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Targeting of circulating hepatocellular carcinoma cells to prevent postoperative recurrence and metastasis

Yu Zhang, Zhi-Long Shi, Xia Yang, Zheng-Feng Yin

Yu Zhang, Zhi-Long Shi, Xia Yang, Zheng-Feng Yin, Molecular Oncology Laboratory, Eastern Hepatobiliary Surgery Hospital, Shanghai 200438, China
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Correspondence to: Zheng-Feng Yin, MD, PhD, Molecular Oncology Laboratory, Eastern Hepatobiliary Surgery Hospital, 225 Changhai Road, Shanghai 200438, China. yinzfk@aliyun.com
Telephone: +86-21-81875354 Fax: +86-21-81875354
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Abstract

Currently, the main treatment for hepatocellular carcinoma (HCC) involves the surgical removal of tumors or liver transplantation. However, these treatments are often not completely curative, as they are associated with a risk for postoperative recurrence and metastasis. Circulating tumor cells (CTCs) are increasingly recognized as the main source for recurrence and metastasis after radical hepatectomies are performed. Many studies have demonstrated the association between the presence of either pre- or postoperative CTCs and an increased risk for HCC recurrence. To improve the therapeutic outcome of HCC, a personalized, comprehensive and multidisciplinary approach should be considered, involving the application of appropriate diagnostic and therapeutic measures targeting HCC CTCs in different stages throughout the course of treatment. This article proposes some HCC CTC-based strategies for the treatment of HCC, including the monitoring of HCC CTCs before, during and after radical hepatectomy, therapeutic targeting of HCC CTCs, prevention of the generation and colonization of CTCs, as well as the use of CTC indexes for the selection of indications, prediction of prognoses, and planning of individualized therapeutic regimens. Innovation and technological development of therapies targeting CTCs, as well as their translation into clinical practice, will help to effectively reduce postoperative recurrence and metastasis, and significantly prolong the survival of HCC patients.

Key words: Hepatocellular carcinoma; Circulating tumor cells; Recurrence and metastasis; Surgical treatment; Individualized treatment

Core tip: Circulating tumor cells (CTCs) can lead to recurrence and metastasis after surgical treatment for hepatocellular carcinoma (HCC). The development and utilization of new methods or techniques to target these cells will help reduce postoperative recurrence and metastasis and prolong the survival of HCC patients. This article proposes CTC-based strategies that provide a more comprehensive and personalized approach for the treatment of HCC. Treatment methods that incorporate multiple aspects of identification, targeting and monitoring of these tumor cells may provide more efficient and effective regimens for HCC patients undergoing radical hepatectomies.

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INTRODUCTION

The current curative therapies for hepatocellular carcinoma (HCC) are limited to hepatectomy and liver transplantation. However, postoperative recurrence and metastasis are common complications[1,2], caused by an extremely complex process that generally requires the entry of circulating tumor cells (CTCs) from the primary tumor into the peripheral blood[3,4]. Clinicians should therefore be aware of this when treating patients with HCC and collaborate with other researchers to develop and employ novel therapeutic techniques that target CTCs to reduce the postoperative recurrence and metastasis of HCC and prolong the survival of patients. This review highlights possible strategies for the therapeutic targeting of CTCs in multiple pre-, intra- and postoperative contexts to prevent postoperative recurrence and metastasis of HCC, and suggests future research directions in related fields.

METHODS FOR ENRICHMENT AND DETECTION OF HCC CTCs

In the past decade, the development of new and robust technologies for the enrichment and detection of CTCs has been an area of active investigation with significant progress[5,6]. However, each method has its own advantages and disadvantages, including limitations in the isolation of CTCs undergoing epithelial-mesenchymal transition or stem cell-like CTCs[3]. At present, the main markers used for CTC isolation are tumor-specific antigens or epithelial cell surface antigens based on the original cancer. Among them, the epithelial cell adhesion molecule (EpCAM) is a typical marker which has been used widely for CTC-capturing techniques[7,8], although the low expression of EpCAM in HCC cells makes this method unsuitable for HCC CTC detection. To date, the methodologies available for HCC CTC enrichment and detection include density gradient centrifugation, RT-PCR or real-time quantitative (q)RT-PCR[9,10], isolation by size of epithelial tumor cells (ISET)[11], fluorescence-activated cell sorting[12,13], and magnetic-activated cell sorting[14]. We recently developed and validated an asialoglycoprotein receptor-based magnetic cell separation method combined with hepatocyte paraffin 1 staining detection, which allows enumeration, immunomorphologic identification, and genetic analysis of CTCs in peripheral blood samples from HCC patients[15]. However, in order for HCC CTC detection to translate to the clinic, the creation of high throughput, reliable, and cost effective platforms is needed. Whether through the refinement of existing technologies or the innovation of multiplexed approaches, these new approaches should target novel biological or physical markers that specifically and selectively capture and detect all subsets of HCC CTCs.

CTCs AS INDICATORS FOR HCC RECURRENCE AND METASTASIS

It was initially suspected that recurrence and metastasis following the treatment of HCC was caused by incomplete surgical resection, and therefore expanded radical resections were employed. However, this approach was generally unsuccessful, leading to new hypotheses that either the intrahepatic dissemination of tumor cells through the portal vein branches or *de novo* tumorigenesis are the cause. Yet these hypotheses fail to explain why early tumor recurrences commonly occur at the site of transplanted allograft in cases of liver transplantation[16], suggesting that there is an alternative source of tumorigenic tissue.

A study by Vona *et al*[11] in 2004 detected CTCs and microemboli in 52% of blood samples from HCC cases using the ISET method. Furthermore, a more recent study from our lab using a novel cell separation method to detect HCC CTCs showed that while CTCs were detected in more than 80% of HCC patients, no CTCs were detected in healthy persons or patients with benign liver diseases or other types of late-stage tumors[15]. Fan *et al*[17] detected CD45(-)CD90(+)CD44(+) cells (termed circulating cancer stem cells) in preoperative blood samples from 56 out of 82 HCC cases using flow cytometry and found that levels greater than 0.01% could be used to predict intrahepatic recurrence and extrahepatic metastasis. Sun *et al*[18] used the Cell Search System to test preoperative blood samples from 123 HCC patients and detected $\geqslant$ 1 EpCAM(+) CTC (termed circulating cancer stem cells) in 66.7% of the samples, among which 41.5% had $\geqslant$ 2 EpCAM(+) CTCs, and therefore suggested that preoperative detection of $\geqslant$ 2 cells could be used as an independent factor for predicting postoperative recurrence. A similar study by Schulze *et al*[19] reported $\geqslant$ 1 EpCAM(+) CTC in 30.5% of HCC patients and in 5.3% of patients with cirrhosis, showing a strong correlation between EpCAM(+) CTCs and survival. Furthermore, Liu *et al*[20] identified 30 out of 60 patients with > 0.157% circulating CD45(-)ICAM-1(+) tumor cells (termed circulating cancer stem cells) in their blood; and these patients had significantly shorter disease-free and overall survival periods. Taken together, these studies indicate that CTCs contribute to HCC recurrence, and may therefore serve as an important therapeutic target for the prevention and treatment of HCC recurrence and metastasis following curative resection.

CTCs AS AN INDICATION FOR CURATIVE SURGERY IN HCC

No uniform screening criterion has been established for surgical resection, aside from the contraindication of extrahepatic metastasis. HCC patients are selected for liver transplantation based on tumor size, nodule number, and

degree of vascular invasion. However, as none of these criteria can accurately define the rational distribution of the donor liver and predict the prognosis of the patient, there is controversy over which of these are most appropriate and feasible[21]. It is therefore necessary to go beyond the clinicopathologic criteria for HCC and incorporate more objective and reliable laboratory indexes. As potential "metastasis-initiating" cells, high preoperative levels of HCC CTCs can predict a poor prognosis, and may therefore prove to be a reasonable candidate index for surgical indications. Thus, in order to evaluate the true benefit of curative treatment, it is pivotal to rule out the possibility for metastatic dissemination at the time of diagnosis.

Cooperation among worldwide leaders in this field is needed to confirm whether HCC CTCs can objectively be used as an indicator or contraindicator for radical hepatectomy, as well as to obtain a consensus on assays and result reporting. Research designs should include (but are not limited to): the detection of pre- and postoperative CTCs, follow-ups for postoperative recurrence, establishment of the correlation between HCC CTCs and the postoperative prognosis, formulation of new indication criteria for radical hepatectomy and liver transplantation, comparison with the other existing criteria, and clinical evaluation of the use of HCC CTCs as a surgical indicator and the ultimate therapeutic outcome.

REDUCTION OF BASAL CTC LEVELS WITH PREOPERATIVE NEOADJUVANT THERAPY

Early detection of metastatic spread provides an opportunity for early perioperative or adjuvant administration of therapeutic agents. However, effective preoperative neoadjuvant therapy regimens for HCC are limited due to the insensitivity of HCC cells to chemotherapy agents[22]. Sorafenib (a small molecule inhibitor of several tyrosine protein kinases) is currently approved to treat advanced HCC and has provided promising results. Some clinical studies indicate that sorafenib can downstage HCC when administered as a preoperative neoadjuvant therapy, providing opportunities for curative resection[23-25], and is cost-effective for HCC patients waiting for liver transplantation[26]. Nevertheless, there is no data showing the effect of sorafenib on CTC levels. As the risk of postoperative recurrence and metastasis increases with the number of preoperative HCC CTCs, the use of preoperative neoadjuvant therapy to eliminate CTCs in patients would theoretically reduce the risk of postoperative recurrence and metastasis. Therefore, clinical studies evaluating the use of sorafenib and other preoperative neoadjuvant therapies targeting HCC CTCs and their effects on the risk of postoperative recurrence and metastasis are needed.

CONTRIBUTION OF SURGICAL TECHNIQUE TO THE INTRAOPERATIVE RELEASE AND POSTOPERATIVE INTRAHEPATIC COLONIZATION OF CTCs

Preventing postoperative recurrence and metastasis requires eliminating iatrogenic tumor cell seeding during the surgical operation, an important principle of surgical oncology. During the surgical procedure, tumor cells are more easily found in surrounding blood circulations, especially in the venous blood from the tumor, which can convert a preoperative absence into a postoperative presence of CTCs. Improper surgical manipulation and squeezing or traction of the liver tumor may facilitate tumor cell dissemination into the blood circulation. For instance, the conventional posterior approach to hepatic lobectomy requires moving the liver, likely resulting in squeezing of the liver and tumor cell dissemination. In contrast, the anterior approach to a right lobe hepatectomy does not require lifting and squeezing of the liver, thus avoiding or reducing the release of CTCs. This free-tumor technique was first devised by Lai *et al*[27] and later modified by Belghiti *et al*[28], resulting in development of the liver hanging maneuver for hemihepatectomy. Both retrospective and prospective studies have demonstrated that this is a practical surgical modality for a right hepatectomy and can effectively reduce postoperative recurrence[29,30]. Likewise, the "no-touch" technique should also be advocated for removal of the diseased liver for liver transplantation. While it is nearly impossible to completely avoid touching the liver during a partial hepatectomy or liver transplantation, surgical oncologists should aim to minimize touching, as improper surgical procedures can cause hematogenous metastasis of tumor cells and increase the risk of postoperative recurrence and metastasis.

Ischemia/reperfusion (I/R) injury is frequently encountered during hepatic surgery. There is controversy over whether I/R injury from hepatectomy adversely affects long-term outcomes by accelerating the outgrowth of residual hepatic micrometastases or by facilitating postoperative intrahepatic invasion and colonization of CTCs. Surgical trauma can trigger the up-regulation of multiple cytokines, thereby promoting intrahepatic invasion, migration and proliferation of CTCs and leading to the formation of a metastatic focus[31-34]. In animal experiments, hepatic I/R injury was shown to accelerate the outgrowth of colorectal micrometastases through multiple mechanisms[35-39]. Clinical research data from 271 HCC patients indicated that ischemic time can markedly affect recurrence after liver transplantation[40]. However, other reported clinical data have indicated no effect of I/R injury on the long-term outcome of liver resection for colorectal metastases[41] and have demonstrated no significant correlation with the postoperative prognosis of HCC[42]. Nev-

ertheless, intraoperative measures to reduce I/R injury of the liver are generally beneficial to the patient.

POSTOPERATIVE ACCESSORY THERAPY FOR ELIMINATION OF RESIDUAL CTCs

Although radical hepatectomy or liver transplantation may not eliminate all preoperatively existing HCC CTCs, the results of CTC dynamics studies in orthotopic tumor models have indicated that the numbers of CTCs and early metastases decrease significantly after resection[43]. However, surgical intervention should not be the endpoint of HCC treatment, and therapeutic targeting of HCC CTCs after surgery should be addressed. Postoperative use of sorafenib was shown to suppress the development of postsurgical intrahepatic recurrence and abdominal metastasis, leading to prolonged postoperative survival in an orthotopic mouse model[44]. Furthermore, results from a pilot study suggested that adjuvant therapy with sorafenib may help prevent early recurrence after hepatic resection in HCC patients[45]. In a rodent model of HCC, adjuvant therapy with sorafenib was also shown to be highly effective in inhibiting cancer recurrence and metastasis after liver transplantation, without exerting influence on the immune balance[46]. Moreover, a clinical study indicated that sorafenib might reduce or delay tumor recurrence after liver transplantation and prolong patient survival[47].

It is important to continue to conduct clinical studies on the therapeutic targeting of HCC CTCs as a postoperative accessory therapy, and to further explore the significance of sorafenib as an adjuvant therapy for eliminating CTCs and reducing the risk of postoperative recurrence and metastasis. It is possible that many CTCs have been in a non-dividing state for a relatively long period of time, or may never divide, and are therefore insensitive to chemotherapy or molecular targeted agents. Therefore, an important direction for future research is to develop new techniques for analyzing and identifying HCC CTCs as well as new strategies to eliminate CTCs based on a more complete understanding of their biological behaviors. As CTCs are independent and non-dividing cells, antibody-based immunotherapy targeting CTCs represents an additional promising avenue for future research.

An additional challenge to the curative treatment of HCC involves the postoperative use of anti-rejection medications that compromise the immune system. Some *in vitro* and *in vivo* studies have demonstrated that immunosuppressive therapy can increase tumor cell escape from immune recognition and enhance tumor cell growth, invasion, and metastasis through various mechanisms. As CTCs that are present before liver transplantation are a source for re-formation of metastatic clones, immunosuppressants should be carefully selected to maintain the body's immune surveillance of residual CTCs. Recently, the mammalian target of rapamycin inhibitor rapamycin has aroused researchers' attention based on these dual functions[48]. Rapamycin directly inhibits tumor angiogenesis, proliferation, and growth by blocking the intracellular signal transduction of vascular endothelial growth factor. Toso *et al*[49] found that compared with other immunosuppressants, rapamycin was able to maintain the basic immunosuppressive state and anti-tumor immune response of the body, and also eliminate cancer cells in a targeted manner, thus reducing the risk of recurrence after liver transplantation.

DYNAMIC POSTOPERATIVE MONITORING OF CTCs AS A CRITERION FOR PLANNING INDIVIDUALIZED THERAPY FOR HCC

As CTCs can be released during surgical procedures, it is important to accurately assess their levels after removal of the tumor load. Changes in CTCs should be monitored regularly in patients whose CTC levels suggest a high risk of recurrence and metastasis. These patients should be followed closely for early signs of recurrence and metastasis to allow for early treatment intervention. Ideally, therapeutic targeting of CTCs should occur in advance to prevent recurrence and metastasis. Dynamic monitoring of CTCs could also be used to assess therapeutic outcome in patients who accept chemotherapy and/or radiotherapy. Additionally, HCC CTCs can be used to identify the target of sorafenib before making a decision about drug administration, as well as to monitor the state of drug resistance during administration. As a result, the therapeutic regimen could be selected or adjusted based on the timely and repeated monitoring of objective indexes related to CTCs in order to achieve effective, individualized treatment of HCC.

CONCLUSION

Surgery for liver cancer has been performed for more than 100 years, which includes a 40-year history of liver transplantation[50]. However, the outcome of radical treatment of HCC by surgical therapy alone has not improved. Similar to CTCs from other types of tumors, HCC CTCs are increasingly recognized as the main source for recurrence and metastasis after radical hepatectomy. We believe that the application of appropriate diagnostic and therapeutic measures targeting HCC CTCs in different stages over the course of treatment may represent a breakthrough to improve the therapeutic outcome of HCC. In this article, we have proposed some HCC CTC-based strategies for the treatment of HCC according to studies published in the recent literature. These strategies will guide future research on HCC CTCs in preclinical and clinical settings and may lead to development of effective therapeutic approaches to prevent metastatic relapse of HCC.

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