

Accelerated carcinogenesis following liver resection in chronically inflamed livers: A window of opportunity for treatment (Review)

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Abstract. The long-term prognosis following resection of hepatocellular carcinoma (HCC) remains unsatisfactory as a result of a high incidence of recurrence. Prevention of recurrence is the most important strategy to improve the long-term survival results. The role of hepatectomy itself, as an accelerator of carcinogenesis, has not been adequately evaluated in HCC patients. Studies in animal models have revealed a link between liver regeneration under chronic inflammation and hepatic tumorigenesis. Inhibiting different signal transduction pathways during liver regeneration without compromising the ability of the liver to regenerate appears to be a rational strategy and may decrease HCC development and recurrence. If this hypothesis is proven using animal models, this strategy could be evaluated in future clinical trials in humans.

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1. Introduction

Studies estimate that >30% of all malignancies worldwide are initiated or exacerbated by inflammation, and preclinical

data also supports the concept that inflammation is a pivotal component of tumor initiation (1). Hepatocellular carcinoma (HCC), the third leading cause of cancer mortality worldwide, commonly develops in an inflamed liver following a prolonged chronic hepatitis state (2). Hepatic resection and liver transplantation are the only treatments with curative intent for HCC, where resection as a bridge to transplantation is also emerging as a possible therapeutic strategy (3-6). For patients with early HCC and decompensated cirrhosis, liver transplantation is the treatment of choice, as the procedure potentially cures the cirrhosis and the HCC, and the outcome is accepted to be better than that of hepatic resection (7). HCC is most prevalent in areas with endemic viral hepatitis B or C, which is typical in many African and Asian countries (8). In these endemic countries transplantation procedures are limited due to a shortage of living donors, legal and economic issues and lack of resources. Therefore, hepatic resection is considered to be the practical curative treatment option for many patients with HCC globally.

2. Different patterns of HCC recurrence

Despite improved resection techniques, and subsequent decreased operative morbidity and mortality in hepatic surgery, survival rates following partial hepatectomy (PH) are suboptimal, predominantly due to tumor recurrence, which within five years occurs in the range of 75 to 100% of cases (9,10). It was estimated that 60-70% of recurrences were attributed to intrahepatic lesions undetected at the time of resection, whereas 30-40% were *de novo* HCCs (Fig. 1) (11,12). The two different patterns of recurrence are proposed to represent distinct carcinogenesis patterns that have markedly different prognoses. Early recurrence usually represents residual tumor spread from the primary main tumor and remains in the remnant liver, which is an indicator of a poor prognosis. Significant risk factors for early recurrence include preoperative tumor rupture, venous invasion and non-anatomic resection (13,14). Late recurrence usually results from multicentric hepatocarcinogenesis. Possible risk factors for late recurrence include cirrhosis, higher grade of hepatitis activity and multiple tumors (11,14,15). In certain studies from areas with endemic viral hepatitis, the majority of the recurrences were multicentric in location and distant from the resection margin (16-18). In one study it was found that there was no significant difference in the recurrence rate

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Abbreviations: HCC, hepatocellular carcinoma; KO, knockout; PH, partial hepatectomy; STAT3, signal transducer and activator of transcription 3

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that occurred between major resection and minor or localized resection of the liver (16). This indicated that in these patients the prominent pattern of failure was *de novo* HCCs. This hypothesis was further confirmed in a study where it was demonstrated that gene expression profiling from liver tissue adjacent to the tumor was correlated with survival in contrast to the genome signature of the tumor itself (19). Therefore, patients with *de novo* HCC recurrence, post-curative PH, are the patients that may benefit from inhibition of the accelerated carcinogenesis following liver resection.

3. Animal models of HCC accelerated carcinogenesis

HCC in rodents and humans share common features, and various mouse models of this disease have been investigated to establish the underlying molecular mechanisms of liver cancer (20). Few animal studies investigating the effects of liver regeneration on tumor progression were performed using transplanted tumor cells (subcutaneously or directly into the liver), or using chemically induced tumors (21-23). In these animal models, PH was shown to affect and enhance the initiation and promotion phases of carcinogenesis when compared with sham surgery. However, these models have no underlying liver inflammation, as is the case in the majority of humans with HCC. Therefore, until recently, there was insufficient information regarding the mechanisms by which the inflammatory microenvironment affects liver regeneration, and the effect of inflammation and regeneration on hepatocarcinogenesis.

The Mdr2-knockout (KO) mouse is a model with similarities to human HCC. These mice lack the Mdr2 P-glycoprotein, which is responsible for phosphatidylcholine transport across the canalicular membrane. The absence of phospholipids from bile leads to portal inflammation and slowly developing HCC, which closely mimics the human disease in this regard (24,25). In the Mdr2-KO mice model Barash *et al* (26) demonstrated that PH, prior to the development of HCC, led to enhanced hepatocarcinogenesis. It was proposed that under the regenerative proliferative stress induced by liver resection in these mice, the genomic unstable hepatocytes, generated during chronic inflammation, escape senescence and apoptosis, and reenter the cell cycle, triggering enhanced tumorigenesis (26).

4. Targeting accelerated carcinogenesis during hepatectomy

If PH potentially accelerates carcinogenesis, it may be worthy to attempt to block potential signaling pathways specifically during this procedure. Numerous cytokines, growth factors and signal transduction pathways are activated during liver regeneration, and some of these may present as potential targets for prevention of accelerated carcinogenesis, although regeneration may be compromised (Fig. 1) (27).

Sorafenib, a multikinase inhibitor, is the only systemic therapeutic modality that significantly prolonged the survival of HCC patients with advanced-stage disease and is considered the standard of care for patients with metastatic or locally advanced HCC (28,29). In a study that used an orthotopic HCC model, sorafenib treatment over a short duration subsequent to PH suppressed accelerated tumor growth (30). It was further demonstrated that postoperative activation of the

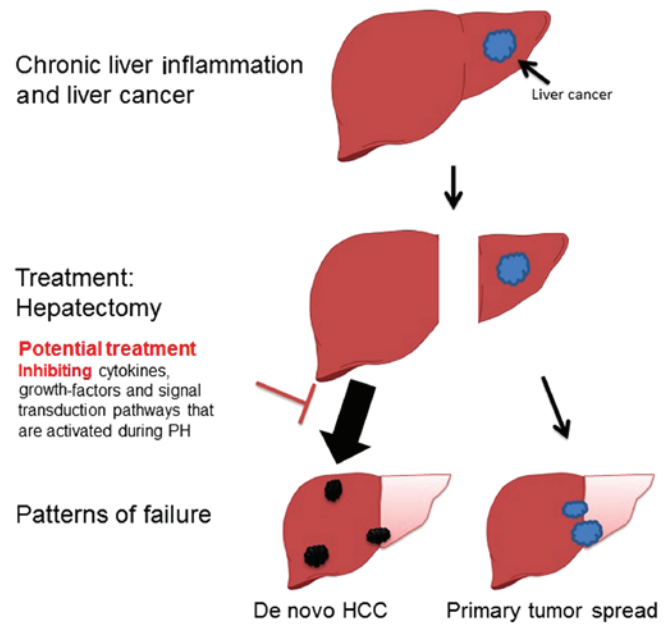


Figure 1. Blocking different signal transduction pathways specifically during PH could present potential targets for prevention of accelerated carcinogenesis. PH, partial hepatectomy.

Raf-MEK-extracellular signal-regulated kinase (ERK) signal transduction pathway sensitizes HCC to sorafenib. Another preclinical study demonstrated that sorafenib treatment around PH did not impact liver regeneration when administered prior to surgery; however, administration following PH reduced liver regeneration (31). Taken together, these studies indicate that short duration sorafenib treatment surrounding PH for early-stage HCC is a promising approach for preventing recurrence. However, these studies do not capture the same scenario as in humans, where it is speculated that, under the regenerative proliferative stress induced by PH, the non-tumoral hepatocytes escape senescence and apoptosis, triggering enhanced tumorigenesis.

While sorafenib inhibits the Raf-ERK/platelet-derived growth factor receptor (GFR)/vascular endothelial GFR signaling pathways, other pathways that are activated during liver regeneration and are crucial for HCC development may be targetable. Signal transducer and activator of transcription 3 (STAT3) and its activating cytokine, interleukin (IL)-6 are key regulators of liver regeneration and act to prime hepatocytes to transition from the G0 phase and progress to the G1/S phase (32,33). Thus, the IL-6/STAT3 signaling pathway may be of central importance to the development and progression of HCC following PH. As many therapeutic agents that target the IL-6/STAT3 pathway were recently developed (34) such an approach appears reasonable, although it may be the case that inhibition of the IL-6/STAT3 axis is detrimental to liver regeneration. In a recent study by Zahavi *et al* (35) it was shown, using the Mdr2-KO mice model, that sorafenib treatment during PH inhibited various signal transduction pathways at the multikinase levels, which did not result in increased morbidity or mortality. In the early stages subsequent to PH, sorafenib treatment resulted in decreased stellate cell activation and inflammatory response. Finally, it was demonstrated that sorafenib treatment during PH at 3 months

of age resulted in decreased fibrosis, and tumor formation at age 8.5 months (35). The study confirmed the hypothesis that short-term treatment during PH is feasible and effective in inhibiting inflammation-associated cancer, and is therefore a potential strategy for recurrence prevention (35).

5. Future challenges

There are two major challenges that will be encountered when evaluating the strategy of treatment using signal transduction blockade during hepatic resection in patients with HCC under inflamed conditions. The first issue includes the high perioperative morbidity and the low survival rate with mortality up to 20% surrounding surgery (36). Using molecular inhibitors, which may inhibit recovery and decelerate the regeneration of the liver, could be devastating for certain patients and result in mortality; therefore, are not accepted as legitimate in clinical trial design. The second issue is the fact that major, sponsored, randomized clinical trials will not be performed in this context, as the treatment duration is very short (surrounding the surgery) and the potential benefit to the pharmaceutical industry is limited. In order to overcome the lack of incentive of the pharmaceutical companies, such studies require sponsorship from academic institutions.

6. Conclusion

Oncologists have long recognized that in certain cancers, surgical treatment demonstrates carcinogenic potential. In the current review, the latest evidence of the potential carcinogenesis of hepatectomy for the treatment of HCC is described. In addition, potential treatment strategies for decreasing this accelerated carcinogenesis were described. Different signal transduction pathway inhibitors are already available and are currently used in many clinical trials for different indications, such as metastatic cancers. Despite the risk to fragile patients with HCC and liver inflammation, and despite the low potential for financial gain, further clinical research using different relevant signaling pathway inhibitors during hepatectomy is encouraged.

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