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Roles of HTLV-I p19 and Natural Antibody to HTLV-I in Host Immune Responses

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A. Introduction

Since the discovery of human T cell leukemia/lymphoma virus type I (HTLV-I) [5], the immune status of HTLV-I-infected hosts, including patients with adult T cell leukemia (ATL), has not yet been sufficiently investigated [2–4]. As the first step in this kind of study, we have studied the nonspecific activity of peripheral mononuclear cells (PMNC) from ATL patients and seropositive HTLV-I carriers and the role of HTLV-I p19 antigen and HTLV-I-producing cell surface antigens in the host immune responses to HTLV-I.

B. Nonspecific Immunity

In ATL patients, the spontaneous DNA synthesis of PMNC increased significantly whereas the mitogen- (PHA, staphage lysate = SPL, or Con-A)-induced DNA synthesis and NK activity of PMNC against human myeloid K562 cells dropped tremendously (Table 1). In most seropositive healthy HTLV-I carriers, the spontaneous DNA synthesis of PMNC relatively increased, but the mitogen-induced DNA synthesis and NK activity were within the normal range. Of course, PMNC from seronegative healthy persons showed completely normal reactions for these functions. These results indicate that PMNC from ATL patients were abnormally changed in all their nonspecific functions tested by both HTLV-I infection and malignant transformation, and that PMNC from HTLV-I carriers showed partial dysfunction, but maintained some functions at normal levels. Thus, it may be concluded that PMNC from HTLV-I carriers were enhanced only in spontaneous DNA synthesis by HTLV-I infection, and that the other functions remained almost normal in HTLV-I infection without malignant transformation.

C. Specific Immunity

By means of immunofluorescence microscopy (IFM) and immunoelectron microscopy (IEM) using viable HTLV-I-producing cells, the presence of HTLV-I p19 on both the cell surface and the viral envelope was observed as spots or small sectors by reaction with mouse monoclonal antibody to HTLV-I p19 [1, 2]. This expression of HTLV-I p19 was quite specific for HTLV-I-producing cells. In the light of the presence of HTLV-I p19 in the periphery of acetone-fixed HTLV-I-producing cells as shown by IFM and on the surface of both the virions and HTLV-I-producing cells by

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Table 1. DNA synthesis and natural killer (NK) activity of peripheral mononuclear cells (PMNC) from patients with adult T cell leukemia (ATL) and from seropositive or seronegative healthy persons

PMNC donors	DNA synthesis		NK activity
	Mitogen-induced	Spontaneous	
ATL patients	Lowered	Heightened	Negative
Seropositive carriers	Normal	Heightened	Normal
Seronegative healthy persons	Normal	Normal	Normal

Table 2. Antibody-dependent cellular cytotoxicity by peripheral mononuclear cells from patients with adult T cell leukemia (ATL) and from seropositive or seronegative healthy persons

Attacker cell donors	Antibody to HTLV-I	Cytolysis			
		HTLV-I-producing cells		HTLV-I-non-producing cells	
		Cultured	Fresh	Cultured	Fresh
ATL patients	+	–	–	–	–
	–	–	–	–	–
Seropositive carriers	+	+	–	–	–
	–	–	–	–	–
Seronegative healthy persons	+	+	–	–	–
	–	–	–	–	–

IEM, it seems most likely that HTLV-I p19 is an internal antigen of HTLV-I with part of its structure protruding from the viral and cellular membrane. Accordingly, this antigen might be involved in the surface immune reaction of HTLV-I-producing cells. However, the mouse monoclonal antibody to HTLV-I p19 did not induce antibody-dependent cellular cytotoxicity (ADCC) with PMNC from either seropositive HTLV-I carriers or seronegative healthy donors. This monoclonal antibody also failed to induce complement-dependent cytotoxicity (CDC). Therefore, HTLV-I p19 does not contribute to any cytotoxicity.

Regardless of the PMNC donors who are seropositive or seronegative for HTLV-I, PMNC from healthy donors clearly revealed ADCC against HTLV-I-producing cells in the presence of serum containing antibodies to HTLV-I-related antigens (Table 2). No differences in the ADCC effects were detected between the antibody-positive sera from healthy donors and from ATL patients. By contrast, the PMNC showed no ADCC in the presence of either antibody-negative serum or fetal calf serum. In addition, PMNC from ATL patients revealed extremely low ADCC or none at all. This may be explained by concluding that; (a) these PMNC became dysfunctional by malignant transformation; (b) the absolute number of effector cells decreased; and/or (c) the relative number of effector cells in this assay diminished according to an increase in malignant cells. Moreover, since cytotoxicity of PMNC was appreciably lowered by incubation with a mixture of anti-Leu 7 monoclonal antibody and rabbit serum as a complement source, the effector cells of ADCC may be K cells. Although NK cells also express Leu 7 antigen, NK activity of PMNC did not contribute to this ADCC because of the necessity of anti-HTLV-I antibody.

When rabbit serum was added as a complement source to a mixture of antibody-positive serum and cultured HTLV-I-producing cells, CDC distinctly occurred

Table 3. Complement-dependent cytotoxicity by sera from patients with adult T cell leukemia (ATL) and from seropositive or seronegative healthy persons in the presence of rabbit serum as a complement source

Serum sources	Cytolysis			
	HTLV-I-producing cells		HTLV-I-non-producing cells	
	Cultured	Fresh	Cultured	Fresh
ATL patients	+	–	–	–
Seropositive carriers	+	–	–	–
Seronegative healthy persons	+	–	–	–

(Table 3). No other complement sources such as human serum and guinea pig serum induced CDC. When fresh malignant cells from ATL patients were used as target cells instead of cultured malignant T cells, no CDC was recognized at all.

D. Remarks

Although PMNC from seropositive carriers were partially dysfunctional in nonspecific immune activities, they clearly showed ADCC against cultured HTLV-I-producing cells in the presence of antibody-positive serum from either seropositive carriers or ATL patients, but no ADCC against fresh malignant T cells from ATL patients. This suggests that fresh malignant T cells do not exhibit any HTLV-I-associated antigens on the surface of these cells, or that the amount of these antigens may be too small to induce ADCC. It has been proven that masked HTLV-I-associated antigens appeared on the cell surface after in vitro culture. The same phenomenon can be adapted to CDC. Thus, in ATL patients or seropositive carriers, malignant T cells can grow constantly without any interference by ADCC and/or CDC. Even the injection of rabbit serum as a complement source may not induce CDC for the same reason.

Is there any difference in the quality of antibodies in sera from ATL patients and HTLV-I carriers? According to the results of the Western blot method using disrupted HTLV-I and cell extracts as antigens, the titer of antibody to p68–70 of HTLV-I-producing cells appeared to be slightly lower in sera from healthy seropositive carriers than in sera from ATL patients (Miyakoshi and Aoki 1984). However, this difference in antibodies of sera does not provide any definite evidence to explain why ATL develops in some seropositive carriers or why carriers can prevent ATL development. The mechanisms of ATL in HTLV-I-infected hosts should be a central problem of future studies.

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