



## Mini-review

## Editorial foreword special issue “Hepatocellular Carcinoma – A Worldwide Translational Approach”

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Primary human liver cancer, of which hepatocellular carcinoma (HCC) is the predominant type, is a major cause of cancer death worldwide, accounting for almost 600,000 deaths per year. Because of poor curability, the number of HCC deaths occurring each year is roughly equivalent to the number of new cases. The global epidemiology of HCC is striking, with both geographic and temporal patterns of incidence paralleling exposure to viral etiologic factors. The highest HCC incidence rates occur in sub-Saharan Africa and parts of Asia, areas endemic for chronic infection with hepatitis B virus. However, liver carcinogenesis is much more complex than simply reflecting the presence or absence of an antecedent viral infection. Given chronic hepatitis B or C viruses (HBV, HCV) infection, there are marked geographical differences in risk for HCC which remain largely unexplained, the other known causes, including aflatoxin exposure, tobacco smoking, alcohol drinking, and diabetes, explaining only a relatively small proportion of cases. Moreover, there is significant variation

in the pathological and natural history of the disease. The pathways by which HCC develop are heterogeneous and influenced by a variety of environmental and host factors.

This special issue of *Cancer Letters* dedicated to HCC includes contributions that address the critical research issues of this disease from etiology and molecular epidemiology, mechanisms and viruses, and molecular carcinogenesis, to preclinical models and therapeutic approaches and biomarkers. The reviews were prepared following the meeting “Hepatocellular carcinoma – A Worldwide Translational Approach” which took place at the International Agency for Research on Cancer, Lyon, France on July 9–10, 2007.

Chronic infection with hepatitis B or C viruses have been recognized as human liver carcinogens with the proportion of HCC attributable to virally induced chronic hepatitis being close to 85% in most populations. An efficient HBV vaccine is available since the early eighties and has been used since for universal infant vaccination in several regions of high endemicity, here **Plymoth et al.** review universal vaccination programmes and designed field efficacy trials. Epidemiological studies on the seroprevalence

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of HBsAg and anti-HCV antibodies in HCC cases show wide international variations. **Franceschi and Raza** present the results of a meta-analysis of 27 881 HCC cases from 90 studies. **Chuang et al.** review established and suspected HCC risk factors other than infections with HBV and HCV. The role of aflatoxin as a carcinogen is clearly recognized in HCC, but the mechanisms of carcinogenicity of this agent, both individually and in conjunction with viral infection are not well understood. Two reviews deal with a number of potential mechanisms underlying the interaction between HBV and aflatoxins in terms of HCC risk (**Wild and Montesano**; and **Gouas et al.**). **Kew** further discusses potential mechanisms by which iron induces malignant transformation and may also be directly hepatocarcinogenic, which has been suggested in African populations. **Mendy et al.** present their perspectives from molecular pathogenesis and early detection of HCC in West Africa, where HCC is the most common cancer form among men and the second most common among women.

The risk of developing HCC associated with HBV infection is influenced by several aspects of the infection such as viral load, HBeAg status, HBV genotypes, possibly also prolonged expression of the viral regulatory X protein and to the large envelope protein LHBs as well as mutations arising during chronic infection. **Chemin et al.** discuss molecular mechanisms of HBV induced HCC and three reviews address the putative roles of HBV X antigen in the pathogenesis of chronic liver disease and the implication of the X gene in the carcinogenicity of HBV (**Koike; Feitelson et al.** and **Chemin et al.**). The genotypes and sub-genotypes of HBV and their role in the development of HCC are reviewed by **Pujol et al.** and systematic-omics analyses of HBV-associated liver diseases are discussed by **Sun et al.**

Over the last 10 years, genetic alterations of HCC have been extensively studied and our knowledge has dramatically increased in this field. Two papers review differen-

tially expressed genes associated with human HCC and altered pathways in hepatocarcinogenesis (**Hui and Sun et al.**).

Globally, there is a lack of suitable biomarkers for early detection and diagnosis of HCC, as well as of reliable and affordable treatment opportunities, explaining in part the high fatality rate. New biomarkers are needed to promote early detection and diagnosis, leading to more effective therapeutic management. Several reviews deal with pre-clinical models and therapeutic approaches for HCC: the induction of senescence is a potential therapeutic strategy in HCC (**Ozturk et al.**). Novel treatment agents for HCC include gene therapy, intrahepatic radiotherapy and cytotoxic prodrug treatment (**Kerr**); the disease relevance of commonly used HCC cell lines and xeno-transplantation models is reviewed by **Kashofer et al.**; and three-dimensional high-dose photon radiotherapy as an innovative therapy for HCC is discussed by **Merle et al.** A novel and powerful strategy for HCC biomarker discovery, based on comparative analysis of the liver and plasma proteomes, is reviewed by **Beretta**. The potential use of the aflatoxin-induced *TP53* mutation at codon 249 (*R249S*) as a biomarker of exposure to aflatoxin, for early detection of HCC and target for therapy, is discussed by **Gouas et al.** The discovery of new biomarkers and drug-targets is limited by difficulties in the access to human samples which are annotated, collected, preserved and distributed under high assurance-quality procedures, according to international standards and ethical rules. This issue is discussed by **Clement et al.** in the context of the French national collection of liver tumours.

This special issue of *Cancer Letters* is expected to provide a comprehensive review of the field of HCC with aim of stimulating efforts for developing concerted, comprehensive approaches to decrease incidence and mortality of liver cancer worldwide.