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Evaluation of the IL-2/IL-2R system in patients with liver cirrhosis or carcinoma

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Abstract

AIM: To evaluate the interleukin-2/interleukin-2 receptor (IL-2/IL-2R) system in patients with liver cirrhosis or carcinoma, and compare the immune function in those patients. The clinical significance of our results is also discussed.

METHODS: Fifty patients with liver cirrhosis (LC), 50 patients with hepatocellular carcinoma (HCC), and 30 normal control subjects were studied. Cellular expression of the interleukin-2 receptor (mIL-2R) was examined by immunofluorescence, and the serum levels of IL-2 and soluble interleukin-2 receptor (sIL-2R) were measured by ELISA.

RESULTS: The levels of IL-2 and mIL-2R expression in carcinoma patients were significantly lower than those in both patients with cirrhosis ($P < 0.01$) and control subjects ($P < 0.01$). The serum levels of IL-2 and the expression of mIL-2R in patients with cirrhosis were also lower than those in normal control subjects ($P < 0.05$). The serum levels of sIL-2R in carcinoma patients were significantly higher than those in both cirrhosis patients ($P < 0.05$) and control subjects ($P < 0.01$), and the sIL-2R levels in cirrhosis patients were higher than those in control subjects ($P < 0.05$).

CONCLUSION: Patients with liver cirrhosis or carcinoma both have decreased immune function; however, this decrease is more pronounced in carcinoma patients. Such similarities in immune disturbances may be an important factor affecting the development of carcinoma in a cirrhotic liver.

Key words: Liver cirrhosis; Liver neoplasms; Interleukin-2/analysis; Receptors interleukin/analysis

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INTRODUCTION

Both liver cirrhosis (LC) and hepatocellular carcinoma (HCC) are common diseases in China. HCC and LC are closely associated with each other in the majority of carcinoma patients (60%-80%), and 10%-30% of patients with cirrhosis will eventually develop HCC. While the various etiologies of HCC are complicated, LC appears to be a major risk factor for the eventual development of carcinoma. In the present study, we determined the serum levels of interleukin-2 (IL-2) and soluble interleukin-2 receptor (sIL-2R), as well as the expression of mIL-2R in patients with liver cirrhosis or carcinoma. The clinical significance of our findings is also discussed.

MATERIALS AND METHODS

Patients and controls

This study enrolled 50 patients with LC, 50 patients with HCC, and 30 normal control subjects. HCC and LC had been diagnosed either clinically or based on a histologic evaluation. None of the patients were taking any medication or had a history of immunotherapy. All of the LC cases were Child's grade B or C.

Assays for IL-2 and sIL-2R

Serum levels of IL-2 and sIL-2R were measured using commercially available ELISA kits. Both assays were performed on the same day and in a single batch to avoid variability. The assay methods are described in detail in a previous publication[1]. Briefly, quadruplicate samples of peripheral blood mononuclear cells (PBMCs) which had been separated by density gradient centrifugation were cultured with phytohemagglutinin (PHA) for 72 h. Following culture, the cells were washed, placed in microtubes, and then incubated with fluorescein-labelled anti-IL-2R monoclonal antibodies. After incubation, the cells were washed 3 times with Hank's balanced salt solution, and then gently resuspended with a Pasteur pipette. One drop of liquid with cells was examined using a fluorescence microscope equipped with a barrier filter. The number of lymphocytes that displayed immunofluorescence staining for IL-2R was recorded, and expressed as a percentage of total cultured PBMCs.

Statistical analysis

The data were analyzed using the *t*-test, and results are expressed as the mean ± SD

RESULTS

The serum levels of IL-2 and sIL-2R and the levels of mIL-2R

Table 1 Serum levels of IL-2 and sIL-2R, and expression of mIL-2R in patients with liver cirrhosis or hepatocellular carcinoma

	IL-2 (μ/mL)	sIL-2R (μ/mL)	mIL-2R (%)
LC	80.1 ± 15.2	264.2 ± 51.3	39.9 ± 7.2
HCC	42.5 ± 11.7	340.7 ± 63.9	33.1 ± 6.4

expression are shown in Table 1. The results showed that IL-2 levels and mIL-2R expression were both significantly lower in patients with HCC, when compared to those parameters in patients with LC ($P < 0.01$) as well as control subjects ($P < 0.01$). Furthermore, IL-2 levels and mIL-2R expression in LC patients were also lower when compared with those parameters in normal subjects (both P-values < 0.05). In contrast, the serum levels of sIL-2R in HCC patients were significantly higher when compared with those in both LC patients, ($P < 0.05$) and control subjects ($P < 0.01$), and the serum levels of sIL-2R in LC patients were also higher than those in control subjects ($P < 0.05$).

DISCUSSION

IL-2 secreted by activated T-lymphocytes interacts with specific membrane receptors (mIL-2R) to upregulate immune reactions in an autocrine manner[2]. In addition to mIL-2R, both *in vivo* and *in vitro* studies have identified a soluble form of IL-2R (sIL-2R) in the supernatant fractions of activated mononuclear cells[3]. This molecule apparently represents the Tac chain of the heterodimeric high affinity IL-2R complex found on the surface of activated T-lymphocytes. sIL-2R displays a lower binding affinity for supernatant IL-2 than it does for mIL-2R. The release of sIL-2R from activated T-lymphocytes may occur due to either proteolysis of mIL-2R or as the result of an alternative mRNA-related process[4].

The decreased IL-2 levels and higher sIL-2R levels in the PBMCs of some individuals may result from several types of liver diseases, including acute and chronic viral hepatitis[5]. High levels of sIL-2R in cases of acute or chronic HBV infection appear to be directly related to the activity of liver diseases, and therefore may reflect the activation of effector cells which help kill the infected hepatocytes. One possible explanation for the reduced IL-2 activity might be that if reflects the compartmentalization of active cells in the liver, and the down-regulated or inhibited production of soluble factors by PBMCs. Similar to hepatitis patients, patients with LC or HCC also show reduced IL-2 activity and mIL-2R expression, accompanied by higher serum levels of sIL-2R. When considering the etiologic and morphologic characteristics of cirrhosis, LC appears to be the most important risk factor for HCC, and HBsAg positivity is one of several factors that increase the risk for HCC in patients with cirrhosis. Our results suggest that patients with LC or HCC have a similar type of immune dysfunction; however, HCC patients have a higher degree of the dysfunction. This similarity in immune disturbances may be an important factor affecting the progression of liver cirrhosis to liver cancer. Our results also indicate that an evaluation of the IL-2/IL-2R system can provide reliable information when selecting an immunotherapy or evaluating the effects of immunotherapy.

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