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Pathogenesis of hepatocellular carcinoma according to aetiology

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A B S T R A C T

Hepatocellular carcinoma is related to various etiologies including hepatitis B, hepatitis C, high alcohol intake, aflatoxin B1 and metabolic syndrome. Most of the time HCC developed on cirrhosis. Consequently, the mechanisms of carcinogenesis of these different risk factors are difficult to separate from the events leading to cirrhosis. In contrast, aflatoxin B1 and hepatitis B have a clear direct oncogenic role through point mutations in the *TP53* tumour suppressor gene and insertional mutagenesis respectively. Finally, next-generation sequencing and transcriptome analysis will refine our knowledge of the relationship between aetiology and the genetic events that draw the mutational landscape of hepatocellular carcinoma.

Introduction

Hepatocellular carcinoma (HCC) is a strongly heterogeneous disease both from a molecular and clinical point of view. It mirrors the different etiologies of HCC worldwide, HBV in eastern countries, and alcohol, Non-alcoholic steatohepatitis (NASH) and hepatitis C in western countries [1]. In addition,

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the severity of the underlying liver disease may vary from normal liver to cirrhosis, although HCC develops on cirrhosis in 90% of patients in western countries [2]. This leads to differences in clinical care of HCC patients treated in western and eastern countries. These differences have been described in Asian and western guidelines and are partly explained by the genetic diversity of HCC [3–5]. HCC are heterogeneous at both the tumoral and non-tumoral level, and a major challenge lies in defining the relationship between aetiology, HCC development and molecular features [6,7]. HCC, like other cancers, is a disease of the genome and is defined by malignant hepatocytes accumulating somatic genetic alterations that combine mutations in both driver and passenger genes [8,9]. The recent technological breakthrough of next-generation sequencing has led to characterization of a whole genome and a whole exome of tumours within a few hours and at lower cost [10]. This again highlights the wide genetic diversity and the influence of aetiology, especially in HCC due to chronic HBV infection [11]. The aim of the present review was to describe the link between aetiology and the pathogenesis of HCC.

Pathogenesis of HCC according to aetiology

Hepatitis B

Hepatitis B virus is a partially double-stranded circular DNA virus belonging to the hepadnavirus family [12]. Pre-S/S ORF encodes three surface proteins, pre-C/C ORF encodes a terminal protein and viral polymerase has a reverse transcriptase and a DNA polymerase function [11]. The X gene encodes the HBx protein that is mandatory for viral replication.

Chronic infection by hepatitis B leads to HCC development, with an added risk that is 25- to 37-fold that of non-infected patients [13,14]. It is the leading aetiology in Asian and African countries. HCC related to HBV infection may develop on both cirrhotic liver and normal liver, whereas most HCC related to high alcohol intake or chronic HCV infection develop on cirrhosis [1]. Along this line, one of the main mechanisms of carcinogenesis due to HBV infection is through chronic inflammation, liver fibrosis and thus development of cirrhosis [11]. In this setting, chronic inflammation, oxidative stress and replicative senescence of hepatocytes due to telomere shortening induce malignant transformation of cirrhotic nodules, as in other cirrhotic backgrounds (Fig. 1) [7]. However, other

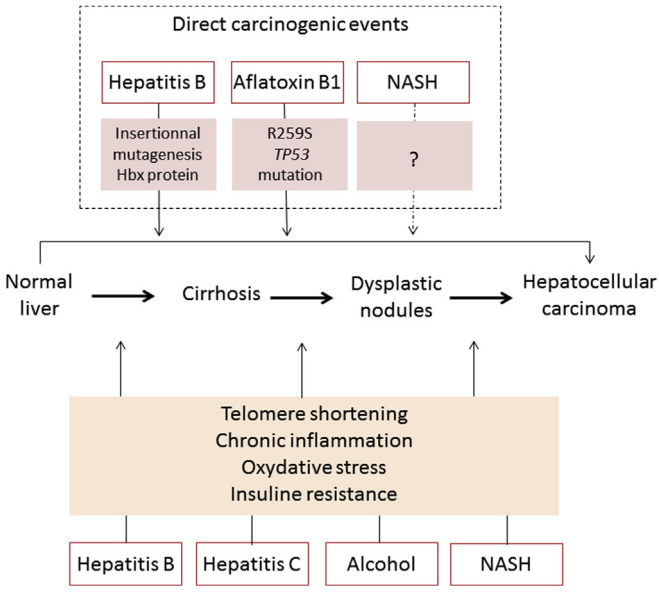

Fig. 1. The multistep process of liver carcinogenesis and the role of etiologies.