CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Jan. 1994, p. 5–10
1071-412X/94/$04.00+0

Vol. 1, No. 1

Immunologic Cross-Reactivity between Structural Proteins of Human T-Cell Lymphotropic Virus Type I and the Blood Stage of *Plasmodium falciparum*

RENU B. LAL,[1]* DONNA RUDOLPH,[1] MICHAEL P. ALPERS,[2] ALEXANDER J. SULZER,[3] SHI YA-PING,[3] AND ALTAF A. LAL[3]

Retrovirus Diseases Branch, Division of Viral and Rickettsial Diseases,[1] and Malaria Branch, Division of Parasitic Diseases,[3] National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, and Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea[2]

Received 6 May 1993/Returned for modification 12 July 1993/Accepted 15 July 1993

To determine the serologic cross-reactivity between human T-cell lymphotropic virus type I (HTLV-I) and parasite antigens, we measured antibody responses against HTLV-I, *Plasmodium falciparum*, *Plasmodium vivax*, and *Brugia malayi* in serum specimens obtained from regions where malaria (n = 482) and filariasis (n = 101) are endemic. Analysis of immune reactivity to HTLV-I antigens showed that specimens from regions where malaria is endemic had significantly higher rates of enzyme immunoassay (EIA) reactivity (76 of 482 [15.8%]) than those from regions where filariasis is endemic (0 of 101 [0%]). Western blot (immunoblot) analysis of the HTLV-I EIA-reactive specimens demonstrated predominant Gag reactivity (HTLV-I^{ind}). Only two specimens each from Indonesia and Brazil and four specimens from Papua New Guinea had Env reactivity by radioimmunoprecipitation analysis. Furthermore, a positive correlation between HTLV-I EIA and titers of antibody to the blood stage of *P. falciparum* (r_s = 0.24, P < 0.005) was discerned; no correlation was observed between antibodies to the blood stage or the circumsporozoite protein of *P. vivax* and the circumsporozoite protein of *P. falciparum*. In addition, *P. falciparum*-infected erythrocyte lysate specifically abrogated binding of Gag-specific antibodies in HTLV-I^{ind} specimens from regions where malaria is endemic without affecting binding in HTLV-I-seropositive specimens, suggesting that the immunologic cross-reactivity between HTLV Gag proteins and malaria parasites is restricted to the blood-stage antigens of plasmodia in specimens from regions where malaria is endemic. However, HTLV-seroindeterminate specimens from the United States did not demonstrate serologic cross-reactivity, suggesting that antigenic mimicry of HTLV proteins extends to other nonplasmodial antigens as well.

Human T-cell lymphotropic virus type I (HTLV-I) is etiologically linked with adult T-cell leukemia and HTLV-I-associated myelopathy, also known as tropical spastic paraparesis (4, 17). Infection with HTLV-I is endemic in southwestern Japan, Papua New Guinea, the Solomon Islands, the Caribbean basin, and Africa (3, 6, 17, 32, 33). HTLV-I infection is also found among blood donors in the United States (4, 17, 23). The seropositivity criteria, as defined by a U.S. Public Health Service working group, require that a specimen exhibiting reactivity to p24^{gag} and either gp46^{env} or gp61/68^{env} be considered seropositive for HTLV-I (HTLV-I^{pos}) (4). However, screening of blood donors and serosurveys in various populations often lead to the detection of isolated and persistent Gag antibodies to HTLV-I (anti-p24 or anti-p19) by Western blotting (immunoblotting); individuals with these antibodies are referred to as seroindeterminate (HTLV-I^{ind}) (4, 13, 19, 20, 30, 32, 33). Recent studies have shown that persons with such Gag reactivities do not have true HTLV-I infection; rather, their immune response is an antigenic mimicry with other proteins (13, 19). In addition, retrospective studies of recipients of blood with such serum reactivity have demonstrated that these recipients do not seroconvert to HTLV-I positivity (23). Taken together, these findings suggest an immunologic cross-reactivity between Gag epitopes of HTLVs and other microbial, cellular, and/or endogenous retroviral proteins.

Indeed, several amino acid stretches of HTLV-I are known to bear sequence homologies to human proteins and several infectious agents, including viruses and protozoan parasites (7, 10, 14, 16, 18). For instance, amino acid sequences from bovine leukemia virus and human endogenous retrovirus have shown homologies to the Gag proteins of HTLV-I (16, 22); however, serologic cross-reactivity between HTLV-I Gag and either virus was not observed (13, 31). More recently, antibodies to *Plasmodium falciparum* were shown to cross-react with HTLV-I antigens in specimens from a region of the Philippines where malaria is endemic (9). This antigenic cross-reactivity was attributed to the epitopes shared by plasmodial and HTLV-I antigens. These findings implied that serum specimens from the regions where malaria is endemic could yield higher nonspecific rates of HTLV-I^{ind} results than specimens from regions where malaria is not endemic. Indeed, serosurveys of individuals in Papua New Guinea, the Solomon Islands, and Africa, all of which are regions where malaria is hyperendemic, have indicated high frequencies of HTLV-I^{ind} persons (1, 6, 32, 33).

To further investigate the nature of serologic cross-reactivities between malarial and HTLV-I antigens, we compared the cross-reactivities of antibodies to plasmodial antigens and antigenic determinants on HTLV-I antigens. Our data dem-

* Corresponding author. Mailing address: Retrovirus Diseases Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, Mailstop G-19, Atlanta, GA 30333. Phone: (404) 639-1036. Fax: (404) 639-1174.

onstrate that serologic cross-reactivity between HTLV-I could be blocked by *P. falciparum*-infected erythrocyte lysates in serum specimens from regions where malaria is endemic. Further, the failure of HTLV-I^{ind} specimens from the United States to block antibody reactivities suggests that antigenic mimicry of HTLV-I antigens extends to antigenic epitopes other than plasmodial antigens.

MATERIALS AND METHODS

Serum specimens. A total of 482 serum specimens from the following regions where malaria is endemic were tested for antibodies to malaria parasites and HTLV-I: Lake Lindu Valley, Central Sulawesi, Indonesia (n = 178) (5); Madang Province, Papua New Guinea (n = 118); and the state of Pará, Brazil (n = 186). In addition, specimens from Papua New Guinea previously shown to be positive (n = 12), indeterminate (n = 27), or negative (n = 12) for antibodies to HTLV-I were included for inhibition experiments. Specimens from individuals infected with the filarial parasite *Wuchereria bancrofti* (n = 101) from Southeast Asia (n = 24), India (n = 35), and Egypt (n = 42) were tested to determine the cross-reactivity between antibodies to filarial and HTLV-I antigens.

Antibodies to plasmodial antigens. Antibodies to blood-stage malaria parasites were tested by a standard indirect immunofluorescence assay (IFA). Briefly, slides coated with *P. falciparum*- and *Plasmodium vivax*-infected erythrocytes were incubated with appropriate dilutions of test sera for 30 min at 37°C, washed with phosphate-buffered saline, and then incubated with fluorescein isothiocyanate-labelled secondary antibody. Specimens which reacted at a dilution of 1:64 or greater were considered positive for plasmodial antigens. In some experiments, HTLV-I^{pos} and HTLV-I^{ind} specimens from the United States were added to inhibit the IFA titers of plasmodium-positive specimens.

The presence of antibodies to the circumsporozoite (CS) protein of *P. falciparum* and *P. vivax* was determined by a FAST enzyme-linked immunosorbent assay (ELISA) (27) with synthetic peptides specific for the CS protein repetitive sequence $[(NANP)_4$ for *P. falciparum* and $(GDRADGQPA)_3$ for *P. vivax*].

Antibodies to filarial antigens. Antibodies to filarial antigens from *Brugia malayi* were determined by an enzyme immunoassay (EIA) as described previously (12).

Antibodies to HTLV-I. Antibodies to HTLV-I were determined by an EIA (Organon Teknika), and reactive specimens were tested by a Western blot assay incorporating purified recombinant HTLV-I envelope (r21e) protein with a whole-virus lysate derived from an HTLV-I-infected cell line, HuT-102 (Cambridge Biotech, Rockville, Md.) and a radioimmunoprecipitation assay (RIPA) with a lysate from the MT-2 cell line (13). A serum specimen was determined to be HTLV-I^{pos} if antibody reactivity to at least two different HTLV-I structural gene products ($p24^{gag}$ and $gp46^{env}$ or $gp61/68^{env}$ and r21e) was detected. The results were considered HTLV-I^{ind} if the Western blot showed isolated bands characteristic of HTLV-I (p19, p24, or r21e) but did not meet the criteria for a positive result. Specimens with no bands were considered negative for antibodies to HTLV-I (HTLV-I^{neg}).

PCR. PCR assays were performed with peripheral blood lymphocytes. Two gene regions from each patient were amplified with *pol* and *tax* primers and hybridized with end-labelled oligonucleotide probes from the respective regions as described previously (13).

Competitive inhibition experiments. To determine if malaria antigen causes HTLV-I reactivity, we performed competitive inhibition experiments with HTLV-I and plasmodial antigens in an HTLV-I EIA and a Western blot assay. The blood-stage plasmodial antigen extract was prepared from human erythrocytes infected with the FCR3 strain of *P. falciparum*. The infected erythrocytes were harvested by low-speed centrifugation when parasitemia reached 5 to 10% with the schizont stage. One milliliter each of infected and uninfected packed cells was lysed in 10 ml of 0.1% (wt/vol) Nonidet P-40 in saline and stored at −70°C.

For inhibition experiments, the sera from HTLV-I^{pos}, HTLV-I^{ind}, and HTLV-I^{neg} specimens were diluted 1:50 with the *P. falciparum*-infected and uninfected erythrocyte lysates, incubated at 25°C for 30 min, and then incubated at 4°C for 18 h. For the HTLV-I EIA, a further dilution (1:4) was made with diluent from the EIA kit, and the remainder of the assay was done as described in the manufacturer's instructions. For the Western blot assay, the sera incubated with infected and uninfected erythrocyte lysates were further diluted (1:2) by addition of an equal volume of blocking buffer. The diluted sera were added to the Western blot strips containing HTLV-I antigens with the recombinant transmembrane protein (r21e), and the strips were incubated at 25°C overnight. The incubation was followed by washes and color development as described previously (13). The purified HTLV-I antigen (Hillcrest Biologicals, Cypress, Calif.) was used as a control to block the binding of homologous antigens.

Statistical analysis. The Student t test was used to compare mean EIA values for different groups, and Spearman's rank correlation (r_s) coefficients were used to assess the associations among the variables.

RESULTS

Antibody reactivity to HTLV antigens. Serum specimens (n = 482) from regions where malaria is endemic were tested by the HTLV-I EIA to determine the antibody to HTLV antigens. Of these, 51 (28.6%) of 178 specimens from Indonesia, 18 (15.2%) of 118 of specimens from Papua New Guinea, and 7 (3.8%) of 186 specimens from Brazil were reactive in the HTLV-I EIA. The Western blot profile of EIA-reactive specimens demonstrated that a number of specimens reacted only with $p24^{gag}$ and/or $p19^{gag}$ and hence were considered HTLV-I^{ind}. The presence of Env reactivity, as determined by radioimmunoprecipitation analysis ($gp61/68^{env}$) of all EIA-reactive specimens, was detected in only two of the Indonesian specimens, four of the Papua New Guinean specimens, and two of the Brazilian specimens; thus, a large proportion of EIA-reactive specimens yielded HTLV-I^{ind} reactivity. None of the specimens from individuals infected with filarial parasites demonstrated reactivity to HTLV-I antigens in the EIA (Table 1).

Correlation between antibody to HTLV-I and malarial antigens. To determine if plasmodial infections were responsible for inducing antibodies that cross-react with HTLV-I antigens, we tested serum specimens from Indonesia for antibodies to *P. falciparum* and *P. vivax* by IFA and for HTLV-I antibody by EIA. While a positive correlation between HTLV-I EIA results and titers of antibody to *P. falciparum* could be discerned ($r_s = 0.24, P < 0.005$) (Fig. 1A), no correlation was observed with *P. vivax* ($r_s = 0.03, P > 0.05$) (Fig. 1B), suggesting that the *P. falciparum* malaria parasite may contain antigenic determinants that bear immunologic homology to HTLV-I. The two HTLV-I^{pos} specimens from Indonesia had IFA titers of 1:1,024 and 1:16,384.

To further explore immunologic cross-reactivity between HTLV-I antigen and the sporozoite stage of the parasite, we

TABLE 1. Reactivities of serum specimens from diverse geographic areas to HTLV antigens

Specimen source (*n*)	No. positive by HTLV EIA	No. positive with indicated HTLV Western blot reactivity[a]				No. positive by HTLV RIPA
		r21$^+$ p24$^+$ p19$^+$	p19$^+$ p24$^+$	p19$^+$ p24	p19$^-$ p24$^+$	
Regions where malaria is endemic						
Indonesia (178)	51	10	16	19	6	2
Papua New Guinea (118)	18	8	4	4	2	4
Brazil (186)	7	4	0	1	2	2
Regions where filariasis is endemic						
Southeast Asia (24)	0	0	0	0	0	0
India (35)	0	0	0	0	0	0
Egypt (42)	0	0	0	0	0	0

[a] None of the specimens demonstrated an HTLV-I^{pos} profile. Specimens with an r21$^+$ p24$^+$ p19$^+$ profile were tested further by RIPA.

determined the presence of antibodies to the CS repeat sequences of *P. falciparum* and *P. vivax* in specimens from Papua New Guinea. No correlation between either of the CS protein antibody responses and HTLV-I antibody could be discerned (data not shown), suggesting that immunologic cross-reactivity between HTLV-I and *Plasmodium* spp. is restricted to blood-stage antigens.

Inhibition of HTLV-I antibodies with *P. falciparum*-infected erythrocyte lysates. Competitive inhibition experiments were conducted to determine the specificity of interaction of malarial antigens with HTLV-I-specific antibodies in specimens from Papua New Guinea. Incubation of HTLV-I-positive specimens with uninfected and infected erythrocyte lysates prior to HTLV-I EIA analysis yielded similar optical densities (ODs) of 2.54 ± 0.80 and 2.11 ± 1.04, respectively (Table 2). In contrast, a marked decrease in ODs was observed when HTLV-I^{ind} specimens were incubated with infected erythrocyte lysates (0.61 ± 0.49) in comparison with uninfected lysates (1.81 ± 0.81; 63% inhibition). Furthermore, PCR analysis of 22 of these 27 HTLV-I^{ind} specimens did not amplify any products specific for either the *pol* or *tax* gene of HTLV-I, further confirming the absence of true HTLV-I infection in these specimens (Table 2). As expected, no differences in the ODs of negative control specimens were observed.

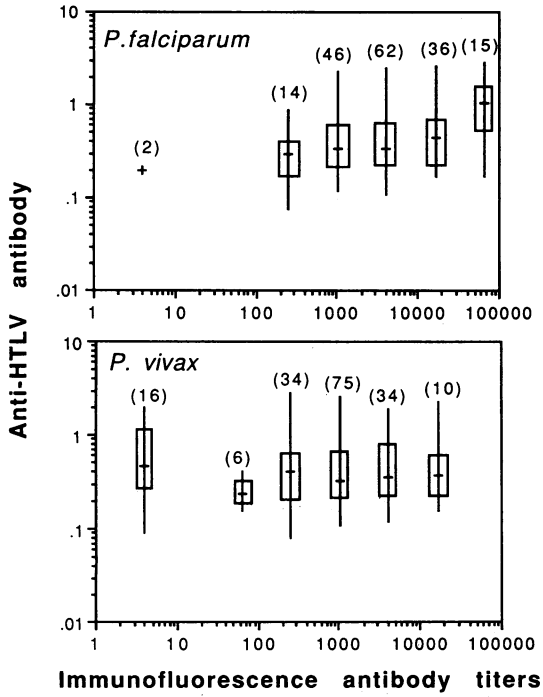

FIG. 1. Correlation between HTLV-I EIA antibody titers and IFA titers for *P. falciparum* (top) and *P. vivax* (bottom) in serum specimens from Indonesia. The number of specimens is indicated above each bar; each box represents the 90% confidence levels for each group.

The antigenic profile of cross-reacting antibodies was determined by Western blot analysis. While neither Gag (p24 or p19) nor Env (r21e) protein bands were inhibited by *P. falciparum*-infected erythrocyte lysates incubated with HTLV-I^{pos} specimens from Indonesia (n = 2), Papua New Guinea (n = 4), and Brazil (n = 2) (Fig. 2A, HTLV-I^{pos} lanes 3), the bands in the HTLV-I^{ind} specimens from Indonesia (n = 2), Papua New Guinea (n = 5), and Brazil (n = 2) were completely inhibited in the presence of infected erythrocyte lysates (Fig. 2A, HTLV-I^{ind} lanes 3). The specificity of the inhibition was confirmed by using uninfected erythrocyte lysates, which did not abrogate binding to any HTLV-I-specific protein (Fig. 2A, lanes 2).

To determine whether cross-reactivity by malarial antigens was restricted to seroindeterminate specimens from regions where malaria is endemic or extended to regions where malaria is not endemic, we tested seroindeterminate specimens from the United States (n = 15) (all negative for the HTLV-I genome) in the inhibition experiment. Neither Gag nor Env reactivity could be inhibited in these U.S. specimens (from regions where malaria is not endemic) (Fig. 2B, HTLV-I^{ind} lanes 3). Furthermore, HTLV-I^{pos} (n = 5) and HTLV-I^{ind} (n = 7) specimens from the United States did not react in a malaria IFA, suggesting that antibodies to HTLV-I antigens do not cross-react with *Plasmodium* antigens in specimens from the United States (data not shown).

TABLE 2. Competitive inhibition of HTLV-I antibody reactivity by *P. falciparum*-infected erythrocyte lysate in serum specimens from Papua New Guinea

HTLV-I result (no. of serum specimens tested)	PCR result (no. positive/no. tested)	OD in HTLV-I ELISA		% Inhibition
		Uninfected erythrocyte lysate	Infected erythrocyte lysate	
Positive (12)	5/5	2.54 ± 0.80	2.11 ± 1.04	21
Indeterminate (27)	0/22	1.81 ± 0.81	0.61 ± 0.49	63
Negative (8)	0/3	0.27 ± 0.13	0.27 ± 0.09	0

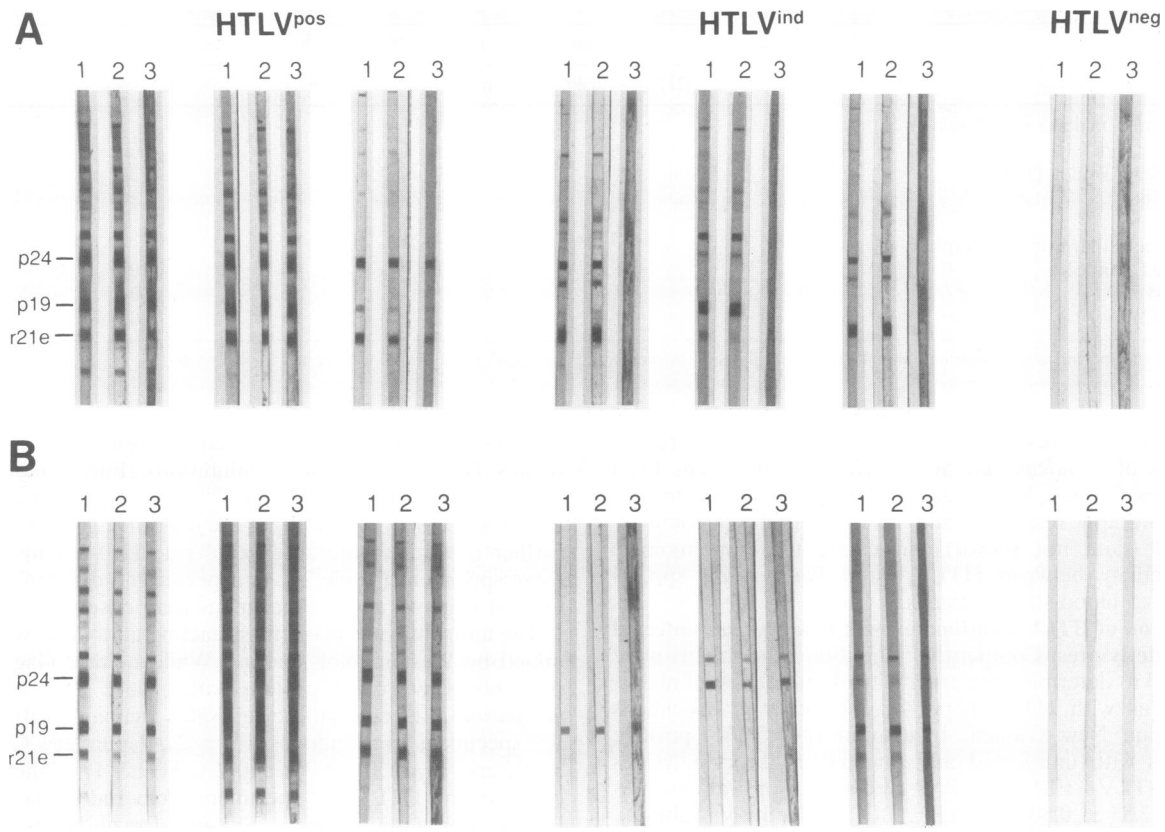

FIG. 2. Competitive inhibition of HTLV-I antibodies with *P. falciparum*-infected erythrocyte lysate in specimens from regions where malaria is endemic (A) or not endemic (B). Each serum specimen was run on a Western blot with no lysate incubation (lane 1), preincubation with uninfected erythrocyte lysate (lane 2), or preincubation with *P. falciparum*-infected erythrocyte lysate (lane 3). Among the HTLV-I^{pos} specimens, panel A shows one specimen each from Papua New Guinea, Indonesia, and Brazil (left, middle, and right blots, respectively), whereas panel B shows three specimens from U.S. blood donors. Among the HTLV-I^{ind} specimens, panel A shows two specimens from Papua New Guinea and one from Indonesia (left to right), and panel B shows three specimens from U.S. blood donors.

DISCUSSION

Screening assays for detection of antibodies to HTLV-I often detect isolated Gag-reactive antibodies, resulting in specimens being classified as HTLV-I^{ind} (4, 17). Such HTLV-I^{ind} Western blot results are frequently observed with specimens from tropical populations such as the Melanesians of the Solomon Islands, the Hagahais of Papua New Guinea, Bismam Asmat groups of Indonesian New Guinea, the Napsan of the Philippines, and certain tropical groups in Africa (3, 6, 9, 15, 20, 32, 33). It has been postulated that such antibodies are induced by an agent(s) that is either immunologically (host or nonhost antigens) or genetically (variant forms of retroviruses) related to, but different from, prototypic HTLVs (13, 19). Highly divergent molecular variants of HTLV-I in Melanesians have been identified (8). However, the variant strain-specific sequences in Melanesian specimens with indeterminate Western blot patterns could not be amplified, suggesting that isolated Gag reactivities are probably due to antigenic mimicry of certain cellular or microbial antigens that share antigenic epitopes present on the Gag proteins of HTLV-I (15, 19). Recent observations of cross-reactions between *P. falciparum* antigens and HTLV-I proteins among individuals living in a region in the Philippines where malaria is endemic suggest that antibodies to the malarial antigens may cross-react in serologic assays, resulting in HTLV-I^{ind} results (9). In this report, we provide evidence for immunologic cross-reactivity between HTLV-I and blood-stage plasmodial antigens.

Analysis of serum antibodies to both HTLV-I by EIA and plasmodial antigens in paired specimens demonstrated a positive correlation between antibodies to HTLV-I and antibodies to *P. falciparum*, but no correlation was observed for antibodies to *P. vivax*. The selective correlation with only *P. falciparum* presumably reflects a higher prevalence for this species of *Plasmodium* in Papua New Guinea. In contrast, none of the specimens derived from regions where filariasis is endemic demonstrated antibody responses to HTLV-I antigens. The initial finding suggesting that repeated exposure to filariasis plays a role in the etiology of adult T-cell leukemia (29) has not been further substantiated. In addition, the cross-reactive antibodies appeared to be restricted to the blood-stage antigens, since none of the immunodominant epitopes of the CS protein (27) induced cross-reactive antibodies. Competitive inhibition experiments demonstrated that *P. falciparum*-infected erythrocyte lysate could abrogate the binding of antibodies to the HTLV-I antigens in HTLV-I^{ind} specimens. These results corroborate recent reports demonstrating serologic cross-reactivity between HTLV-I and *P. falciparum* in regions of the Philippines and Africa where malaria is endemic (3, 9)

and contrast with a previous study in which no correlation between seroreactivity to malarial and HTLV-I antigens was observed (6). These discrepant results could either be due to technical differences in the assay procedures or due to strain differences in the parasite.

Of greater importance is the finding that in HTLV-I^{ind} specimens from regions where malaria is endemic, *P. falciparum*-infected erythrocyte lysate not only blocked the binding to the Gag proteins (p24 and p19) but also inhibited binding to a recombinant transmembrane protein (r21e) of HTLV-I. The inhibition did not appear to be due to erythrocyte proteins, such as immunoreactive glycophorin proteins (11), since uninfected erythrocyte lysate did not abrogate the binding of cross-reactive antibodies in HTLV-I^{ind} specimens. While the cross-reacting *Plasmodium* epitopes leading to antigenic mimicry were not identified in our study, they could represent small stretches of amino acids, as reported by McLaughlin et al. (18). Furthermore, the retroviral transmembrane protein contains a conserved immunodominant motif containing two cysteine residues flanked by six amino acids (CxxxxxxCC) (25); therefore, antigenic mimicry of this epitope could induce antibodies cross-reactive with HTLV r21e.

The antigenic cross-reactivity of *Plasmodium* antigens was restricted to the specimens from regions where malaria is endemic; none of the seroindeterminate specimens from the United States (where malaria is not endemic) were inhibited by plasmodial antigens. Reciprocally, none of the HTLV-I sera reacted in IFAs for detection of malarial antibodies. The antigenic basis for these isolated Gag antibodies in specimens from the United States remains to be defined (7). In addition, of the human endogenous retroviruses that have been sequenced, several have sequence similarities to the Gag proteins of HTLV-I and human immunodeficiency virus (2, 16). Indeed, a 28-kDa protein of an HTLV-I-related endogenous sequence (HRES-1) has similarities to the $p24^{gag}$ protein of HTLV-I, and this antigen may serve as an autoantigen eliciting autoantibodies cross-reactive with HTLV-I Gag antigens (2).

The antigenic cross-reactivity of $p19^{gag}$ is well defined. Monoclonal antibodies to p19 have previously been shown to react with antigens of normal thymus and placenta and with epithelial cytoplasmic protein derived from the salivary glands of patients with Sjögren's syndrome (10, 14, 26, 28). More importantly, because the antigen recognized by one of these antibodies is an inducible antigen, immune activation of cells in vivo may be able to upmodulate expression of this antigen, resulting in cross-reactive antibodies (26). The C-terminal region of $p19^{gag}$ also shows structural homologies to human DNA or RNA viruses, such as Epstein-Barr virus, encephalomyocarditis virus type B, herpes simplex virus type 1, and influenza virus, as well as certain human cellular proteins, such as complement, collagen, thyroglobulin, human leukocyte antigens, and cytokines (14, 21). More recently, an immunologically cross-reactive epitope in varicella-zoster virus has been mapped to the C terminus of $p19^{gag}$ protein of HTLV-I (24).

In conclusion, our results demonstrate that the immunologic cross-reactivity between HTLV Gag proteins and malarial parasites occurs with the blood-stage but not the CS antigens of *P. falciparum* in specimens from certain regions where malaria is endemic. However, indeterminate specimens from a region where malaria is not endemic did not demonstrate serologic cross-reactivity, suggesting that antigenic mimicry of HTLV-I proteins extends to nonplasmodial antigens as well.

ACKNOWLEDGMENT

We thank K. Porter, Naval Medical Research Institute, Rockville, Md., for his help with inhibition experiments.

REFERENCES

1. **Asher, D. M., J. Goudsmit, K. L. Pomeroy, R. M. Garruto, M. Bakker, S. G. Ono, N. Elliott, K. Harris, H. Askins, Z. Eldadah, A. D. Goldstein, and D. C. Gajdusek.** 1988. Antibodies to HTLV-I in populations of the southwestern Pacific. J. Med. Virol. **26:**339–351.
2. **Banki, K., J. Maceda, E. Hurley, E. Ablonczy, D. H. Mattson, L. Szegedy, C. Hung, and A. Perl.** 1992. Human T-cell lymphotropic virus (HTLV)-related endogenous sequence, HRES-1, encodes a 28-kDa protein: a possible autoantigen for HTLV-I *gag*-reactive autoantibodies. Proc. Natl. Acad. Sci. USA **89:**1939–1943.
3. **Biggar, R. J., P. L. Gigase, M. Melbye, L. Kestens, P. S. Sarin, A. J. Bodner, P. Demedts, W. J. Stevens, L. Paluku, C. Delacollette, and W. A. Blattner.** 1985. ELISA HTLV retrovirus antibody reactivity associated with malaria and immune complexes in healthy Africans. Lancet **ii:**520–523.
4. **Centers for Disease Control.** 1990. Human T-lymphotropic virus type-I screening in volunteer blood donors, United States, 1989. Morbid. Mortal. Weekly Rep. **39:**915, 921–922.
5. **Clarke, M. D., W. P. Carney, J. H. Cross, P. Hadidjaja, S. Oemijati, and A. Joesoef.** 1974. Schistosomiasis and other human parasitoses of Lake Lindu in Central Sulawesi (Celebes), Indonesia. Am. J. Trop. Med. Hyg. **23:**385–392.
6. **Delaporte, E., M. Peeters, M. Simoni, and P. Piot.** 1989. HTLV-I infection in western equatorial Africa. Lancet **ii:**1226.
7. **Doolittle, R. F., D. F. Feng, M. S. Johnson, and M. A. McClure.** 1989. Origins and evolutionary relationships of retroviruses. Q. Rev. Biol. **64:**1–30.
8. **Gessain, A., E. Boeri, R. Yanagihara, R. C. Gallo, and G. Franchini.** 1993. Complete nucleotide sequence of a highly divergent human T-cell leukemia (lymphotropic) virus type I (HTLV-I) variant from Melanesia: genetic and phylogenetic relationship to HTLV-I strains from other geographical regions. J. Virol. **67:** 1015–1023.
9. **Hayes, C. G., J. P. Burran, and R. B. Oberst.** 1991. Antibodies to human T-lymphotropic virus type I in a population from the Philippines: evidence for cross-reactivity with *Plasmodium falciparum*. J. Infect. Dis. **163:**257–262.
10. **Haynes, B. F., M. Robert-Guroff, R. S. Metzgar, G. Franchini, V. S. Kalyanaraman, T. J. Palker, and R. C. Gallo.** 1983. Monoclonal antibody against human T-cell leukemia virus p19 defines a human thymic epithelial antigen acquired during ontogeny. J. Exp. Med. **157:**907–920.
11. **Lacombe, J. M., B. Ferrari, R. Andriamanpisoa, and A. A. Pavia.** 1988. Malaria invasion of human erythrocytes: synthesis of peptides relevant to glycophorin A and evaluation of their inhibitory properties. Int. J. Pept. Protein Res. **32:**104–116.
12. **Lal, R. B., and E. A. Ottesen.** 1988. Increased diagnostic specificity in human filariasis through IgG4 antibody assessment. J. Infect. Dis. **158:**1034–1037.
13. **Lal, R. B., D. L. Rudolph, J. E. Coligan, S. K. Brodine, and C. R. Roberts.** 1992. Failure to detect evidence of human T-lymphotropic virus type I and type II in blood donors with isolated *gag* reactivities. Blood **80:**544–550.
14. **Lal, R. B., D. L. Rudolph, K. P. Griffis, K. Kitamura, M. Honda, J. E. Coligan, and T. M. Folks.** 1991. Characterization of immunodominant epitopes of *gag* and *pol* gene-encoded proteins of human T-cell lymphotropic virus type I. J. Virol. **65:**1870–1876.
15. **Lal, R. B., D. L. Rudolph, V. R. Nerurkar, and R. Yanagihara.** 1992. Humoral immune responses to the immunodominant *gag* and *env* epitopes of human T-lymphotropic virus type I among Melanesians. Viral Immunol. **5:**265–272.
16. **Mager, D. L., and J. D. Freeman.** 1987. Human endogenous retroviruslike genome with type C *pol* sequences and *gag* sequences related to human T-cell lymphotropic viruses. J. Virol. **61:**4060–4066.
17. **Manns, A., and W. A. Blattner.** 1991. The epidemiology of the human T-cell lymphotropic virus type I and type II: etiologic role in human disease. Transfusion (Arlington) **31:**67–75.
18. **McLaughlin, G. L., M. J. Benedirk, and G. H. Campbell.** 1987. Repeated immunogenic amino acid sequences of *Plasmodium* species share sequence homologies with proteins from human and human viruses. Am. J. Trop. Med. Hyg. **37:**258–262.

19. **Nerurkar, V. R., M. A. Miller, M. E. Leon-Monzon, A. B. Ajdukiewicz, C. L. Jenkins, R. C. Sanders, M. S. Godec, R. M. Garruto, and R. Yanagihara.** 1992. Failure to isolate human T-lymphotropic virus type I and to detect variant-specific genomic sequences by polymerase chain reaction in Melanesians with indeterminate Western immunoblot. J. Gen. Virol. **73:**1805–1810.
20. **Re, M. C., M. Tommaseo, G. Furlini, and M. L. Placa.** 1989. High prevalence of serum antibody against human T cell leukemia virus type I (HTLV-I) among the Bismam Asmat population (Indonesian New Guinea). AIDS Res. Hum. Retroviruses **5:**551–554.
21. **Renan, M. J.** 1985. Sequence homologies in the control regions of c-*myc*, c-*fos*, HTLV-I and the interleukin-2 receptor. Cancer Lett. **28:**69–76.
22. **Sagata, N., T. Yasunaga, J. Tsuzuku-Kawamura, K. Ohishi, Y. Ogawa, and Y. Ikawa.** 1985. Complete nucleotide sequence of the genome of bovine leukemia virus: its evolutionary relationship to the other retroviruses. Proc. Natl. Acad. Sci. USA **82:**677–681.
23. **Sandler, S. G., C. Fang, and A. Williams.** 1990. Retroviral infections transmitted by blood transfusion. Yale J. Biol. Med. **63:**353–360.
24. **Sato, A., Y. Isaka, F. Morita, A. Ishii, Y. Goto, J. Imai, H. Igarashi, O. Yoshie, and Y. Hinuma.** 1992. Human sera from varicella-zoster virus (VZV) infections cross-react with human T-cell leukemia virus type 1 (HTLV-1): common epitopes in VZV gene 22 protein and HTLV-1 p19 *gag* protein. J. Gen. Virol. **73:**2969–2973.
25. **Schulz, T. F., B. A. Jameson, L. Lopalco, A. G. Siccardi, R. A. Weiss, and J. P. Moore.** 1992. Conserved structural features in the interaction between retroviral surface and transmembrane glycoproteins? AIDS Res. Hum. Retroviruses **8:**1571–1580.
26. **Shattles, W. G., S. M. Brooks, P. J. W. Venables, D. A. Clark, and R. N. Maini.** 1992. Expression of antigen reactive with a monoclonal antibody to HTLV-I p19 in salivary glands in Sjogren's syndrome. Clin. Exp. Immunol. **89:**46–51.
27. **Shi, Y. P., V. Udhayakumar, M. P. Alpers, M. M. Povoa, A. J. Oloo, T. K. Ruebush II, and A. A. Lal.** 1993. Natural antibody responses against the non-repeat-sequence-based B-cell epitopes of the *Plasmodium falciparum* circumsporozoite protein. Infect. Immun. **61:**2425–2433.
28. **Suni, J., A. Narvanen, T. Wahlstrom, P. Lehtovirta, and A. Vaheri.** 1984. Monoclonal antibody to human T-cell leukemia virus p19 defines polypeptide antigen in human trimester placentas. Int. J. Cancer **33:**293–298.
29. **Tajima, K., F. Koichiro, S. Tsukidate, T. Oda, S. Tominaga, T. Suchi, and Y. Hinuma.** 1983. Seroepidemiological studies on the effects of filarial parasites on infestation of adult T-cell leukemia virus in the Goto Islands, Japan. Gann **74:**188–191.
30. **Verdier, M., G. Leonard, A. Sangare, M. Prince-David, J. Bonis, F. Borin, and F. Denis.** 1990. Confirmatory tests for human T-cell leukemia virus type 1 (HTLV-1): Western blot compared with RIPA on African sera. J. Virol. Methods **30:**283–290.
31. **Whetstone, C. A., K. R. Sayre, N. L. Dock, M. J. VanDerMaaten, J. M. Miller, E. Lillehoj, and S. S. Alexander.** 1992. Examination of whether persistently indeterminate human immunodeficiency virus type 1 Western immunoblot reactions are due to serological reactivity with bovine immunodeficiency-like virus. J. Clin. Microbiol. **30:**764–770.
32. **Yanagihara, R., C. Hefner, and A. B. Ajdukiewicz.** 1992. Human T lymphotropic virus type I infection among blood donors in the Solomon Islands. Transfusion (Arlington) **32:**89–94.
33. **Yanagihara, R., V. R. Nerurkar, and A. B. Ajdukiewicz.** 1991. Comparison between strains of human T lymphotropic virus type I isolated from inhabitants of the Solomon Islands and Papua New Guinea. J. Infect. Dis. **164:**443–449.