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OVERVIEW

C Brechot

Inserm Direction Générale, Cedex, Aris, France

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Hepatocellular carcinoma (HCC), the most prevalent histopathological form of primary liver cancer, is seeing a striking increase in its worldwide incidence; HCC is a major long-term complication of chronic hepatitis and cirrhosis which are generally associated with this tumour. Moreover, cholangiocarcinoma is also an increasingly important concern in some parts of the world, albeit to a lesser extent. Unfortunately, early diagnosis of these tumours, and their therapy, remain extremely problematic. Environmental aetiological factors, such as chronic Hepatitis B (HBV) and C (HCV) viral infections and alcohol, have clearly been identified. Study of the molecular and cellular mechanisms underlying primary liver cancer has given rise to an interesting paradigm whereby liver cancer results from a combination of chronic inflammation and fibrosis (the hallmarks of cirrhosis), and the direct effects of the aetiological factor implicated, such as HBV or HCV. In fact, studies of HBV-and HCV-related liver carcinogenesis have enabled identification of the molecular mechanisms, which may be triggered whether or not the tumour is apparently associated with these viral infections. At the same time, major advances have been achieved with respect to characterising the genetic abnormalities, which drive liver carcinogenesis; thus, the sequential activation of different cellular pathways has been defined in both animal models of liver cancer and in human tumours. Also, the cellular lineages implicated are now better documented, in the light of current progress in determining potential liver progenitor and stem cells. Finally, given the disappointing results of the therapies available at present, new treatments have been proposed, with particular emphasis on gene therapy and RNA interference. This Oncogene review offers an updated appraisal of these various issues, and aims to adopt a multidisciplinary approach to understanding a human tumour, which represents a major preventive and therapeutic challenge that oncologists will face for the next 30 years.

Correspondence: Dr C Brechot, Inserm Direction Générale, 101 rue de Tolbiac,Cedex 13, Aris 75654 France.
E-mail: Christian.brechot@tolbiac.inserm.fr