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Original Article

Differential Expression of Insulin-like Growth Factor 1 in Human Primary Liver Cancer

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Abstract

Insulin-like Growth Factor 1(IGF-1) antigen was immunohistochemically examined in 28 patients of the primary hepatocellular carcinoma with hepatectomy. IGF-1 was expressed in 93% (26/28) of the primary lesion and 100% (28/28) of the normal liver. Compared with expression in normal liver, decreased expressions in primary lesions were noted in 36% (10/28) for IGF-1.

Histological examination revealed that there were significant correlations between patients with decreased expressions of IGF-1 in primary lesions and poor differentiated hepatocellular carcinoma, and portal vein infiltration.

These results indicate that expression of IGF-1 has the relationship with the differentiation in human primary hepatocellular carcinoma.

Key words : HCC・IGF-1

Introduction

Insulin-like growth factor 1 (IGF-1) is believed to play an important role in fetal growth and development[1)]. Recently, several investigators have reported that IGF-1 is expressed in human gene in variety of human tumors[2)3)]. It has also been reported that IGF-1 is expressed in human hepatocellular carcinoma (HCC) with high frequency, suggesting that IGF-1 may be involved in hepatocarcinogenesis[2)]. Insulin-like growth factors have been implicated in the deregulation of growth control in hapatocytes during malignant transformation via an autocrine mechanism[4)]. We examined immunohistochemical expression in primary tumor and normal liver in 28 cases of hepatocellular carcinoma, using the monoclonal antibody (IGF-1), and our observation are reported herein.

Patients and Methods

We examined 28 HCCs surgically resected at the Second Department of Surgery, Kyushu University and registered in the Second Department of Pathology, Kyushu University. All resected specimens were cut into serial 5 to 10 mm thick slice and fixed in 10% formalin. The slices through the maximum diameter of the tumor were divided into blocks, and the blocks were then embedded in paraffin and stained with

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Table 1 The expression of IGF-1 in the normal liver and primary tumors who underwent hepatic resection with HCC

Factors	IGF-1	
	Negative (%)	Positive (%)
Normal liver	0 (0%)	28 (100%)
Tumor	2 (7%)	26 (93%)

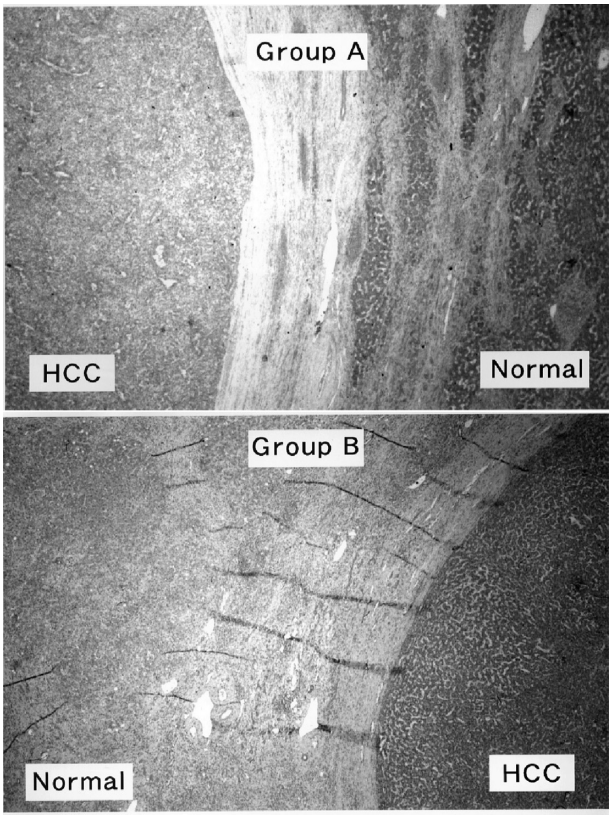

Fig. 1 Group A : compared with expression in normal liver, decreased expressions in hepatocellular carcinoma were noted for IGF-1.
Group B : compared with expression in normal liver, increased or equal expressions in hepatocellular carcinoma were noted for IGF-1.

hematoxylin and eosin.

Immunohistochemical studies were performed in 28 tumors using the avidin-biotin-peroxidase complex technique. The primary antibodies, sources, and dilutions used in this study are indicated in Table 1. Four-micron-thick sections of 10% formalin-fixed, paraffin-embedded material were cut, deparaffinized in xylene, and rehydrated in descending dilutions of ethanol. After treatment with 3% hydrogen peroxide, the sections were incubated at 4℃ overnight with monoclonal antibody to IGF-1 (Upstate Biotechnology, NY, USA). The sections were treated with anti-mouse IgG-biotin complex followed by avidin-peroxidase complex and then were stained with 3,3'-diaminobenzidine (DAB) solution with 0.15 % hydrogen peroxide. All sections were briefly counterstained with Mayer's Haematoxylin. Distinct staining for IGF-1 in normal tissue and tumor tissue was scored as positive. Cases with absent IGF-1 staining in the normal tissue or the tumor tissue were scored as negative.

Group A : compared with expression in normal liver, decreased expressions in primary lesions were noted for IGF-1.

Group B : compared with expression in normal liver, increased or equal expressions in primary lesions were noted for IGF-1 (Fig. 1).

Proliferation activity was assessed by using the MIB1 antibody (Immunotech S. A., Marseille, France) which detects the Ki-ii67 antigen.

Statistical analyses were performed using the chi-square and Student's t test. A p value of < 0.01 was considered to be significant.

Results

Table 1 summarized the expression of IGF-1 in the normal tissue and primary tumors in the liver of hepatocellular carcinoma patients. In all patients, cytoplasm of the normal tissue showed positive expression of IGF-1. However, IGF-1 was not expressed in the nucleus. In the tumor, IGF-1 was expressed in 26/28 (93%) of the primary tumors. IGF-1 was located mainly in the cytoplasm, too.

Table 2 summarized the expression of IGF-1 according to the clinicopathological factors. Decreased expressions of IGF-1 was in *0/5(0%)* of the well differentiated, 4/17(23.6%) of moderately differentiated and 6/6 (100%) of undifferentiated carcinoma($p < 0.01$).

In patients with portal vein infiltration, the numbers were significantly higher in patients with decreased expressions of IGF- 1 ($p < 0.01$). However, There was not significant difference between the two groups of microscopic capsular

Table 2 The expression of IGF-1 and clinicopathological factors who underwent hepatic resection with HCC

Factors	Group A (n = 10)	Group B (n = l 8)	p
Sex			N.S.
Male	6	8	
female	4	10	
Histology			< 0.01
well (%)	0 (0)	5 (30)	
moderately (%)	4 (40)	13 (70)	
poorly (%)	6 (60)	0 (0)	
fc (%)	9 (90)	9 (50)	N.S.
fc-inf (%)	8/9 (82.6)	8/9 (87.8)	N.S.
vp (%)	6 (60)	1 (7)	< 0.01
im (%)	3 (30)	2 (14)	N.S.

fc, microscopic capsular formation ; fc-inf, microscopic intracapsular infiltration ; vp, microscopic invasion to the portal vein ; im, microscopic intrahepatic metastases

Table 3 The expression of IGF-1 and Ki-67 who underwent hepatic resection with HCC

Factors	IGF-1		
	Group A	Group B	p
Ki-67			N.S.
Positive	2	5	
Negative	8	13	

formation and microscopic intrahepatic metastases.

Table 3 summarizes the relation between the expression of IGF-1 and Ki-ii67. There was no significant difference between two groups.

Discussion

Adami and colleages[5] reported diabetes mellitus to be a risk factor for primary liver cancer in a cohort study. We reported[6] that the diabetes mellitus was a risk factor for recurrence after hepatic resection with hepatocellular carcinoma. The onset of clinical diabetes is also preceded by years of chronic hyperinsulinemia, with an elevated proportion of proinsulin and split products of proinsulin, molecules with some homology to insulin-like growth factor-1 (IGF-1)[7]. Insulin or its precursors have also been shown to interact with liver cells and to stimulate mitogenesis or carcinogenesis[8)~10)]. It has been reported that IGF-1 was synthesized by the liver[11]. And are increasingly recognized as important mitogens in many tumor[12)13)]. Several studies have demonstrated over-expression of IGF receptors by tumor cells compared with the corresponding normal tissues in hepatoma[14)15)]. On the other hand, Aihara and colleagues [16] reported that the IGF II gene expression level showed a significantly increase in dysplastic nodules, but in the well differentiated carcinoma of the liver. A further decrease was seen in the moderately differentiated carcinoma.

The present study demonstrates that IGF-1 was more expressed in the well differentiated carcinma than the poor differentiated carcinoma of the liver. It is considered that IGF-1 is mainly produced from a normal liver and a differentiated tumor. The positive expression of IGF-1 depended on the degree of tumor differentiation.

Shoda et al. reported that the pattern of localization of IGF-1 was almost identical with that of Ki-67 antigen[17], and may play an important role in the development of hepatocellular carcinoma. However, in this study comparing with the expression of IGF-1 and Ki-67 antigen positive cells, there was no relations between two groups. And Ki-67 antigen may play an important role in the stimulating mitogenesis or carcinogenesis of hepatic cells but not participating in the degree of specialization.

In conclusion, based on the above findings

expression of IGF-1 has the relationship with the histological differentiation and portal vein infiltration in human primary hepatocellular carcinoma.

References

1) Macaulay VM : Insulin-like growth factors and cancer. Br J Cancer. 65 : 311-320, 1992.
2) Kim SO, Park JG and Lee YI : Increased expression of the insulin-like growth factor I (IGF-1) receptor gene in hepatocellular carcinoma cell lines : Implications of IGF-1 receptor gene activation by hepatitis B virus X gene product. Cancer Res. 56 : 3831-3836, 1996.
3) Heaton JH, Krett NL and Gelehrter TD : Regulation of insulin and insulin-like growth factor (IGF) responsiveness by IGFs in rat hepatoma cell. Endocrinol. 118 : 2555-2560, 1986.
4) Spon MB and Robert AB : Autocrine growth factors and cancer. Nature 313 : 745-747, 1985.
5) Adami HO, Chow WH, Nyren O, Berne C, Linet MS, Ekbom A, Wolk A, JK Mclaughlin and JF Fraumeni Jr : Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst. 88 : 1472-1477, 1996.
6) Ikeda Y, Shimada M, Hasegawa H, Gion T, Kajiyama K, Shirabe K, Yanaga K, Takenaka K and Sugimachi K : Prognosis of hepatocellular carcinoma with diabetes mellitus after hepatic resection. Hepatology 27 : 1567-1571, 1998.
7) Davies MJ, Rayman G, Gray IP, Day JL and Hales CN : Insulin deficiency and increased plasma concentration of intact and 32/33 split proinsulin in subjects with impaired glucose tolerance. Diabet Med 10 : 313-320, 1993.
8) Kahn CR and White MF : Molecular mechanism of insulin action. In : DeGroot LJ, editor. Endocrinology. Philadelphia : Saunders, 1373-1388, 1995.
9) Russel WE and VanWyk JJ : Peptide growth factors. In : DeGroot LJ, editor. Endocrinology. Philadelphia : Saunders, 2590-2623, 1995.
10) Tabor E : Tumor suppressor genes, growth factor genes, and oncogenes in hepatitis B virus-associated hepatocellular carcinoma. J Med Virol 42 : 357-365, 1994.
11) D'Ercole AJ, Stiles AD and Underwood LE : Tissue concentrations of somatomedin C : Further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action. Proc Natl Acad Sci. 81 : 935-939, 1984.
12) Daughaday WH, Wu JC, Lee SD and Kapadia M : Abdominal processing of pro-IGF-11 in patients with hepatoma and in some hepatitis B virus antibody-positive asymptomatic individuals. J Lab Clin Med. 116 : 555-562, 1990.
13) Cho EJ, Lee JH, Yoo JJ, Choi WM, Lee MJ, Cho Y, Lee DH, Lee YB, Kwon JH, Yu SJ, Lee JM, Suh KS, Kim K, Kim YJ, Yoon JH, Kim CY and Lee HS : Serum insulin-like growth factor-1 level is an independentpredictor of recurrence and survival in early hepatocellular carcinoma : a prospective cohort study. Clin Cancer Res. 19 : 4218-4227, 2013.
14) Hartshorn MA, Scott CD and Baxter RC : lmmunofluorescent localization of type II insulin-like growth factor receptor in rat liver andhepatoma cells. J Endocrinol. 121 ; 221-227, 1989.
15) Yue L, Wang Y, Wang H, Gao H, Liang J, Sui A, Xiang J, Zhou F, Xu C, Zhao W, Liang W and Yao R : Inhibition of hepatocellular carcinoma cell growth by an anti-insulin-lile growth factor-1 receptor monoclonal antibody. Oncol Rep .28 : 1453-1460, 2012.
16) Aihara T, Noguchi S, Miyoshi Y, Nakano H, Sasaki Y, Nakamura Y, Monden M and lmaoka S : Allelic imbalance insulin-like growth factor II gene expression in cancerous and precancerous lesions of the liver. Hepatology 28 : 86-89, 1998.
17) Shoda T, Oka Y, Iwata K, Gunn J, Kamimura S, Shijo H, Okumura M and Yun K : Co-localization of insulin-like growth factor II and the proliferation marker MIB1 in hepatocellular carcinoma cells. J Clin Pathol 50 : 135-137, 1997.

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（和文抄録）

肝細胞癌における Insulin-like growth factor（IGF-1）発現に関する検討

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【はじめに】肝細胞癌における IGF-1 発現の意義を検討し，IGF-1 が肝細胞癌脱分化にどのように関与しているかを検討した．
【対象および方法】肝細胞癌切除症例 28 例のホルマリン固定パラフィン包埋標本で IGF-1 を免疫染色した．細胞増殖活性の指標としては Ki-67 の発現を検討した．IGF-1 は癌部と非癌部の発現を比較して，非癌部が癌部より過剰に発現したものを A 群（n=10），癌部が非癌部と同等または過剰に発現したものを B 群（n=18）とした．Ki-67（細胞増殖活性）は Labeling Index（LI）を用いて判定した．
【結果】IGF-1 は非癌部で 28 例/28 例（100%），肝細胞癌部では 26 例/28 例（93%）で発現を認めた．癌部が非癌部と同等または過剰発現する B 群は 18 例/28 例（64%）であった．病理組織学的分化度では IGF-1 発現の B 群は高分化型肝細胞癌が多く，A 群では低分化型肝細胞癌が有意に多く認めた（$p < 0.01$）．また A 群では脈管侵襲（vp）が多く認められた（$p < 0.01$）．しかしながら，肝内転移（im），被膜形成（fc），被膜内浸潤（fc-inf）との相関はなかった．IGF-1 と Ki-67 との間にも相関関係は認めなかった．
【まとめ】肝細胞癌切除例における IGF-1 の発現は細胞増殖活性との明らかな関係は認められなかったものの，肝細胞癌の脱分化並びに門脈侵襲に関与していると判明した．