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EDITORIAL

Novel therapeutic approaches for hepatocellulcar carcinoma: Fact and fiction

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and accounts for 80%-90% of this class of malignancy. So far, understanding of its pathogenesis and effective therapeutic methods are rather limited. In this issue, 11 invited review articles are published to address current advance of underlying molecular mechanisms for the deve-lopment of HCC, and novel therapeutic approaches for HCC. This series of review articles provide an in-depth unders-tanding of HCC that has led to or may lead to the development of novel therapies for HCC.

Key words: Hepatocellular carcinoma; Pathogenesis; Treatment

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Liver cancer is the fifth most common cancer worldwide and the third most common cause of cancer mortality[1]. Hepatocellular carcinoma (HCC), which accounts for 80%-90% of primary liver, is characterized by a very poor prognosis and is associated with high mortality[1-3]. It has been well known that chronic viral hepatitis B and C infections are the most important risk factors, responsible for 80% of HCC worldwide[1-3]. However, current available therapeutic modalities for HCC are largely inadequate. Surgical approaches such as resection and transplantation are the treatment of choice for HCC; however, because of underlying liver disease, only a minority of patients are suitable for resection, and access to transplantation is limited by organ availability. Local tumor ablation is effective for early HCC, and chemoembolization is of benefit in intermediate-stage disease. So far, no first-line therapy has emerged for advanced HCC. Cytotoxic chemotherapy has proven ineffective[3]. Therefore, research efforts are focused on novel targeted therapies.

In this issue of the *World Journal of Gastroenterology*, 11 invited review articles are published to reflect the current advance in understanding the etiology of HCC and underlying molecular mechanisms for the development of HCC, and, particularly, to provide expert opinions and new insights on the potential novel therapeutic approaches for HCC.

But *et al* update the incidence and describe different patterns and risk factors for HCC, speculate on carcinogenesis in hepatitis B virus (HBV), and hepatitis C virus (HCV), point out the clinical difference between HBV- and HCV-related HCC, and describe the natural history of HCC, prediction factors for survival, and HBV vaccination[4]. Macdonald *et al* emphasize that the incidence of HCC in patients with immunodeficiency virus (HIV) is increasing, and HCC in HIV almost invariably occurs in the context of HBV or HCV co-infection. Moreover, human HIV co-infection seems to accelerate disease progression and reduces the efficacy of anti-HBV and anti-HCV therapy[5]. Further, Macdonald *et al* point out updated information on the screening, prevention and treatment of HCC in patients with HIV in the HAART (highly active antiretroviral therapy) era[5]. The knowledge on HCC etiology and epidemiology is of significant value in guiding the clinical practice including diagnosis, prevention and treatment.

Various treatments options have been under investigation in order to achieve the greatest survival benefit with the least toxicity. Salem *et al* highlight the use of segmental infusion of intra-arterial radiotherapy with Yttium-90 (Y90) or Phenium-188 (Ph-188) for the treatment of inoperable HCC and update the recent clinical and research advancements in radiotherapy[6]. Maruyama *et al* discuss the increasingly important roles of ultrasound (US) in the diagnosis (e.g. US-guided needle puncture, color Doppler US, and real-time 3-dimensional US images), and in the treatment of HCC (e.g. high intensity focused ultrasound)[7].

Many studies have been carried out with the aim of developing a systematic treatment and/or achieving targeted therapy at the molecular level. Silencing HCC-related cellular oncogenes or the HBV and HCV viruses has been attempted for HCC treatment. Many studies have

demonstrated promising results, and an early clinical trial assessing RNAi-based HBV therapy is currently in progress. However, there are several significant hurdles that need to be overcome before the goal of RNAi-based therapy for HCC is realized. This aspect has been well covered by Arbuthnot *et al*[8]. Di Maio *et al* review the association between sex hormones and HCC tumorigenesis and the efficacy of anti-hormone therapy. Although epidemiological and pre-clinical studies support a strong association, several clinical trials have virtually produced negative results. Thus, there is no robust evidence that HCC is a hormone-responsive tumor, and hormonal therapy should not be a part of current management for HCC[9]. Breuhahn and Schirmacher focus on the alterations in the insulin-like growth factor (IGF)-Ⅱ signaling pathway and *in vivo* models that support the central role IGF-Ⅱ signaling during HCC development and progression[10]. This pathway has become the center of interest as a target for potential anti-cancer therapy in many types of malignancies. Therefore, inhibitors targeting IGF-IR and other RTKs or combinations of different specific substances targeting distinct pathways might be attractive therapeutic approaches for HCC in the future. The contribution by Deli *et al* reviews the alterations in components of the activin signaling pathway that have been observed in HCC and discuss their potential significance for liver tumorigenesis[11]. Activin A, and possibly activin E, may have a similar tumor suppressive function in the liver as TGF-β although whether activins may also shift to a pro-tumorigenic function during tumor progression is little explored. Activin antagonists may serve to block the growth inhibitory and pro-apoptotic activity of activin A on hepatocytes. Therefore, a targeted inhibition of activin antagonists might restore sensitivity to activin-induced growth inhibition and apoptosis, and may thus represent a feasible strategy to inhibit tumor growth. Future studies will clarify whether such approaches may offer new therapeutic opportunities for combating liver cancer[11].

The review of Martin and Dufour address the various tumor suppressors which have been implicated in HCC[12]. Specifically, they discuss the function of these tumor suppressors and the related signaling pathways such as p53, Wnt, Ras/Jak/Stat and other pathways and the involvement of inactivation of these tumor suppressors in the initiation or progression of HCC as well as the underlying mechanisms of their inactivation[12]. Matsuda provides evidence that p16 and p27, two potent tumor suppressors that inhibit cyclin-dependent kinase, are functionally related, i.e. loss of p16 expression is associated with over-expression but functional inactivation of p27 in HCC. In addition, loss of p16 expression is an independent prognostic factor for a poor outcome in HCC cases expressing high levels of p27. Thus, p16 and p27 may become more accurate biomarkers predicting the prognosis of HCC[13]. Moreover, comprehensive understanding of the functions of and interactions among these tumor suppressors and the underlying mechanisms of their inactivation is a prerequisite to design innovative treatments of HCC.

It has been well known that development of HCC is a multistep process with accumulation of genetic and epigenetic alterations in regulatory genes, leading to activation of oncogenes and inactivation or loss of tumor suppressor genes (ref. above). Tischoff *et al* further discuss the epigenetic alterations in HCC focusing on DNA methylation[14]. In HCC, aberrant methylation of promoter sequences occurs not only in advanced HCC, but also in premalignant conditions such as chronic viral hepatitis B or C and hepatic cirrhosis. Therefore, epigenetic changes in preneoplastic or early neoplastic stages may serve as an indicator or "biomarker" for screening of patients with an increased risk for HCC. Moreover, it has been demonstrated that reexpression of TSGs that are epigenetically silenced is possible by using demethylating and histone modifiying agents, indicating a potential therapeutic approach by specifically modulating DNA hypermethylation[14].

It is our hope that this series of review articles will give our readers an in-depth understanding of all aspects of HCC that have led to or may lead to the development of novel therapeutic approaches for HCC.

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