Criteria for non-hepatitis B patients. In contrast, a high or rising serum alpha-fetoprotein level is a reflection of liver regeneration, a favorable prognostic marker. Criteria of age, acuteness, etiology and severity of liver failure are also stated in the King’s College criteria. However, in the face of more advanced intensive care and potent antiviral therapeutic agents for viral hepatitis, other parameters might be useful.

A practical approach used by most clinicians is close monitoring of clinical parameters of progression of hepatic encephalopathy, coagulopathy and liver function tests. When a suitable donor is available, either deceased or living, the decision to go ahead with liver transplantation becomes imminent as development of complications from liver failure deprives the potential recipient of the chance of survival.

In this article in the Journal of Gastroenterology and Hepatology, Takayama et al. show that lower serum levels of platelet-derived growth factor-BB (PDGF-BB) and vascular endothelial growth factor (VEGF) were associated with FHF. Importantly, serum levels of PDGF-BB and VEGF were even lower in patients who did not recover from FHF. Among the 17 patients with FHF, five recovered spontaneously. Those categorized as having poor outcomes included six who had undergone liver transplantation and six who died without liver transplantation. The serum PDGF-BB and VEGF levels of these 12 patients who did not recover spontaneously were the lowest in the series. As already stated, FHF carries a high mortality without liver transplantation. Therefore, diagnostic tests with high negative predictive value are most worthwhile. Although lower serum levels of PDGF-BB and VEGF were indicative of poor prognosis, quite a number of patients who had low levels eventually had a good outcome. Thus, these parameters are restricted in guiding the clinical decision of liver transplantation. Nevertheless, when these factors, and in particular the trend of changes, are interpreted in conjunction with other parameters, the prediction of clinical course should be more accurate.

The ideal site to study the most effective medical treatment for FHF is where liver transplantation is not available. This allows clearer delineation of clinical and laboratory indices of patients with irreversible FHF despite best medical treatment. In practice, such regions often are deficient in research and clinical facilities, and resources. Collaboration between centers that are able to provide laboratory support might enable studies in this important area.

In summary, in contemporary clinical practice, use of standard criteria might still lead to some patients being transplanted who might have recovered. Identification of novel parameters should help to improve the accuracy of timing for embarking on liver transplantation—that is, it should be carried out as early as necessary, and as late as possible. An important point already emphasized by Takayama et al. is the administration of PDGF-BB and VEGF in treating FHF. This is logical when these factors are low in the serum. Should FHF not be reversible, the potential of using these factors as a bridge to liver transplantation is an area worthy of further investigation. This might buy time to await for a deceased-donor liver graft or working up a suitable living liver donor.

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Angiogenesis blockade as therapy for hepatocellular carcinoma: Progress and challenges

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It has been well established that hepatocellular carcinoma (HCC) is one of the most vascular solid tumors, and that angiogenesis plays an important role in both growth and metastasis. It follows that angiogenesis could provide a potentially potent therapeutic target for the treatment of HCC.

The role of angiogenesis in tumors was first shown over half a century ago. Since then, tumor angiogenesis has been intensively studied, and it has become accepted as an important prerequisite for tumor formation in solid malignancies. The growth of a tumor mass requires a sound network of blood vessels that provide oxygen and

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metabolites, and the angiogenic response will parallel such growth. Several growth factors are involved in angiogenesis. They include vascular endothelial growth factors (VEGF), angiopoietins, epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). Such peptides are released by the neoplastic, hematopoietic, stromal and the endothelial cells. The final status of cancer angiogenesis is determined by the dynamic balance between pro- and anti-angiogenic factors. When the effects of the pro-angiogenic factors are balanced by those of the anti-angiogenic factors, angiogenesis will be switched off, a relative abundance of pro-angiogenic factors will tip the balance in favor of angiogenesis.\(^2,3\) Given the characteristically abundant vascularity and production of pro-angiogenic growth factors in HCC, targeting the tumor vasculature is a particularly promising strategy for this most common and highly fatal cancer.

Our increased understanding of the balance between angiogenesis and mechanisms of vascular control has led to the development of novel therapeutic agents that influence the process in different ways. For example, work accomplished over the past decade has elucidated the essential role of VEGF in the regulation of biological and pathological angiogenesis. Therefore, the blockade of VEGF receptor signaling is currently a major part of strategies for the therapy of malignant tumors, including HCC. Several studies tested neutralizing antibodies against mature VEGF proteins, blockade of VEGF receptors by VEGF receptor antibodies, soluble VEGF receptor mutants or fusion-proteins, and intra-cellular interference with VEGF mRNA or kinase signaling pathways in the target cell. Inhibiting the process of angiogenesis by knocking out the activity of VEGF has a significant impact on tumor growth and patient survival. However, it does not seem to be enough for a complete cure. So it is still necessary to explore as many regulatory steps as possible in the complex sequence of tumor-induced angiogenesis.

Besides the VEGF, FGF and its family of receptors (FGFR) are potent inducers of angiogenesis in HCC.\(^4,5\) Elevated serum FGF levels are an important prognostic factor in HCC,\(^6\) and the aberrant activation of FGFR has been shown to drive hepatocarcinogenesis.\(^7\) FGF might also modulate the resistance to VEGF/VEGFR inhibition. For example, FGF2 has been shown to synergistically augment the VEGF-mediated HCC development and angiogenesis\(^8\) and might play a central role in the “escape mechanisms” implicated in VEGF/VEGFR targeting. Clinical and translational studies suggest that FGF blockade might circumvent resistance to the VEGFR modulating agents.\(^9\) In a study of patients undergoing surgery for HCC, the high serum levels of FGF2 was shown to be a predictor for invasiveness and recurrence.\(^10\)

Although the VEGF inhibitors can reduce the growth of the primary tumors, there are data showing that they might also promote the invasiveness and metastasis of the tumor.\(^11\) Accordingly, novel anti-angiogenic therapies targeting FGF to synergize with VEGF-mediated anti-angiogenesis might provide a mechanism to overcome resistance to VEGF-targeted agents in HCC. So we should use the knowledge to inhibit the process of angiogenesis at a more sensitive point of angiogenesis, or at several points simultaneously. To achieve this goal, the newly developed in vitro models of tumor growth and of blood vessel formation could be helpful. Actually, several agents that target the VEGF pathway have been tested in patients with advanced HCC, such as the oral multikinase inhibitors, sorafenib and sunitinib, whose antitumor effects are partly as a result of the inhibition of VEGF receptors. Although the SHARP trial showed only a 2.8-month improvement in median overall survival rate (\(P=0.0006\)), along with very limited increased time to disease progression and disease control rate, and a 2.3% response rate, sorafenib became the first targeted agent approved to use in advanced HCC by the USA Food and Drug Administration.\(^12\) The monoclonal antibody against VEGF, bevacizumab, either used alone or in combination with erlotinib, has shown improved survival in advanced HCC patients.

In this issue of the Journal, Jie et al. report the inhibitory effect of berberine, which is a herbal alkaloid extracted from *Rhizoma coptidis*, on angiogenesis induced by human HCC cells.\(^3\) They show, using in vitro experiments, that the berberine might block the angiogenetic potential of HepG2 cell lines by downregulating VEGF expression. They further proposed a possible mechanism correlated with the human ether-a-go-go related gene potassium (HERG K+) channels. Previous studies have shown that berberine has multiple antitumor mechanisms, such as cell-cycle arrest, apoptosis induction, anti-inflammatory, inhibition of DNA and protein synthesis.\(^14,15\) On the basis of these studies, it is rational to hypothesize that berberine might impact a synergistic effect on HCC through both the aforementioned effects and its anti-angiogenic potential. Although all the hypotheses are very attractive, they need confirmation by in vivo studies. An important message from this study is that some agents, such as berberine, could have an anti-angiogenic effect through multiple mechanisms. If this is correct, combined use of these agents with other modalities might lead to radically new treatment regimens to achieve maximal efficacy in the management of HCC.

Besides berberine, scientists have also explored the anti-angiogenic effect of other individual Chinese medicines or composites in different tumors. Although most studies have been carried out in vitro using cell lines, and the exact ingredients are not definite nor their pharmacokinetic disposition defined, the role of alternative medicine, such as Chinese medical herbs, in this field remains worthy of further exploration. Obviously, well-designed and properly carried out clinical trials are critical to translate all these interesting and promising pre-clinical findings into convincing clinical evidence. Given that liver carcinogenesis and tumor growth are multistage processes with many factors involved, aiming at one single target or one single signaling pathway often fails to fully halt HCC progression. In order to achieve satisfactory efficacy of the management of HCC, novel agents, such as berberine, might be combined with other conventional therapies, such as chemo- and/or radiation therapy. Clinical trials with anti-angiogenic therapy for HCC have already shed light on this promising novel modality for this disease. However, the molecular and cellular mechanisms that regulate angiogenesis in HCC still remain largely unidentified. Further studies to elucidate the mechanisms involved in HCC angiogenesis are not only crucial to our understanding of the tumor biology of this disease, but might also provide guidance to the use of appropriate anti-angiogenic agents for HCC.

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Duodenal chemosensing: Master control for epigastric sensation?

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The duodenum, so named for its length of 12 fingers, is a prime segment of the gastrointestinal (GI) tract regarding luminal chemosensing due to its strategic positioning between the pylorus and the pancreatobiliary ducts. As a consequence, the duodenal mucosa is regularly exposed to strong gastric acid (pH ~2), high PO43− (up to ~400 mmHg) from the neutralization of secreted HCO3−, digestive enzymes, bile acids, and foodstuffs. Physiologically, processes such as secretion, digestion, absorption, and motility occur in response to these luminal substances, implying the presence of mucosal chemosensors, which evoke protective mucosal defense mechanisms.1 The duodenal mucosa rapidly responds to luminal chemical stimuli, not only by enhancing local defense factors, such as mucosal blood flow and HCO3− and mucus secretion, but also by inhibiting gastric emptying and secretion, in addition to producing symptoms, such as bloating, nausea, and fullness. Gastric inhibition in response to duodenal luminal substances is termed “duodenal feedback” or “duodenal brake”, originally described by Andersson in 1960.2 Intraduodenal acid inhibits gastric acid secretion and delays gastric emptying via neuronal reflexes and the release of gastric inhibitory peptide/glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide-1 (GLP-1), glucagon, cholecystokinin (CCK), secretin, and somatostatin.

Our laboratory has provided data supporting the hypothesis that luminal acid is sensed via submucosal cation channels expressed on afferent nerves. Luminal acid is converted to CO2 at the surface of the epithelial cells through mixture with secreted HCO3− and membrane-bound carbonic anhydrase activity.3 CO2 enters the cell and is hydrated to HCO3− and H+ by cytosolic carbonic anhydrase, with the H+ exiting across the basolateral membrane via the Na+/H+ exchanger NHE1, with HCO3− secreted across the apical cell membrane.4 In this fashion, large quantities of gastric acid are absorbed as the non-toxic acid equivalent CO2, which will not injure the epithelial cells. As a consequence, luminal acid is rapidly sensed by submucosal chemosensors, such as transient receptor potential vanilloid-1, which transduce the luminal chemical signal into neural afferent responses and can then trigger effenter neurohormonal responses.5 Disruption or dysregulation of these duodenal physiological responses to postprandial luminal acid could be related to the pathogenesis of mucosal injury and nociception.

Functional dyspepsia (FD) is a heterogeneous symptom complex including upper abdominal discomfort or pain, postprandial fullness, early satiety, nausea, vomiting, and bloating in the absence of organic disease, as defined by the Rome III criteria.6 Although the pathogenesis of FD is unknown, dysmotility, gastric relaxation disorders, or sensory disorders have been hypothesized. Recently, FD symptoms were correlated with duodenal acidity in patients with functional dyspepsia.7,8

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