Human Pathology (2016) **50**, 135–139

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Human PATHOLOGY

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Original contribution

Expression of liver fatty acid binding protein in hepatocellular carcinoma☆

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Received 29 August 2015; revised 28 November 2015; accepted 5 December 2015

Keywords:
Liver fatty acid binding protein;
Hepatocellular carcinoma;
Hepatocellular adenoma;
HNF1A;
Well differentiated hepatocellular neoplasm

Summary Loss of expression of liver fatty acid binding protein (LFABP) by immunohistochemistry has been shown to be characteristic of a subset of hepatocellular adenomas (HCAs) in which *HNF1A* is inactivated. Transformation to hepatocellular carcinoma is thought to be a very rare phenomenon in the *HNF1A*-inactivated variant of HCA. However, we recently observed 2 cases at our institution, 1 definite hepatocellular carcinoma and 1 possible hepatocellular carcinoma, with loss of LFABP staining, raising the possibility that LFABP down-regulation may be associated with hepatocellular carcinogenesis. Our aim was to evaluate hepatocellular carcinomas arising in various backgrounds and with varying degrees of differentiation for loss of LFABP staining. Twenty total cases of hepatocellular carcinoma were examined. Thirteen cases arose in a background of cirrhosis due to hepatitis C (n = 8) or steatohepatitis (n = 5); 7 cases arose in a noncirrhotic background, with 2 cases arising within *HNF1A*-inactivated variant HCA and 2 cases arising within inflammatory variant HCA. Complete loss of expression of LFABP was seen in 6 of 20 cases, including 2 cases of hepatocellular carcinoma arising within *HNF1A*-inactivated variant HCA. Thus, loss of staining for LFABP appears to be common in hepatocellular carcinoma and may be seen in well-differentiated hepatocellular carcinoma. Therefore, LFABP loss should not be interpreted as evidence for hepatocellular adenoma over carcinoma, when other features support a diagnosis of hepatocellular carcinoma. The findings raise consideration for a role of *HNF1A* inactivation in hepatocellular carcinogenesis, particularly in less differentiated tumors.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common malignant primary tumor in the liver with most cases arising in the setting of chronic liver disease, often in patients with cirrhosis. Common etiologic associations include cirrhosis, viral hepatitis (specifically in chronic hepatitis B and C infection), aflatoxin B1, hereditary hemochromatosis, alcohol, and fatty liver disease. HCC arising outside the setting of cirrhosis has been particularly noted in patients with metabolic syndrome, emphasizing that multiple mechanisms of disease likely account for progression to HCC.

Hepatocellular adenoma (HCA), on the other hand, is a benign liver tumor, often seen in the setting of oral contraceptive use. Recent molecular studies have allowed for subclassification of HCAs [1-7]. One subtype, accounting for approximately 30% to 40% of HCAs, is defined by biallelic inactivating mutations in *HNF1A* (on chromosome

Abbreviations HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; LFABP, liver fatty acid binding protein; WD, well differentiated.

☆ Disclosures: The authors have no conflict of interest to declare.

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http://dx.doi.org/10.1016/j.humpath.2015.12.002
0046-8177/

12q), which encodes hepatocyte nuclear factor 1α [7,8]. Hepatocyte nuclear factor 1α belongs to the hepatocyte nuclear factor family of proteins and is a key transcription factor known to be involved in the control of hepatocyte differentiation as well as glucose and lipid metabolism in the liver [9-11]. *HNF1A*-inactivated HCAs are characterized by marked steatosis, but steatosis can be seen in other subtypes of HCA. Steatosis may also be present in other well-differentiated (WD) hepatocellular lesions (ie, focal nodular hyperplasia and WD HCC) that may be considered in a differential diagnosis with HCA, especially on core biopsy. Further analysis has shown that expression of liver fatty acid binding protein (LFABP), which is normally expressed at high levels within hepatocyte cytoplasm and involved in fatty acid trafficking, is down-regulated in *HNF1A*-inactivated HCAs [8]. This down-regulation of LFABP can be demonstrated by immunohistochemical methods, with loss of hepatocyte staining for LFABP reported in all *HNF1A*-inactivated HCAs [2].

The risk of transformation of HCA to HCC is highest in the β-catenin–mutated subtype of HCAs but was originally described as a rare phenomenon in *HNF1A*-inactivated HCAs [7,12]; thus, the molecular mechanisms of carcinogenesis may be distinct in this scenario. Early studies of LFABP expression in HCC considered LFABP as a potential positive marker of HCC [13]. *FABP1* (the murine homolog of *LFABP*) down-regulation has been demonstrated in a murine model of hepatocellular carcinogenesis [14], and *hnf1a*-deficient mice have been shown to develop liver enlargement associated with increased hepatocyte proliferation, with some cases associated with hepatocyte dysplasia [10,15,16]. However, there has been no systematic study of LFABP staining in HCC. In this study, we evaluated a range of HCC differentiation (well to poorly differentiated) arising in various clinical settings (eg, hepatitis C, steatohepatitis, HCA) for LFABP loss.

2. Materials and methods

2.1. Study population

The cases (n = 20) included in this study (Table 1) were selected from our institutional archives with the goal of selecting cases with a representative mix of background liver disease and with a spectrum of HCC differentiation. Thirteen cases (65%) of HCC arose in a background of cirrhosis due to hepatitis C (n = 8) or steatohepatitis (n = 5). Seven cases (35%) of HCC arose in a noncirrhotic background. Two of these cases (cases 1 and 2) had WD HCCs arising within *HNF1A*-inactivated variant HCAs; 1 case (case 1) had 2 separate HCCs, both arising within separate HCAs. Two other cases had HCC arising within inflammatory variant HCA (cases 3 and 9). Differentiation of HCC ranged from well to poorly differentiated, with a few cases demonstrating 2 distinct regions of differentiation (ie, well to moderately differentiated or moderately to poorly differentiated, as designated) (Table 2). The diagnosis of HCC was established using a combination of clinical, imaging, and histopathologic findings, including histochemical staining for reticulin,

Table 1 Cases selected for study

Case	Age	Sex	Cirrhosis	Background liver disease
1	65	F	No	Multiple *HNF1A*-inactivated HCAs
2	19	F	No	Multiple *HNF1A*-inactivated HCAs
3	29	F	No	Inflammatory HCA
4	67	F	Yes	Hepatitis C
5	61	M	Yes	Steatohepatitis
6	48	M	Yes	Steatohepatitis
7	53	M	Yes	Hepatitis C
8	56	M	Yes	Hepatitis C
9	40	F	No	Inflammatory HCA
10	36	M	No	Mild steatosis
11	65	F	No	None
12	59	M	No	None
13	52	M	Yes	Hepatitis C
14	68	F	Yes	Steatohepatitis
15	59	F	Yes	Steatohepatitis
16	59	M	Yes	Hepatitis C
17	48	M	Yes	Hepatitis C
18	71	M	Yes	Steatohepatitis
19	53	M	Yes	Hepatitis C
20	59	F	Yes	Hepatitis C

Abbreviations: HCA, hepatocellular adenoma; F, female; M, male.

Table 2 LFABP expression in hepatocellular carcinoma

Case	Degree of HCC differentiation	LFABP expression
1	WD	−
2	WD	−
3	WD	+
4	WD	+
5	WD	+
6	WD	+
7	WD	+
8	WD	+
9	WD	+
10	WD-MD	+
11	WD-MD	−
12	MD	+
13	MD	+
14	MD	+
15	MD	+
16	MD	−
17	MD-PD	+
18	PD	+
19	PD	−
20	PD	−

Abbreviations: HCC, hepatocellular carcinoma; LFABP, liver fatty acid binding protein; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.