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ORIGINAL RESEARCH

Cellular immune function and liver damage in post-hepatitic cirrhosis

Zhi-Jie Feng, Ran-Ming Niu, Xi-Ling Ren, Xi-Xian Yao

Zhi-Jie Feng, Ran-Ming Niu, Xi-Ling Ren, Xi-Xian Yao, Department of Internal Medicine, Second Affiliated Hospital, Hebei Medical University, Shijiazhuang 050000, Hebei Province, China

Dr. Zhi-Jie Feng, MD, Physician in Chief, with 21 papers and 3 books published.

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Correspondence to: Dr. Zhi-Jie Feng, Department of Internal Medicine, Second Affiliated Hospital, Hebei Medical University, Shijiazhuang 050000, Hebei Province, China
Telephone: +86-311-7046975

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Abstract

AIM: To study cellular immune function in patients with post-hepatitic cirrhosis (PHC) and its relationship with different types of liver damage.

METHODS: Fifty-one patients with PHC, including 20 cases of Child-Pugh class A, 18 of class B, 13 of class C and 22 normal subjects as controls were studied. After peripheral blood mononuclear cells were isolated by Ficoll-Hypaque gradient centrifugation, lymphocyte transformation (LT) test, IL-2 activity and NK cell activity were measured by the ^{3}H-TdR incorporation technique.

RESULTS: Changes of LT stimulation index (SI), IL-2 activity (SI) and NK cell activity (%) in patients with PHC were significantly decreased compared with in the healthy controls (18.1 ± 13.0 *vs* 34.9 ± 21.7, $P < 0.01$; 8.1 ± 6.0 *vs* 13.6 ± 5.8, $P < 0.01$; 40.3 ± 21.7 *vs* 61.3 ± 20.5, $P < 0.01$; respectively). The defects of cellular immune function were closely related to Child-Pugh classification. The values in class C were much lower than those in B and A ($P < 0.01$) and those in B were lower than those in A ($P < 0.05$).

CONCLUSION: Defective cellular immune functions in patients with PHC are connected with the degree of liver damage.

Key words: Hepatitis; Liver cirrhosis; Immunology; Immunity, cellular; Killer cells, natural; Lymphocyte transformation; Interleukin

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INTRODUCTION

Recent evidence has shown that deficiency of cell mediated immunity may play an important role in the pathogenesis of chronic HBV infection[1-3]. About 5%-10% cases of chronic hepatitis B develop into post-hepatitic cirrhosis (PHC). In order to study the relationship between immune function and liver damage, a lymphocyte transformation (LT) test, IL-2 activity and NK cell activity were measured in peripheral blood mononuclear cells (PBMC) taken from 51 patients with PHC.

MATERIALS AND METHODS

Subjects

Fifty-one PHC patients and 22 age and sex matched healthy controls were included. The diagnosis of PHC was based on clinical manifestations, serum biochemical findings and hepatitis B history or seropositive HBsAg for more than 12 mon. Diagnostic liver biopsy was performed in 12 patients. Patients with liver cirrhosis caused by other diseases were excluded. Of the 51 PHC patients, there were 36 males and 15 females, ranging in age from 22 to 68 years (mean 47.5 years). The course of disease varied from 1 mon to 30 years (mean 4.7 years). The complications of PHC included ascites (35 cases), upper gastrointestinal tract bleeding (28 cases), encephalopathy (5 cases) and hepatocellular carcinoma (7 cases). Twenty cases belonged to Child-Pugh class A, 18 cases to class B and 13 cases to class C. None of these patients had received corticosteroids or other immunosuppressive therapy within 6 mon.

Methods

LT test The PBMC were isolated by Ficoll-Hypaque gradient centrifugation, then washed and suspended at a concentration of 1 × 10^6/mL. The cells were stimulated with PHA (final concentration 25 μg/mL). The assay was made by the ^{3}H-TdR incorporation technique and individual sample results were expressed as a stimulation index (SI):

SI = cpm (PHA)/cpm (control)

IL-2 activity PBMC were stimulated with PHA (final concentration 150 μg/mL) to produce IL-2. After incubation, the supernatants were filtered and stored at 20 ℃. The method of mouse thymus cell multiplication was used to assay IL-2 activity, using SI to express results.

SI = [cpm(IL-2 supernatant) - cpm (background)]/[(cpm control) cpm (background)]

NK cell activity The activity was measured with the ^{3}H-TdR post

Table 1 Immune function assay in post-hepatitic cirrhosis patients ($\bar{x} \pm s$)

Assays	PHC (n)[b]	Control (n)
LT test (SI)	18.1 ± 13.0 (48)	34.9 ± 21.7 (22)
IL-2 activity (SI)	8.1 ± 6.0 (41)	13.6 ± 5.8 (20)
NK activity (%)	40.3 ± 21.7 (49)	61.2 ± 20.5 (22)
IgG (g/L)	17.9 ± 7.7 (29)	10.0 ± 5.1 (22)
IgA (g/L)	3.2 ± 2.4 (29)	1.6 ± 0.8 (22)
IgM (g/L)	1.4 ± 0.8 (29)	0.8 ± 0.2 (22)
Complement C_3 (g/L)	0.5 ± 0.2 (29)	1 ± 0.6 (22)

[b]$P < 0.01$, *vs* control for all assays. PHC: Post-hepatitic cirrhosis; LT: Lymphocyte transformation; SI: Stimulation index.

Table 2 Cellular immune function in post-hepatitic cirrhosis patients and Child-Pugh classification ($\bar{x} \pm s$)

Assays	Child-Pugh class		
	A (n)	B (n)	C (n)
LT test (SI)	20.9 ± 16.7 (17)	19.9 ± 11.1 (18)	10.1 ± 5.4 (13)[a]
IL-2 activity (SI)	10.7 ± 7.9 (16)	7.4 ± 3.4 (13)[a]	5.2 ± 3.3 (12)[b]
NK activity (%)	46.5 ± 19.9 (18)	38.5 ± 15.4 (18)[a]	19.5 ± 11.3 (13)[b]

[a]$P < 0.05$, [b]$P < 0.01$, *vs* class A. LT: Lymphocyte transformation; SI: Stimulation index.

incorporative technique. The PBMC (effector cells) were suspended at a concentration of 2×10^6/mL. Target cells (Heper-2 cells), a cell line of carcinoma of the larynx, were at 2×10^4/mL. Effector/target ratio was 100:1. NK cell activity was calculated as follows:

NK activity (%) = {1-[cpm (effector+target) - cpm (effector)]/[cpm (target) - cpm (background)]} × 100%

The levels of serum IgG, IgA, IgM and complement C3 were measured by a simple agar immunodiffusion test.

Statistical analysis

Results were expressed as $\bar{x} \pm s_{\bar{x}}$. Comparisons between groups were made using the *t*-test. Linear regression analysis was performed to evaluate the correlation between LT test, IL-2 and NK cell activity.

RESULTS

The results of the LT test, IL-2 activity and NK cell activity were significantly decreased in PHC patients compared with the healthy controls. The IgG, IgA and IgM were remarkably elevated and complement C3 was lowered in the PHC group (Table 1). The abnormalities of cellular immune function were closely related to the severity of liver damage determined by the Child-Pugh classification. The defects in patients with Child-Pugh class C were lower than that in patients with class A and B (Table 2). The linear regression analysis showed that there was strong positive correlation between LT test and NK cell activity ($r = 0.4774$, $P < 0.01$) and between IL-2 and NK cell activity ($r = 0.3975$, $P < 0.05$). There was no correlation between LT test and IL-2 activity ($r = 0.3579$, $P > 0.05$).

DISCUSSION

Defective cellular immune function, for example, T cell blastogenesis, CD4/CD8 ratio, lymphokine production, killer cell activity, *etc.*, was found in patients with chronic HBV infection[3-6]. The present study showed that there was a significant decrease in levels of the LT test, IL-2 activity and NK cell activity in PHC patients and that they were related to the Child-Pugh classification, suggesting that immunological abnormalities were closely related to the degree of liver damage. The more severely the liver was damaged, the more prominent the cellular immunological abnormalities. There was evidence to suggest that HBV-DNA may be duplicated and transcripted in PBMC, so that the immune function of T lymphocytes would be suppressed. It was shown that HBV-DNA was detected in PBMC of patients with HBV infection by the transfer hybridization technique[7]. The disturbance of T cell subsets, especially a decrease of CD4, may induce drawbacks of IL-2 production. IL-2 is a lymphokine which supports the immunoregulatory function of T cells and its deficiency may either suppress T cell proliferation or NK cell activity. Our present study showed that IL-2 activity was positively correlated with NK cell activity. Due to the destruction of cellular immunoregulation networks, hepatocyte damage was induced by impaired immune function of virus-infected hepatocytes and auto-immunoreaction. In addition, disturbances of immune function may also influence collagen metabolism and promote fibroplasia. Liver damage may lead to the defectiveness of hepatic immunoregulation and the decrease of number and function of Kupffer cells, which support the immune function of T, B and NK cells[8]. Therefore, cellular immunodeficiency was worsened more severely. Defectiveness of suppressor T cell function may lead to an increased B cell activation and its antibody production[9].

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