and cancer behavior and to guide the reader to relevant primary and secondary sources for further reading.

Discussion

Preclinical Evidence

Hepatic Ischemia–Reperfusion Injury Enhances Hepatic Tumor Growth

There are reports dating back to the 1960s where ischemic tissue was observed to offer a favorable environment for the implantation and growth of blood-borne metastases [30, 31]. In the liver, to evaluate the link between hepatic I/R injury and cancer behavior, research groups have used several hepatic I/R injury models complemented with the inoculation of different tumor cell lineages (Table 1). In a rat colon adenocarcinoma metastasis model, Kurata et al. [32] showed that, compared to sham-operated animals, 30-min partial (median and left lobes) ischemia to the liver induced a 14-fold increase in the number of metastatic nodules ($p < 0.01$). Using a mouse colon adenocarcinoma model, Gorden et al. reported similar findings, with an increase in both the number of nodules and tumor volume in animals undergoing a 30-min course of 70 % ischemia (via clamping of the median and left lobes) [33]. In another experiment using a hepatocellular carcinoma (HCC) cell line, Man et al. [34] observed markedly higher tumor growth and invasiveness in those animals subjected to a 60-min period of ischemia followed by 60 min of reperfusion as compared to sham-operated animals. Several other preclinical reports [35–38] explored the impact of hepatic I/R injury on tumor growth and metastatic potential, as illustrated in Table 1.

Table 1 Ischemia–reperfusion injury fosters liver metastases, experimental models

Doi [40]	Rat	30 versus 60 min 70 % ischemia	Colon adenocarcinoma (RCN-H4)	↑ E-selectin in liver tissue of ischemic groups compared to control
Doi [35]	Rat	60 min 70 % ischemia	Colon adenocarcinoma (RCN-H4)	Administration of neutrophil elastase inhibitor (ONO-5046) after I/R reduced the number of hepatic metastases
Yoshida [37]	Rat	*Continuous*: 60 min 70 % ischemia *Intermittent*: 15 min periods of 70 % ischemia (4×), with 15 min of reperfusion between ischemia	Colon adenocarcinoma (RCN-H4)	↓ E-selectin in liver tissue of the intermittent ischemia group compared to continuous ischemia
Van der Bilt [62]	Mouse	*Continuous*: 45 min 40 % ischemia *Intermittent*: 15 min periods o 40 % ischemia (×3), with 5 min of reperfusion between ischemia *Ischemic pre-conditioning*: 10 min 40 % ischemia, followed by 15 min of reperfusion, before 45-min 40 % ischemia	Colon adenocarcinoma (C26)	Accelerated tumor growth localized around necrotic tissue areas. Ischemic lobes show lowered levels of glutathione compared to non-ischemic lobes
Kurata [32]	Rat	30 min 70 % ischemia followed by resection of non-ischemic lobes	Colon adenocarcinoma (RCN-H4)	Antithrombin inhibited the increase in the number of metastatic nodules in animals subjected to I/R injury, by blunting the TNF-α-induced expression of E-selectin, through an increase in endothelial PGI_2 production
Man [34]	Rat	60 min 60 % ischemia 60 min 60 % ischemia plus major hepatectomy	Hepatoma (MCA-RH7777)	↑ Proliferation (PCNA staining) of tumor cells and VEGF in the ischemic group, ↑ invasiveness genetic profile (expression of ROCK and Cdc-42) in animals receiving both I/R and hepatectomy
Van der Bilt [82]	Mouse	45 min 40 % ischemia	Colon adenocarcinoma (C26)	I/R injury-mediated tumor growth occurs preferentially in areas of tissue hypoxia, and elevated HIF-1α expression HIF-1α was detected in nuclei of tumor cells at the tumor-necrosis margin in the ischemic group Attenuation of microcirculatory damage, hypoxia and hepatocellular damage by atrasentan/L-arginine allows a reduced tumor outgrowth
Nicoud [33]	Mouse	30 min 70 % ischemia	Colon adenocarcinoma (MC38)	↑ MMP9 mRNA and protein expression in liver tissue of ischemic group Doxycycline inhibits I/R-induced MMP9, and decreases hepatic metastases Genetic deletion of MMP9 prevents hepatic metastases
Van der Bilt [39]	Mouse	*Ischemia time*: 20 min versus 30 min versus 45 min 40 % ischemia *Steatosis*: 6-week high-fat diet versus normal diet *Age*: Adult mice (12–13 months) versus 10–12 weeks *Gender*: male versus female	Colon adenocarcinoma (C26)	Steatosis and male gender lead to heightened I/R-mediated tumor outgrowth
Tamagawa [36]	Rat	60 min 70 % ischemia	Colon adenocarcinoma (RCN-H4)	↑ Plasma and liver tissue VEGF in the ischemic group compared to control
Yoshimoto [38]	Nude mouse	20-min total ischemia	Human pancreatic cancer (Capan-1)	↑ E-selectin in liver tissue of the ischemic group compared to control

I/R ischemia/reperfusion, *VEGF* vascular endothelial growth factor, *MMP-9* matrix metalloproteinase-9, *HIF-1α* hypoxia-inducible factor 1α, *PCNA* proliferating cell nuclear antigen, *PGI_2* prostaglandin I_2, *ROCK* Rho-associated protein kinase, *Cdc-42* cell division control protein 42 homolog

Looking at the impact of duration of ischemia on I/R injury-mediated metastasis development, van der Bilt et al. reported significant differences in terms of hepatic metastases growth according to the duration of warm ischemia. Mice subjected to 20 min of ischemia had a similar tumor burden compared to non-ischemic liver tissue (sham-operated animals or non-clamped liver lobes). In contrast, after 30 and 45 min of ischemia, mice had a significantly increased tumor burden compared to non-ischemic controls [39]. In the same way, Doi et al. observed that rats undergoing 60-min segmental (70 %) hepatic ischemia developed significantly more nodules than rats subjected to 30-min pedicle clamping. Contrasting with the findings by the Utrecht group that observed a five- to sixfold accelerated tumor outgrowth in the ischemic liver as compared to non-occluded lobes, Doi et al. reported that I/R injury leads to increased tumor growth in all liver lobes (even the non-clamped lobes), suggesting a dissemination of the effect of I/R injury to liver tissue not directly enduring parenchymal damage [40]. Although apparently self-contradictory, these differences could be linked to several divergences in the models used. First, the experiments were undertaken in two different animal models (rat [40] vs. mouse [39]) reminding that pathophysiological pathways may differ according to the species under investigation. Second, the sequence of procedures applied in these two studies were not strictly comparable: while Doi et al. [40] inoculated cancer cells in the spleen after 60 min of reperfusion, van der Bilt et al. [39] allowed pre-inoculated cells to circulate for 5 days before the induction of I/R injury. Based on these observations, one could speculate that variability in terms of cancer cell concentration in the portal system (markedly more increased after an intrasplenic bolus administered following 60 min of reperfusion [40] than after a 5-day-long homogeneous dilution in the blood stream [39]), could affect their implantation in the liver. Altogether, regardless of heterogeneity in the experimental models used, there is accumulating experimental evidence uniformly reporting I/R injury to be associated with increased hepatic metastatic potential and increased tumor growth (Table 1).

The Impact of Liver Resection and Small-for-Size Livers on Tumor Behavior

The association between partial liver resection and increased metastases growth was originally described in the semantic experiments by Fisher and colleagues in the 1950s, where rats undergoing partial hepatectomy (70 %) were threefold more likely to develop liver metastases after intraportal cancer cell injection as compared to controls [41]. Since then, numerous research groups have confirmed that hepatic resection induced by itself increased tumor recurrence [42–47]. The two pivotal components of post-resection tumor recurrence (the engraftment of circulating cancer cell and the increased tumor growth of micrometastases) were thoroughly reviewed by de Jong et al. [48]. More recently, insufficient post-hepatectomy remnant liver parenchyma, referred to as small-for-size syndrome, has been evaluated as a determinant of tumor recurrence [34]. On top of being a potential cause of post-operative liver failure and a common clinical challenge in liver surgery [49, 50], small-for-size syndrome causes acute phase mechanical injury, which induces lesions similar to those observed in hepatic I/R injury [51, 52]. Therefore, small-for-size liver models have been used to assess the relationship between parenchymal injury and circulating tumor cell engraftment. Man and co-workers evaluated the invasiveness and cell migration pathways of intraportally injected HCC cells in rats undergoing major hepatectomy (left and caudate lobes, 50–60 % of total liver volume) with or without 60-min ischemia and 60-min reperfusion to the right and median lobes (40–50 % of total liver volume) [34]. This experiment showed not only that small-for-size injury increases tumor growth by itself, but also that I/R injury of the liver remnant leads to increased tumor aggressiveness and metastatic potential (both intra- and extra-hepatic) [34]. Going one step further, rat tumor tissue harvested from original livers was re-implanted in the livers of nude mice undergoing different surgical stress conditions (major hepatectomy alone, I/R injury alone, I/R injury and major hepatectomy, and sham). This unique experimental design allowed demonstrating that the surgical stress resulting from hepatic I/R injury and/or major hepatectomy not only makes the hepatic microenvironment favorable for tumor cell growth, migration, and invasion through stimulation of acute phase inflammatory response and disturbance of microcirculatory barrier function, but it also makes the tumor cells more aggressive by directly activating cell migration and invasion pathways [34].

In addition to its impact on the remnant liver after hepatectomy, small-for-size syndrome is a frequent scenario affecting graft function in the transplantation setting. Small-for-size injury has been pointed out as a potential mediator of post-liver transplantation tumor recurrence. Thus, to export the evidence gathered from the liver resection setting, Man et al. [53] analyzed, in a rat liver transplantation model, the effect of small-for-size injury (achieved by removal of the left and caudate liver lobes) on post-liver transplantation tumor growth. Animals receiving small-for-size livers experienced early endothelial injury, and sinusoidal damage, followed by parenchymal necrosis and sinusoidal microthrombi, characterizing the role of small-for-graft size injury. Hepatic replacement area by circulating HCC cells was significantly increased in the small-for-size group compared to the whole liver group. To assess the stimulation of I/R injury on tumor invasiveness,

Man et al. [53] used again an orthotopic xenogeneic tumor model, harvesting tumor tissue grown in rat liver grafts and implanting it in the liver of nude mice. Six weeks post-implantation, tumors arising from the small-for-size graft group reached higher tumor volumes and developed more distant metastases. These findings show that on top of damaging graft function, acute phase I/R injury promotes late phase tumor growth and invasiveness.

Although the use of marginal liver grafts, including from donation after cardiac death (DCD), has been shown to be a reasonable option in the face of organ shortage, marginal grafts are more susceptible to I/R injury [54]. The current authors have shown that I/R lesions associated with rat liver transplantation from DCD donors lead to increased post-transplant HCC recurrence and growth [55]. Moreover, looking at potential therapeutic strategies, it could be demonstrated that the use of normothermic reperfusion modalities allows a reduction in I/R lesions, and in turn of post-transplant HCC recurrence and growth, restoring HCC tumor volume to the level of non-ischemic, control animals [55].

Clinical Implications

Liver Resection

The impact of vascular inflow control procedures on the risk of cancer recurrence after liver surgery has been evaluated in a limited number of clinical studies. Nijkamp et al. have shown that severe ischemia, defined as a continuous portal triad clamping for more than 20-min or more than three cycles of 15-min intermittent clamping, was associated with increased cancer relapse rates after liver resection for colorectal metastases [adjusted hazard ratio (HR) = 1.37 (95 % CI 1.02–1.85), $p = 0.038$] [56]. In contrast, Giuliante et al. [57] observed no difference in terms of hepatic recurrence rate according to the use, type, and duration of hepatic pedicle clamping [57]. In another recent retrospective series including 386 patients undergoing hepatectomy for HCC with ($n = 224$) or without ($n = 162$) pedicle clamping, Xia et al. [58] reported no difference between study groups in terms of 1-, 3-, and 5-year disease-free or overall survival. The overall recurrence rate was 67 % (66.1 and 67.3 % for patients with or without pedicle clamping, $p = 0.828$), with a median time to recurrence of 26 months. Intra- versus extra-hepatic recurrence was also comparable between study groups [58]. A long-term analysis of a randomized clinical trial assessed the role of Pringle maneuver on post-resection colorectal liver metastases recurrence and did not detect differences between those undergoing vascular inflow control or not [overall survival at 1, 3, and 5 years, portal clamping group: 100, 86.1, and 49.4 % vs. no clamping group: 92.6, 65.8, and 48.2 % ($p = 0.704$)] [59]. Disease-free survival was also similar between the two groups: 1-, 3- and 5-year survival rates were 85.7, 51.4, and 34.3 % in the HPC group versus 84, 51.5, and 37.9 %, respectively ($p = 0.943$). Although these data arise from a prospective randomized study, between-group follow-up differences [median follow-up was 67.1 ± 20 months in the Pringle maneuver group versus 77.5 ± 16.6 months in the control group ($p = 0.07$)] and the small sample size represent shortcomings to this secondary analysis [59]. A recent meta-analysis did not detect any pooled difference in terms of intra-hepatic recurrence, disease-free survival, or overall survival between patients undergoing liver resection for colorectal metastases with or without pedicle clamping [60]. A prospective randomized study evaluating the effect of the Pringle maneuver on the risk of post-hepatectomy recurrence is currently ongoing [61]. This trial should shed the light on an unresolved issue and will help determining whether findings of experimental studies translate to the clinical setting.

In contrast to preclinical models that showed intermittent portal clamping as an efficacious means of reducing I/R injury-mediated tumor growth in the rodent [37, 62], the evidence supporting the benefit of intermittent pedicle clamping on tumor behavior remains very limited in the clinical setting. In a large retrospective analysis of 563 patients undergoing liver resection for colorectal metastases, Wong et al. [63] did not find any significant difference in terms of disease-free survival between those receiving intermittent pedicle clamping or not. Of note, there was a large variability in the duration of vascular occlusion (2–104 min, median 22 min), which could have led to a dilution effect between study groups, limiting the generalizability of these findings [63].

In a retrospective analysis comparing selective and total portal vein occlusion in 86 patients undergoing curative hepatectomy for HCC found, Makino et al. [64] reported a significantly longer recurrence-free survival for patients subjected to selective portal vein occlusion (1,520 vs. 561 days, $p = 0.017$) in univariate analysis. After adjusting for vascular invasion and number of HCC nodules, the difference was of borderline significance [HR = 1.82 (95 % CI 0.996–3.32), $p = 0.052$] [64].

Because 75 % of liver blood flow that carries only 20–30 % of oxygen runs into the portal vein, it could be argued that maintaining arterial blood flow while clamping the portal vein only may reduce intraoperative blood loss while minimizing I/R injury. Based on these observations, Yang and co-workers performed a nested case–control study evaluating the impact of portal vein occlusion with maintenance of arterial flow (vs. complete portal triad occlusion) on the risk of post-hepatectomy HCC recurrence [65]. In this cohort of 169 patients, compared to those in

whom arterial blood flow was left untouched ($n = 51$), patients undergoing combined arterial and portal blood flow occlusion ($n = 118$) experienced a significantly lower disease-free survival both in univariate analysis ($p = 0.0013$), and after allowing for confounding factors such as tumor size and grade, blood levels of alpha-fetoprotein and presence of microvascular invasion [HR = 0.68 (95 % CI 0.54–0.86), $p = 0.0015$)]. In addition, arterial blood flow maintenance was accompanied by lessened hepatocellular injury and liver function at postoperative day one, three, and seven [65]. Of note, tumor localization was not adjusted for, although it may affect blood loss and the risk of post-resection recurrence. In other words, it could be argued that surgeons tend to apply vascular control procedures in face of more difficult cases, which, besides being at increased risk of surgical bleeding, probably also carry an increased risk of cancer recurrence.

Although more robust data are needed, altogether, these findings suggest that surgical innovation may allow a blunting in pedicle clamping-induced I/R lesions and help achieving better oncological outcomes.

Liver Transplantation

I/R lesions, including organ injury caused by small-for-size livers, have been repeatedly observed to be associated with poor oncological outcomes in liver transplantation, and a recent meta-analysis identified 16 studies comparing living-donor liver transplantation (LDLT, a surrogate for lower graft size) with deceased-donor liver transplantation (DDLT) [66]. Statistical pooling of disease-free survival revealed an aggregate HR of 1.59 (95 % CI 1.02–2.49; $p = 0.041$), showing that LDLT was significantly associated with higher post-transplant HCC recurrence rates. In contrast, pooled overall survival was not different between LDLT and DDLT [HR = 0.97 (95 % CI 0.73–1.27; $p = 0.808$)] [66]. Noteworthy is that there is a lack of evidence as to whether common markers of I/R injury (e.g., cold and warm ischemia time, presence of graft steatosis, donor age) are correlated with the risk of post-transplant tumor recurrence. Recently, Mathur et al. [67] have shown that increasing BMI was associated with a significantly higher and earlier HCC recurrence rate. Looking at the extreme scenario of marginal grafts such as DCD, Jay et al. [68] and Croome et al. [69] pointed out that the use of DCD donors was associated with a synergistically increased death rate after transplantation in HCC-bearing patients as opposed to patients without HCC. However, HCC patients undergoing liver transplantation may die of other reasons than tumor recurrence. In addition, these studies did not determine actual HCC recurrence, providing only indirect evidence of an association between donor characteristics and poor oncological. Hence, the interpretation of donation after cardiac death as a risk factor for post-transplant HCC recurrence deserves further validation in the clinical setting.

No clinical liver transplantation studies evaluating the effectiveness of strategies blunting I/R injury as a means of achieving improved oncological outcomes could be identified.

Mechanisms

Underlying Parenchymal Abnormalities

The hepatic tissue does not systematically react to the ischemic insult in the same way. Owing to the diverse clinical situations underlying liver cirrhosis and HCC (hepatitis B, C, alcohol, steatohepatitis) and to the complex therapeutic strategies (chemotherapy, radiofrequency ablation, transarterial chemoembolization) potentially applied to patients before liver surgery, parenchymal abnormalities appear to be involved in the post-surgical course of patients undergoing either hepatectomy or liver transplantation [22, 70, 71]. Fatty livers show alterations in mitochondrial metabolism as well as increased production of insulin-like growth factor 1, which promotes cell growth and proliferation, and inhibits apoptosis [17, 72–74]. These pathological changes could in turn stimulate carcinogenesis, making steatosis a favorable microenvironment for tumor growth. In this mind, the Utrecht group demonstrated that aging (12–13 months) and steatosis, as induced by feeding mice with a high-fat diet, intensified the I/R-induced outgrowth of colorectal adenocarcinoma micrometastases as compared to lean animals exposed to I/R injury [39]. Another group went on investigating the relationship between steatosis and hepatic tumor growth and observed spontaneous hepatic dysplastic tumor occurrence as early as 9 months after the introduction of a high-fat diet [75]. The number and size of tumor nodules increased over time, and at 20 months after high-fat diet introduction, all animals developed tumor nodules. In contrast, no tumor was detected (neither after gross or histological assessment) in mice maintained on regular diet at the same time points. The same group confirmed the role of a steatotic microenvironment at favouring hepatic metastases implantation upon observation of a significantly greater hepatic tumor load in those animals allocated to high-fat diet as compared to control, 21 days after tumor cell injection in the portal system [75]. From a clinical standpoint, Hamady et al. reported the results of a large cohort ($n = 2{,}715$) of patients undergoing hepatectomy for colorectal liver metastases, comparing livers with or without steatosis (defined as a diffuse accumulation of fat droplets affecting more than 5 % of hepatocytes) with regard to hepatic disease-free survival [76]. After adjusting for relevant

confounders, the Cox proportional model showed a significantly higher recurrence rate at 1, 3, and 5 years post-surgery in the steatosis versus non-steatosis group (79.6, 59.2, and 52.9 % vs. 85.3, 67.1, and 61.9 %, respectively, $p < 0.001$). These results were confirmed in a matched propensity score analysis. Although providing novel insights into the debate of the oncological impact of fatty liver disease, this recent study lacks a formal histological assessment of the precise nature of fatty infiltration, which can diverge considerably (e.g., macro- vs. microvesicular steatosis) and differently affect post-surgical outcomes [22].

Microcirculatory Lesions, Tissue Hypoxia, and Angiogenesis

Microcirculatory dysfunction has been repeatedly reported to constitute a source of hypoxia and tissue disruption in the setting of I/R injury (Fig. 1) [77, 78]. Sustained hypoxia to the liver promotes hypoxia-inducible factor (HIF-)1α, which acts as a cell survival factor, and is a promoter of tumor cell proliferation, angiogenesis, and cell migration [79–81]. Van der Bilt et al. [39, 62, 82] demonstrated on several occasions that, after I/R injury, accelerated tumor growth predominantly surrounded necrotic parenchyma and that I/R-mediated tumor growth was linked to increased parenchymal HIF-1α expression [82]. Moreover, prevention of ischemia-induced microcirculation disturbance with L-arginine (an enhancer of endothelial NO synthesis) reduced the outgrowth of micrometastases by minimizing tissue hypoxia and avoiding HIF-1α stabilization [82]. Nijkamp et al. [56, 83] have shown that I/R-mediated tumor outgrowth was also portended by Fas–Fas ligand interactions, which appear to be pivotal in the process of necrotic tissue formation.

Several reports have shown that the ischemic liver upregulates vascular endothelial growth factor (VEGF) expression, a well-known angiogenic factor. In the context of liver surgery for cancer, surgical stress and I/R injury appear to stimulate VEGF expression, which could foster

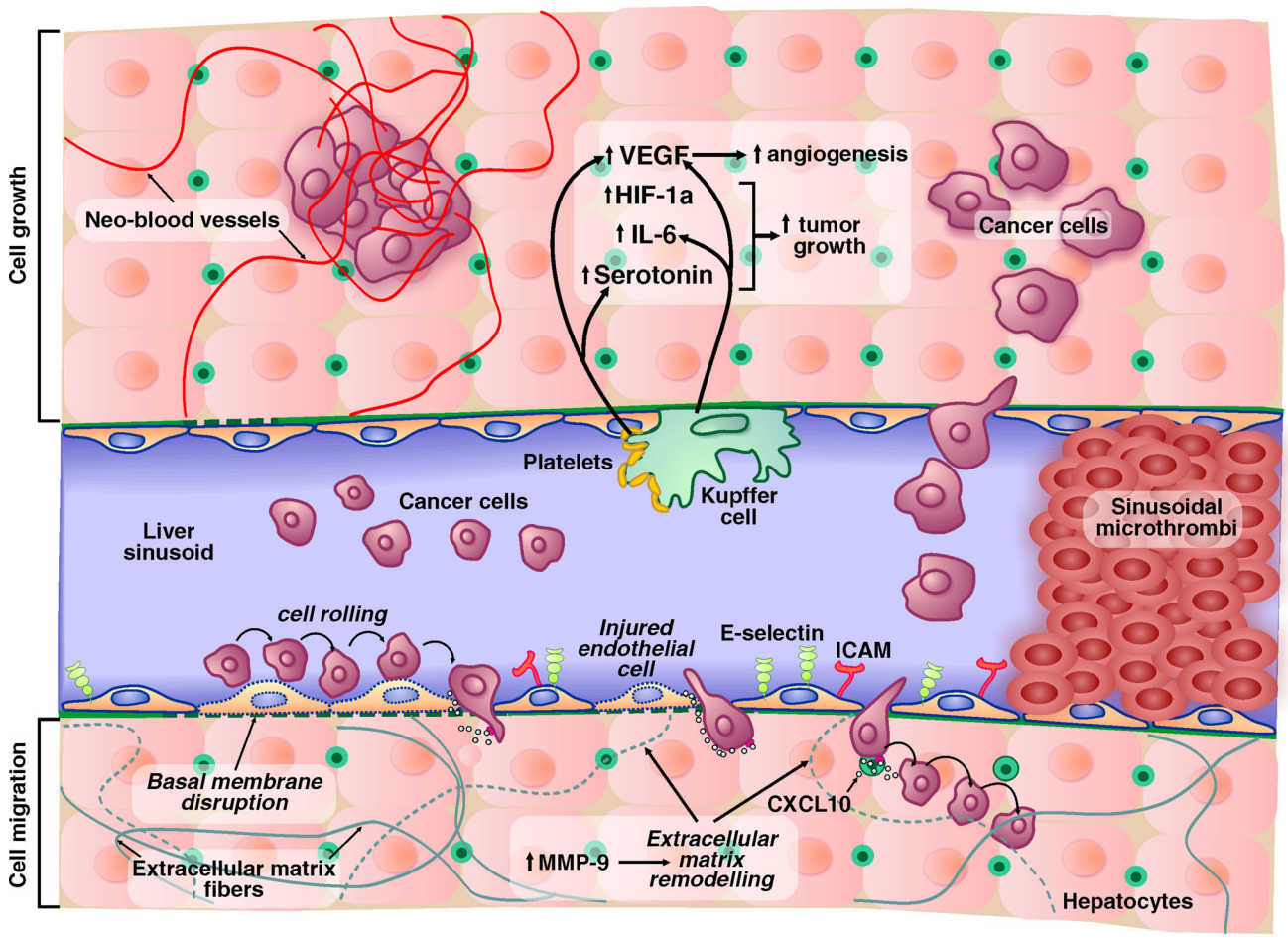

Fig. 1 Explored mechanisms suggesting a role between liver ischemia/reperfusion injury and cancer cell migration (*bottom*) and growth (*top*). *VEGF* vascular endothelial growth factor, *HIF* hypoxia-inducible factor, *IL* interleukin, *MMP* matrix metalloproteinase, *ICAM* intercellular adhesion molecule, *CXCL* [chemokine (C-X-C motif) ligand]

tumor growth through two main mechanisms. First, there is overwhelming evidence that VEGF assumes a pivotal role in tumor angiogenesis, and in the liver, I/R-mediated VEGF upregulation leads to improved tumor vascularization. Second, VEGF receptor is overexpressed on several types of cancer cells, including colorectal cancer [36, 84, 85] and hepatocellular carcinoma cells [86], suggesting an autocrine effect of VEGF on tumor cells expressing VEGF receptors. Similarly, novel functions of VEGF have been reported in various oncological settings, including the promotion of cancer cell survival [87–89] and migration [90].

Cell Adhesion, Migration, and Extracellular Matrix Remodeling

Leukocyte adhesion molecules, which are expressed upon the activation of inflammatory pathways, have been repeatedly correlated with progression of several types of carcinoma [91–93]. In a rat adenocarcinoma metastasis model, Kurata et al. [32] showed the expression of E-selectin to be significantly increased after I/R injury, peaking at 120 min after reperfusion. E-selectin expression correlated with ischemia duration and its expression in ischemic tissue was accompanied by a higher number of metastatic nodules. Intriguingly, the administration of antithrombin reversed this IR/mediated increased tumor burden by inhibiting TNF-α secretion and by blunting the expression of E-selectin. Furthermore, antithrombin-KO mice developed significantly less metastatic nodules compared to wild-type animals. Altogether, these observations highlight the relevance of microvasculature ultrastructure in the process of tumor cell trafficking and migration. Although its clinical effectiveness has been questioned when administered to critically ill patients [94], antithrombin therapy may represent a potential option, and further investigation is needed.

Chemokines are critical mediators involved in the process of I/R injury [95–97]. On top of their chemotactic activity on inflammatory cells, chemokines and their receptors are involved in cancer cell invasive potential [98–100]. Man and colleagues demonstrated that CXCL10 (interferon γ-induced protein 10) was overexpressed in small-for-size livers and that upon CXCL10 stimulation, hepatocellular carcinoma cells displayed pro-migration morphological changes such as stress fiber and lamellipodia formation [53]. In addition to these phenotypical changes, CXCL10 directly impacted on cell motility as assessed in an in vitro wound healing assay [53] and appeared as pivotal with regard to endothelial progenitor cell migration [101].

There is a body of evidence supporting the role of extracellular matrix remodeling in promoting tumor invasiveness and metastasis [102]. In particular, matrix metalloproteinases (MMPs) have been shown to be crucial mediators of the invasive potential of several cancers, including colon adenocarcinoma [103] and HCC [104]. Previous research indicates that extracellular matrix remodeling arising in the setting of I/R injury is mediated by an increase in MMP-9 expression [105]. Nicoud et al. demonstrated in a series of elegant experiments that MMP-9 upregulation after I/R injury promoted the outgrowth of colorectal carcinoma micrometastases and that doxycycline-mediated MMP inhibition, as well as MMP-9 genetic silencing, reversed the I/R-related accelerated tumor growth. Of note, these observations lack confirmatory evidence from human studies, as Xia et al. [58] did not report differences in terms of liver tissue mRNA and blood levels of MMP-2, MMP-9, and E-selectin between patients undergoing pedicle clamping or not.

Conclusion and Perspective

Although data accumulated from preclinical models uniformly point out liver quality as a determinant of cancer cell implantation and growth, the evidence gathered from the clinical setting is still limited and ongoing research in the form of prospective randomized trials should shed light on this so far unresolved issue. In the meantime, it appears as reasonable to implement therapeutic approaches to minimize I/R injury, especially in patients with more advanced tumor, given their potentially higher pool of circulating cancer cells. Several therapeutic interventions such as ischemic pre-conditioning [106], intravenous corticosteroids [4], prostaglandin E [107], and volatile anesthetics [108] have been shown to improve ischemia–reperfusion, and their specific impact on oncological outcomes should be assessed. In this regard, we have shown that graft reperfusion prior to retrieval reduces the HCC growth in a rat liver transplantation model [55]. Moreover, neoadjuvant and downstaging strategies appear justified, provided they do not harmfully delay the access to definitive therapy. Long-term oncological outcomes should be assessed when comparing various vascular inflow control procedures and conclusions of RCTs examining early morbidity, and post-operative hepatocellular damage [109] may not apply to delayed cancer recurrence. Although there is better understanding of the interaction between I/R injury and tumor recurrence, biological mechanisms underlying these observations remain largely unresolved. Thus, future research should investigate the cell signaling pathways involved in cell survival of the injured liver in the presence of cancer.

Acknowledgments We are grateful to Mrs. Dawne Colwell for her precious input in graphic design. This study was supported by the

Ligue genevoise contre le cancer, the Henri Dubois-Ferrière/Dinu Lipatti Foundation, and the Artères Foundation. Lorenzo Orci and Christian Toso were supported by the Swiss National Science Foundation (Grants 323530-151477, 3232230-126233).

Conflict of interest None.

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