

## Solid Tumour Section

### Mini Review

## Liver: Hepatocellular carcinoma

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### Clinics and pathology

#### Disease

Hepatocellular carcinoma (HCC) is an aggressive malignancy with a poor prognosis.

#### Etiology

Eastern Asia and sub-Saharan Africa are the most prevalent regions. Hepatitis B virus (HBV) is a major risk factor. In some geographic areas (e.g. Asia, Southern Africa), aflatoxin B1 (AFB1) is also considered to be a significant etiologic factor. Exposure to dietary AFB1 and chronic HBV infection are synergistic risk factors in Chinese areas of high-HCC incidence. HCC is also a late complication of Hepatitis C virus (HCV) infection as observed in Western countries and Japan. The prevalence of cirrhosis in individuals with HCC and chronic hepatitis B or C is reported to be 80 and 75 % respectively. Other etiologic factors include being male (sex ratio M/F = 4/1), the use of sex hormones (both androgens and progestins) and conditions associated with chronic necroinflammatory liver disease and cirrhosis such as alcohol consumption or metabolic disorders of the liver (i.e. hemochromatosis, Wilson's disease, citrullinemia or tyrosinemia).

#### Epidemiology

One of the most common cancers worldwide affecting 250,000 to 1,000,000 individuals annually.

#### Pathology

Edmonson's staging system.

#### Treatment

Resection with or without adjuvant chemotherapy, liver transplantation, transarterial chemo-embolisation, intrahepatic alcoholization.

### Genetics

#### Note

Little is known about the hepatocarcinogenesis mechanisms which seem to differ according to the risk factor involved.

**HBV impact:** In HBV carriers most HCCs contain DNA sequences integrated into the host chromosomal DNA. Integration is at random except in rare cases in which HBV integration at specific sites has been shown to activate endogenous genes such as retinoic acid b-receptor, cyclin A, mevalonate kinase and SERCA-1. In addition, HBx is a potent co-transactivator of viral and cellular promoters such as c-myc and c-fos.

### Cytogenetics

#### Note

**LOH** The most frequently altered genes in HCC are tumor suppressor genes; deletions have been reported at ten chromosome arms, 8p (48%), 17p (45%), 4q (38%), 1p (33%), 13q (31%), 16q (30%), 6q (29%), 16p (24%), 1q (22%) and 9p (20%) with a frequency higher than 20%. For chromosome arms 17p, 13q, 9p, 6q and 16p, LOH has been related to p53, RB1, p16, IGF2R and Axin 1 inactivation.

### Genes involved and proteins

#### P53

**Location:** 17p13

**DNA / RNA**

11 exons.

#### Protein

Tumor suppressor; 5 highly conserved domains. The central portion of the gene encodes the sequence-specific DNA binding domain which mediates

transcriptional activation and is the target of the majority of mutations observed in many human cancers. The P53 protein is involved in cell cycle control, senescence, DNA repair, genomic stability and apoptosis.

#### **Somatic mutations**

The frequency and type of P53 mutations differ according to the geographic origin and suspected etiology of HCC. A specific codon 249 mutation (AGG → AGT) leading to an arginine to serine substitution (R249S) has been linked to aflatoxin exposure in 36% of tumors from Africa and 32% of tumors from China, respectively. Worldwide, the frequency of codon 249 mutations is 11%. Other codons of the p53 gene can be altered in HCC and overall this gene is mutated in about one third of these tumors. The wild type p53 protein can also be overexpressed in HCC. Experimentally, the HBx protein encoded by the x region of HBV has been shown to interact with wild type p53 and to inhibit its function. P53 antibodies have been detected in the serum of HCC patients. P53 alterations have been associated with poorly differentiated, large tumors and with a lower overall survival.

#### ***b-catenin***

**Location:** 3p21.3

#### **DNA / RNA**

16 exons

#### **Protein**

Oncogene. Has physical and functional interactions with APC in the Wnt/wingless carcinogenesis pathway. Also forms complexes with E-cadherin. Thus, b-catenin participates in cell-to-cell interactions. It also appears to play a part in transcriptional regulation.

#### **Somatic mutations**

The b-catenin gene is mutated in about 20-25% of HCCs. The mutations occur at the 5' end of the gene (exons 2-4) and lead to an accumulation of aberrant b-catenin proteins in the nucleus. Most of b-catenin point mutations alter 1 of the 4 serine or threonine residues which are targets for phosphorylation by GSK3 and are crucial for the down-regulation of the protein. Major hot spots are on amino acids S33, T41, and S45.

#### ***Axin 1***

**Location:** 16p13.3

#### **DNA / RNA**

11 exons

#### **Protein**

Putative tumor suppressor.

#### **Somatic mutations**

The Axin 1 gene is mutated in about 5-10% of HCCs. Point mutations are the most frequent alterations although small deletions, homozygous deletions and

small duplications can be found. The majority of Axin 1 mutations in HCC are nonsense or frameshift mutations.

#### ***IGF2R***

**Location:** 6q26

#### **DNA / RNA**

48 exons

#### **Protein**

Putative tumor suppressor. IGF2R is involved in the TGF- $\beta$ -mediated growth control which induces both growth inhibition and apoptotic cell death in hepatocytes.

#### **Somatic mutations**

LOH at the IGF2R locus has been reported and the IGF2R gene is mutated in 18-33% of HCCs.

#### ***SMAD2***

**Location:** 18q21

#### **DNA / RNA**

12 exons.

#### **Protein**

Candidate tumor suppressor; SMAD2 and SMAD4 (see below) are intracellular mediators of TGF- $\beta$ .

#### **Somatic mutations**

SMAD2 and SMAD4 are mutated in less than 10% of HCCs.

#### ***SMAD4***

**Location:** 18q21

#### **DNA / RNA**

11 exons.

#### **Protein**

Candidate tumor suppressor.

#### ***RB1***

**Location:** 13q14

#### **DNA / RNA**

27 exons

#### **Protein**

pRB, 110kDa, is phosphorylated during the G1 phase of the cell cycle by members of the cyclin-dependent kinase (cdk) system. Hypophosphorylated pRB binds to members of the E2F family of transcription factors.

#### **Somatic mutations**

LOH at the RB1 gene locus and RB1 mutations have been observed in about 15% of HCCs.

#### ***p16 INK4A***

**Location:** 9p21

#### **DNA / RNA**

3 exons. The INK4A-ARF locus gives two transcripts, the alpha transcript which encodes p16 INK4A and the beta transcript which encodes p19 ARF.

**Protein**

Inhibitor of cyclin-dependent kinases (CDK) 4 and 6.

**Somatic mutations**

Both somatic and germline mutations have been found in HCC. In addition, 50% of HCCs display de novo methylation of p16 INK4A, probably leading to gene silencing and loss of a cyclin-dependent kinase inhibitor protein.

**Cyclin D1**

**Location:** 11q13

**DNA / RNA**

5 exons.

**Protein**

Involved in cell cycle control: G1 progression and G1/S transition.

**Somatic mutations**

Cyclin D1 gene has been shown to be amplified in 10-20% of HCCs.

**To be noted****Note**

At least three genes, IGF2R, SMAD2, SMAD4, involved in TGF- $\beta$ -mediated growth control are altered in HCC. Overall the TGF- $\beta$  pathway is altered in about 25% of HCCs.

RB1, p16 INK4A and cyclin D1 are involved in the regulation of the G1 phase of the cell cycle. When combined the mutations of these genes, although relatively low individually, lead to a loss of growth control in more than 30% of HCCs.

Other genetic alterations Insulin-like growth factor 2 (IGF2) as well as insulin receptor substrate 1 (IRS-1) are overexpressed in many human HCC tumor tissues and cell lines. BRCA2, p21 and p15 INK4B are rarely involved in HCC.

Many genes are altered in hepatocarcinogenesis but the frequency of individual gene mutations is low. Genes involved in important regulatory pathways are the targets of these mutations. Four main pathways can be distinguished: the p53 pathway involved in DNA damage response and apoptosis, the b-catenin/APC pathway involved in intercellular interactions and signal transduction, the TGF- $\beta$  pathway involved in growth inhibition and hepatocyte death and the RB1 pathway involved in cell cycle control. Connections between these different pathways are most probable.

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