

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8051

Title: Significance of downregulation of liver fatty acid-binding protein in hepatocellular carcinoma

Reviewer code: 00182114

Science editor: Ya-Juan Ma

Date sent for review: 2013-12-13 09:14

Date reviewed: 2014-01-08 12:39

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

Dear Author Author conclude "In most cases of small HCC, downregulation of L-FABP expression may have resulted from phenotypic changes during tumor progression. In addition, in cases of small HCC, the downregulation of L-FABP expression was significantly associated with poor differentiation and lack of inflammation as well as high expression of β -catenin and GS." I ask question to author. 1. Page 9, Most small HCC cases exhibited focal downregulation, and most large HCC cases exhibited diffuse downregulation. Please explain me the reason why the down regulation pattern of L-FABP expression was different between cases of small and large HCC. 2. Please explain the reason why you decide that small HCC is <2cm and large HCC is >2cm.

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8051

Title: Significance of downregulation of liver fatty acid-binding protein in hepatocellular carcinoma

Reviewer code: 02528139

Science editor: Ya-Juan Ma

Date sent for review: 2013-12-13 09:14

Date reviewed: 2014-01-12 18:29

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS
Title: Significance of downregulation of liver fatty acid-binding protein in hepatocellular carcinoma

In this paper Dr. Inoue et al. studied the significance of liver fatty acid-binding protein (L-FABP) expression in hepatocellular carcinoma (HCC) by using immunohistochemical staining. This study found that most cases of small HCC (≤ 2 cm in diameter) exhibited focal downregulation and most cases of large HCC (> 2 cm in diameter) exhibited diffuse downregulation. In cases of small HCC, L-FABP downregulation might be due to phenotypic changes during tumor progression; further, it was correlated with tumor differentiation and intra-tumorous inflammation. These topics are important for understanding the tumor differentiation and intra-tumorous inflammation. However, several points require improvements.

1. The author should describe the results following the several main topics since they described their results following the table or figures. We usually do not use these construct. The main focus of their study is not clear.
2. The sample size is very small to conclude the correlation between L-FABP downregulation pattern and tumor size (Table 2).
3. What is the reason why the age was statistically different between L-FABP positive and negative?
4. The most of the data could be subjective. Therefore, they should do some in vitro experiments.

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8051

Title: Significance of downregulation of liver fatty acid-binding protein in hepatocellular carcinoma

Reviewer code: 00159425

Science editor: Ya-Juan Ma

Date sent for review: 2013-12-13 09:14

Date reviewed: 2014-02-17 08:05

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This is a well written and interesting manuscript. Despite the findings are not very definitive they are valuable for further researches on this topic.

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8051

Title: Significance of downregulation of liver fatty acid-binding protein in hepatocellular carcinoma

Reviewer code: 00069630

Science editor: Ya-Juan Ma

Date sent for review: 2013-12-13 09:14

Date reviewed: 2014-02-18 09:04

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

In the present study, the authors found that approximate 10% (16/146) of HCC exhibited downregulation of L-FABP expression using immunohistochemical staining, and the pattern of L-FABP downregulation was different between the cases of small and large HCC. It was speculated that L-FABP downregulation might be due to phenotypic changes during tumor progression in small HCC. However, this conclusion was not supported by sufficient evidence, which include the following two aspects: 1. The negative ratio is too low: only 16 cases (~10%) of L-FABP were negative in HCC. Accordingly, the number of cases was too few in each subgroup (Table 3) to draw a convinced statistical conclusion. 2. The L-FABP gene is positively regulated by HNF1 α . It is unclear whether the downregulation of L-FABP expression in HCC was caused by inactivating mutation of HNF1A (the gene encoding HNF1 α) in the paper. Therefore, the author should detect expression of HNF1 α protein or mutation of HNF1A.

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8051

Title: Significance of downregulation of liver fatty acid-binding protein in hepatocellular carcinoma

Reviewer code: 00503516

Science editor: Ya-Juan Ma

Date sent for review: 2013-12-13 09:14

Date reviewed: 2014-02-19 18:22

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Masafumi Inoue et al studied the expression level of the liver fatty acid-binding protein (L-FABP) in hepatocellular carcinoma (HCC). The authors report that in cases of small HCC, L-FABP is down regulated and that down-regulation might be related to phenotypic changes during tumor progression; additionally they propose that FABP down-regulation is correlated with tumor differentiation and intra-tumorous inflammation. The work is of potential interest, however some aspects need to be clarified. Major comments 1) Page 9 lines 8-10 from top: "Ten cases exhibited focal downregulation (Figure 1C) and 6 cases exhibited diffuse downregulation (Figure 1D). It is not clear whether or not these cases belong to the 16 mentioned on page 9 line 2 from top. 2) Page 9 lines 11-14 from top: "When the correlation between the downregulation pattern of L-FABP expression and tumor size was examined, most small HCC cases (≤ 2 cm in diameter) exhibited focal downregulation, and most large HCC cases (> 2 cm in diameter) exhibited diffuse downregulation". Also in this case it is not clear whether or not these cases belong to the 16 mentioned on page 9 line 2 from top. 3) This is just an observational study with no mechanistic inside; whereas I understand that mechanistic data may be above the scope of the paper, some in vitro studies may be performed and/or some consideration should be introduced. Minor comments 4) It is not clear why the authors considered the cut off of 2 cm to discriminate small and large HCC; an explanation should be provided in this regard. 5) In the core tip I would not insert the sentence: "While the downregulation of liver fatty acid-binding protein (L-FABP) expression is critically important in the diagnostic classification of hepatocellular adenoma and it is correlated with various clinicopathological features..." as this concept is not presented in the abstract but only later in the



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introduction. 6) Please substitute in the core tip on page 3 line 7 from bottom "L-LABP" with "L-FABP".

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8051

Title: Significance of downregulation of liver fatty acid-binding protein in hepatocellular carcinoma

Reviewer code: 00680628

Science editor: Ya-Juan Ma

Date sent for review: 2013-12-13 09:14

Date reviewed: 2014-02-22 02:34

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

MAJOR COMMENTS: The authors aimed to “investigate the significance of L-FABP expression in hepatocellular carcinoma (HCC)”. However, the study design is poor. The major shortage of this study is the unscientific criteria used for defining the L-FABP expression in the immunohistochemical staining (IHCS) and the number of tumor cells used for the IHCS. The high prevalence of L-FABP in patients with HCC (89.0%) may be due to the false positivity by the unscientific criteria. i, e., the positive tumor cells was defined as “positive if almost all tumor cells stained positively and as negative if almost all tumor cells stained negatively. The results in this study showed that increased the number of tumor cells for IHCS measurement may increase the frequency of L-FABP expression. In Table 2 and Table 3, the authors used the same IHCS to define the L-FABP expression. However, the number of tumor cells used is different. The sample was prepared from 3-mm tissue cores (Table 2) and from representative whole tissue sections (Table 3), respectively. The tumor cells used for IHCS in Table 3 were more than those in Table 2. Such a difference in tumor cell number may result in sampling bias, as shown in this study. Based on this criteria, 16 (10.9%) patients with HCC were categorized as negative for L-FABP expression (Table 2), however, when sampling tumor cells increased (Table 3), all 16 patients became positive for IHCS (Table 3; panel C and panel D of Fig. 1). Since the sensitivity of IHCS is the same, the results in Table 3 was derived from increased tumor cells. It is obvious that all 16 patients negative for L-FABP IHCS are false negative owing to small tumor cells tested (Table 2). In reference 15, only 18.6% (12/62) of patients with HCC are positive for L-FABP. In another report for detecting the L-FABP expression in 68 patients with metastatic colon cancer, L-FABP was found in 38 (56%) patients (Journal of Surgical Oncology 1999;72:83–87). In

that article, tumor cells were classified as either L-FABP negative (positive cells <10%) or positive (positive cells ≥10%). Such a criteria is more scientific than that used in this study. The possibility of false positive may explain the high prevalence of L-FABP (89.0%; 130/146) in this study. Based on these comments, the data are inadequate to support the conclusions of this study. MINOR COMMENTS: 1. Table 2 should be revised extensively. 1a) Not all parameters could be presented as %. For example, age and tumor size. 1b) In viral infection, what is the meaning for “negative”? 1c) Elements in tumor part and non-tumor part should be separated and shown. For example, intra-tumor fibrosis vs. non-tumor fibrosis 1d) The prevalence of liver cirrhosis and Child-Pugh grading in patients with HCC should be presented. 1e) If the result of L-FABP related to tumor size, the HCC should be categorized by tumor size (≤1, 1.1 ~ 2, 2.1~3, >3.1 cm, etc) for comparison, rather than described as the mean size of tumor. 2. In this study, the detailed procedure for each immunohistochemical staining method was not described. Table 1 could be omitted. The amount of antibodies used, time and temperature for incubation and other reagents used in different cytokeratin examination should be described in methods. 3. The authors should consult a statistician for statistical analysis. 3a) “Statistics” in Material and Methods should be changed to “statistical analysis”, 3b) Since data were presented as mean ± standard deviation, why use Mann-Whitney U test for comparison? In addition, the statistical methods used and number of patients analyzed should be shown. 3c) “Other frequency and categorical data were compared using the Fisher’s exact test.” is not always correct. For example, comparison of tumor cell differentiation are 3x 2 χ^2 test (Table 5). It is incorrect to use the Fisher’s exact test for statistical comparison. 3d) If the calculated P value is 0.003, it is not necessary