INFECTION AND IMMUNITY, June 1985, p. 638–643
0019-9567/85/060638-06$02.00/0

Vol. 48, No. 3

Pretreatment with Lipoteichoic Acid Sensitizes Target Cells to Antibody-Dependent Cellular Cytotoxicity in the Presence of Anti-Lipoteichoic Acid Antibodies

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Received 9 January 1985/Accepted 22 February 1985

This study was performed to determine whether antibody-dependent cellular cytotoxicity (ADCC) could be directed against mammalian cells sensitized with spontaneously adhering bacterial substances. ^{51}Cr-labeled SB leukemia cells were incubated with purified S43 group A streptococcal lipoteichoic acid (LTA; 0.001 to 100 μg/ml). Purified leukocyte ADCC effector cells were added to the LTA-coated target cells at various effector-to-target ratios (100:1 to 12:1), followed by the addition of rabbit anti-LTA. After incubation for 4 h, target cell lysis was calculated based on the release of label into the medium. As little as 1 ng of LTA per ml was sufficient to sensitize the target cells to ADCC lysis (12%); however, concentrations above 0.1 μg/ml generally resulted in 60 to 80% lysis. LTA alone was not cytotoxic to these target cells. Targeting did not occur if effector cells were sensitized or if free LTA was added to the medium. Specificity was demonstrated by cold-target inhibition, which showed that anti-LTA cytotoxicity could be inhibited only by unlabeled, LTA-treated target cells but not by cold SB cells alone. The findings indicate that certain soluble bacterial components, when bound to mammalian cells in the presence of specific antibody, can target ADCC effectors to these cells. This mechanism may be an important factor in the delayed sequelae of bacterial infections.

Antibody-dependent cellular cytotoxicity (ADCC) is an immune mechanism mediated by effector cells (K cells, monocytes, and neutrophils) possessing Fc receptors capable of recognizing and lysing antibody-coated target cells and tissues. ADCC has been proposed as an important antimicrobial mechanism in parts of the body deficient in complement, such as cerebrospinal fluid and mucous membrane secretions (15, 24, 25, 30). Many of these infectious agents or their subcellular components are capable of adhering to host tissues (2, 20, 32, 37). These components are antigenic, as demonstrated by circulating antibodies or sensitized lymphocytes. In addition, the immune system has been implicated in some disease sequelae and hypersensitivity reactions to antigen-sensitized host tissue (12, 16, 33, 36). However, the manner in which immunologic damage is directed to tissues coated with antigenic microbial preparations is not well characterized. ADCC could be responsible for host tissue damage during or after bacterial infection in such sites. Therefore, we sought to determine the ability of ADCC to mediate damage of bacterial antigen-coated target cells.

We selected lipoteichoic acid (LTA) as the bacterial substance with which to develop the model of bacterial targeted ADCC. LTA is an amphiphile associated with the cell membranes of gram-positive microorganisms and is found in the extracellular culture fluids (36). Amphiphiles are of particular interest because of their ability to adsorb spontaneously to a variety of mammalian cells (2, 8, 16, 20, 36, 37) and because of their association with several inflammatory diseases (16, 33). Since the antibodies to LTAs are ubiquitous in humans, all of the key components for ADCC are present during gram-positive bacterial infection (effector cells, putative LTA-coated tissue, and anti-LTA antibody). In this report, we describe the sensitivity of the ADCC mechanism to LTA-coated target cells and the ability of different effector cell populations to mediate cytotoxicity against sensitized targets.

MATERIALS AND METHODS

PBMC isolation. Peripheral blood mononuclear cells (PBMC) were isolated from heparinized venous blood from healthy donors of both sexes (aged 18 to 45) as previously described by Boyum (1). Donors were apprised of the study and consents were obtained consistent with the policies of The University of Michigan and the National Institutes of Health. The isolated PBMC were suspended in RPMI 1640 culture medium (GIBCO Laboratories, Grand Island, N.Y.) supplemented with 25 mM HEPES (*N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid) buffer, 2 mM glutamine, and 50 μg of gentamicin (Schering Corp., Bloomfield, N.J.) per ml. Viability was determined by trypan blue exclusion and always exceeded 95% in freshly isolated cell preparations.

Monocyte depletion. PBMC suspensions in RPMI 1640 medium supplemented with 20% newborn calf serum were depleted of monocytes by chromatography on a column of Sephadex G-10 beads (Pharmacia Fine Chemicals, Piscataway, N.J.). The columns were incubated for 30 min at 37°C under 5% CO_2 in air. Cell recovery was approximately 65 to 70% of the total cells passed through the column. The nonadherent cells contained less than 2% contaminating monocytes as determined by nonspecific esterase staining.

PMN isolation. Polymorphonuclear leukocytes (PMNs) were isolated from the erythrocyte pellet after Ficoll-Hypaque density isolation of mononuclear cells. The contaminating erythrocytes in the pellet were lysed with cold ammonium chloride (0.85%) and washed three times in

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TABLE 1. Influence of LTA treatment on SB target cells[a]

LTA concn (μg/ml)	% Cpm released[b]	
	L. fermentum 6991 LTA	Streptococcal LTA
0	1.9	1.9
0.002	1.7	1.8
0.02	1.9	2.1
0.2	2.0	1.7
2	2.1	1.9
20	2.1	2.3
200	3.4	2.0

[a] ^{51}Cr-labeled SB target cells (10^4 cells per well) were incubated for 4 h at 37°C in the presence of various concentrations of the LTA preparations. Label released into the medium after 4 h was counted and compared with the total label in 10^4 cells. Results are the mean values of three experiments.

[b] LTA preparations were extracted from *L. fermentum* NCTC 6991 and group A *Streptococcus* sp. strain S43; cpm, counts per minute.

RPMI 1640. This procedure yielded fewer than 5% contaminating cells.

Target cells. Three targets were used in this study. For most of the study, the human B-cell leukemia line (SB) was used because of its resistance to natural killer cell activity in the 4-h assay. In addition, the human T-lymphoblastoid cell line (CEM) and chicken erythrocytes (CRBC) were used as targets. Antisera to these cells were prepared by subcutaneous hyperimmunization of rabbits with suspensions of the specific cells without the use of adjuvant.

Preparation of target cells. The tumor targets were serially passaged in RPMI 1640 containing 10% fetal calf serum and used in the cytotoxicity assays no more than 48 h after the last passage. The cells were washed twice in RPMI 1640 and tested for cell viability with trypan blue exclusion, and the concentration was adjusted to 5×10^6 cells per ml. To 0.2-ml portions of RPMI-1640 containing 5×10^6 viable tumor cells, 200 μCi of ^{51}Cr as sodium chromate (New England Nuclear Corp., Boston, Mass.) was added. The cells were incubated at 37°C for 1 h in a humidified atmosphere of 5% CO_2 with intermittent shaking. After incubation, the cells were washed three times in RPMI 1640 and adjusted to a concentration of 5×10^5 cells per ml. The CRBC targets were prepared in a similar manner.

Purification of LTA. Lipoteichoic acid (LTA) was obtained by aqueous phenol extraction (34, 35) of group A streptococcus (originally provided by R. Lancefield) and chromatography on either a Sepharose CL-6B–Sephadex G-75 system (Pharmacia) or AcA 22 (LKB Instruments, Inc., Rockville, Md.) as previously described. LTA preparations were analyzed for phosphorus, amino acid, carbohydrate, and the presence of fatty acids after purification (10, 31). The phosphorus/glucose/alanine ratio was 1:0.097:0.65. Other amino acids were <1% of the total dry weight. No sugars other than glucose were detectable by gas-liquid chromatography. The estimated chain length was 22 glycerol-phosphate units. Antisera to these LTAs were prepared by hyperimmunization of rabbits (11). The LTA from *Lactobacillus fermentum* NCTC 6991 was generously provided as a reference standard by A. J. Wicken, University of New South Wales, Kensington, Australia.

LTA coating of target cells. In studies involving LTA-sensitized target cells, ^{51}Cr-labeled target cells (5×10^6 cells per ml) were incubated with various concentrations of LTA (1 ng to 100 μg/ml) for 1 h at 37°C. The radiolabeled, LTA-sensitized target cells were washed twice in RPMI and suspended at 2×10^5 cells per ml.

ADCC assay system. The ADCC activity of effector cells was determined by the original method of Perlmann and Perlmann (23). Briefly, in the wells of V-bottomed tissue culture plates (no. 3897; Costar, Cambridge, Mass.) 50 μl of various concentrations of viable effector cells were added in triplicate to 50 μl of complete medium containing 10,000 ^{51}Cr-labeled target cells and 100 μl of a dilution of rabbit anti-target serum. The plate was centrifuged at $40 \times g$ for 2 min at room temperature and then incubated for 4 h at 37°C in 5% CO_2. After incubation, the plate was centrifuged at $40 \times g$ for 10 min. Samples of the supernatant (100 μl) from each well were counted in a gamma counter. Percent ADCC activity was calculated as % cytotoxicity = experimental release − spontaneous release/total release − spontaneous release × 100, where spontaneous release represents counts released in control wells containing effector and labeled target cells and media, instead of antibody, and total release represents counts obtained in a sample of 10^4 ^{51}Cr-labeled target cells. Because the maximum releasable counts (total label obtained by either lysing a sample of labeled target cells or using unlysed target cells) were the same, the latter method was employed to obtain total release.

Statistical analysis. The statistical significance of differences in the mean values of various treatment effects was determined by paired *t* test.

RESULTS

Lack of direct cytotoxicity of LTA preparations. LTAs of various bacterial species have been reported to be cytotoxic to various cultured mammalian cells (27). To distinguish between possible direct cytotoxic effects of LTA and those mediated by the ADCC mechanism, ^{51}Cr-labeled SB target cells were exposed to concentrations of LTA (0.001 to 100 μg/ml) that would be used to sensitize target cells in subsequent ADCC assays. SB cells were chosen for use as targets because they tend to be less susceptible to natural killer activity which might tend to complicate the results (13). No significant radiolabel was released from the target cells in excess of the spontaneous release level (1.9%; Table 1). Thus, within the concentration range employed in the 4-h assay, these LTA preparations did not have a deleterious effect on target cell viability.

Determination of optimal LTA concentration to sensitize SB target cells to ADCC activity. SB target cells sensitized with LTA (LTA-SB) (0.001 to 100 μg/ml) were incubated with PBMC (effector to target cell [E:T] ratio, 100:1), various dilutions of heat-inactivated (30 min, 60°C), rabbit anti-LTA antisera (1/1,000, 1/5,000, 1/10,000), and unimmunized, pooled rabbit serum as described above. ADCC-mediated cytotoxicity (12%) could be detected in the 4-h assay when target cells were sensitized with as little as 1 ng of LTA per ml when the antibody was used at a 1/1,000 dilution (Table 2). However, the maxiumum cytotoxicity (59 to 63%) was observed at LTA-sensitizing concentrations of 1 to 100 μg/ml. All reported values of ADCC-mediated cytotoxicity represent the difference between total cytotoxicity (over spontaneous release) and that of LTA-SB plus effector cells (without antibody). In all experiments, only >10% release (above target plus effector without antibody) was considered significant cytotoxicity, since in the absence of antibodies, target cell-effector cell mixtures (E:T ratio, 100:1) yielded approximately 10% release of the label over that of target cells incubated alone. The release of ^{51}Cr from target cells incubated with anti-LTA antibodies alone was less than or equal to spontaneous release. In other experiments (not

shown) similar LTA titration curves were obtained when purified lymphocytes or PMN effector cells were used.

Characterization of effector cell populations. Since LTA-associated cytotoxicity could be the result of a nonspecific effect of the LTA, the specificity of the interaction between antibody-coated, LTA-sensitized target cells and the various effector cell populations was assessed. When the homologous (SB plus anti-SB) E:T system was examined (no LTA), significant cytotoxicity directed against the unsensitized target cell was measured at all E:T ratios tested with either the PBMC or the lymphocyte effector cells (Table 3). As the anti-SB antibody was diluted, ADCC activity was finally lost at the 10^{-6} dilution. With a neutrophil (PMN) effector cell, negligible ADCC activity was detected at all but the highest E:T ratio (100:1) and antibody dilution. The inefficiency of PMN tumoricidal activity in vitro has been previously reported (17). The addition of anti-LTA antibodies had no effect on the cytotoxicity of the system (>95% viability).

When LTA-SB (100 μg/ml) targets were substituted for unsensitized SB targets, all three effector cells categories mediated cytotoxic activity against LTA-SB in the presence of anti-LTA antibodies (Table 4). The ability of anti-SB antibodies to mediate ADCC against LTA-sensitized targets was, in most cases, reduced by approximately 50% (attributed to steric effects), and the ability of the PMN to lyse the target continued to be almost undetectable.

Requirement for target cell sensitization with LTA. Although LTA and specific anti-LTA antibody mediated target cell cytolysis, it was not clear that target cell sensitization, rather than effector cell sensitization or merely free LTA and antibody, was required for the lytic activity. To test this, PBMC effector populations were also treated with LTA (100 μg/ml). In the presence of anti-SB antibodies, LTA treatment of the effector cell had no significant effect on (untreated) SB target cell cytolysis when compared with the untreated effector cell (Table 5). Anti-LTA antibodies appeared to reduce nonspecific cytolysis by PBMC-LTA (0%) compared with untreated PBMC (16%) at the higher concentration of anti-LTA antibody (10^{-3}).

With anti-SB antibody, there was no difference between the ability of PBMC or PBMC-LTA to lyse the LTA-coated target. However, the amount of lysis was reduced in both cases when compared with non-LTA-coated SB cells. Anti-LTA antibodies permitted lysis of the LTA-treated SB target cells by the untreated PBMC effector cell. Lysis mediated by PBMC-LTA was blocked by this antibody, possibly because of steric factors preventing close contact between the effector and target. Microscopic examination suggested that this inhibition was caused neither by agglutination of the effector cells nor by loss of viability of the effector.

Since LTA might be causing the release of soluble regulatory factors that modulate cytotoxic activity, the effect of adding free LTA on the lytic activity in the SB–anti-SB system was assessed. As shown, the presence of LTA (100

TABLE 2. LTA sensitization of SB target cells and susceptibility to ADCC[a]

Antibody dilution	% Cytotoxicity at LTA concn (μg/ml) of:					
	100	10	1	0.10	0.01	0.001
1/1,000	63	53	51	59	16	12
1/5,000	57	61	50	32	0	5
1/10,000	46	43	45	28	0	0
1/1,000 (control)[b]	3	2	3	0	0	0

[a] SB target cells were sensitized with S43 LTA and then incubated for 4 h in the presence of PBMC effector cells (E:T ratio, 100:1) and dilutions of heat-inactivated rabbit anti-LTA antisera. Cytotoxicity was calculated as described in the text. Results are the mean values of six experiments.
[b] Unimmunized, pooled rabbit serum.

TABLE 3. ADCC of untreated SB target cells[a]

Effector cells	Antibody	Dilution	% Cytotoxicity at E:T ratio of:			
			100:1	50:1	25:1	12:1
PBMC	Anti-SB	10^{-3}	51	47	36	17
		10^{-4}	42	40	27	19
		10^{-5}	23	19	8	11
		10^{-6}	13	5	2	0
	Anti-LTA	10^{-3}	ND[b]	6	ND	ND
		10^{-4}	ND	6	ND	ND
Lymphocyte	Anti-SB	10^{-3}	40	40	36	23
		10^{-4}	33	30	23	17
		10^{-5}	10	15	10	5
		10^{-6}	5	7	7	0
	Anti-LTA	10^{-3}	ND	4	ND	ND
		10^{-4}	ND	5	ND	ND
PMN	Anti-SB	10^{-3}	19	10	11	3
		10^{-4}	9	1	12	0
		10^{-5}	5	0	0	0
		10^{-6}	0	0	0	0
	Anti-LTA	10^{-3}	ND	1	ND	ND
		10^{-4}	ND	0	ND	ND

[a] Untreated, ^{51}Cr-labeled SB target cells were incubated with effector cells PBMC purified lymphocytes, or PMN at E:T ratios of 100:1 to 12:1. Hyperimmune rabbit anti-LTA or SB was added to the mixtures and incubated for 4 h at 37°C. Calculation of cytotoxicity is described in the text. Results are the mean values of three experiments.
[b] ND, Not done.

TABLE 4. ADCC of LTA-SB target cells[a]

Effector cell	Antibody	Dilution	% Cytotoxicity at E:T ratio of:			
			100:1	50:1	25:1	12:1
PBMC	Anti-LTA	10^{-3}	78	73	59	27
		10^{-4}	76	57	39	26
		10^{-5}	50	43	28	24
		10^{-6}	42	31	9	17
	Anti-SB	10^{-3}	ND[b]	21	ND	ND
		10^{-4}	ND	12	ND	ND
Lymphocyte	Anti-LTA	10^{-3}	62	60	54	42
		10^{-4}	51	62	54	42
		10^{-5}	28	51	39	26
		10^{-6}	16	29	27	19
	Anti-SB	10^{-3}	ND	24	ND	ND
		10^{-4}	ND	16	ND	ND
PMN	Anti-LTA	10^{-3}	86	84	77	62
		10^{-4}	42	31	15	21
		10^{-5}	16	7	14	18
		10^{-6}	9	2	0	4
	Anti-SB	10^{-3}	ND	6	ND	ND
		10^{-4}	ND	4	ND	ND

[a] LTA-coated, ^{51}Cr-labeled SB target cells were incubated with effector cells PBMC, purified lymphocytes, or PMN at E:T ratios of 100:1 to 12:1. Hyperimmune rabbit anti-LTA or SB was added to the mixtures, and the mixtures were incubated for 4 h at 37°C. Calculation of cytotoxicity is described in the text. Results are the mean values of three experiments.
[b] ND, Not done.

TABLE 5. Effect of LTA treatment of effector cell or addition of free LTA[a]

Target cell	Antibody	Dilution	% Cytotoxicity	
			PBMC	PBMC-LTA[b]
SB	Anti-SB	10^{-3}	70	70
		10^{-4}	73	76
		10^{-5}	56	70
	Anti-LTA	10^{-3}	16	0
		10^{-4}	8	2
		10^{-5}	8	5
SB-LTA	Anti-SB	10^{-3}	41	51
		10^{-4}	42	49
		10^{-5}	33	45
	Anti-LTA	10^{-3}	58	10
		10^{-4}	53	19
		10^{-5}	56	11
SB[c]	Anti-SB	10^{-3}	62	
		10^{-4}	70	
		10^{-5}	66	
	Anti-LTA	10^{-3}	14	
		10^{-4}	11	
		10^{-5}	10	

[a] Standard assay conditions were employed as described in the text. PBMC were employed as effector cells (E:T, 100:1). Results of four experiments.
[b] LTA-treated (100 μg/ml) PBMC are designated as PBMC-LTA. LTA treatment was performed according to the protocol for the treatment of target cells.
[c] LTA added to effector-target-antibody mixture (no pretreatment).

μg/ml) had no effect on lytic activity. When LTA was added in the presence of SB and anti-LTA, no cytotoxicity was demonstrated. This suggested that either the antibody bound all of the free LTA, preventing LTA binding to the target cell, or the antibody blocked effector activity as found in the SB-LTA and PBMC-LTA categories. PBMC-LTA and the cell category in which free LTA and anti-LTA were added both demonstrated viabilities of >95%. These results indicate that lysis of LTA-coated targets was due to specific recognition by ADCC effector cells (plus antibody) and was not the result of LTA enhancement of nonspecific cytotoxicity.

Cold target inhibition. As a final test of the specificity of the LTA-directed ADCC, the ability of unlabeled target cells to inhibit chromium release was assessed (Table 6). In these studies, unlabeled (cold) target cells were added to labeled (hot) target cells in ratios of 1:1 to 16:1 (cold/hot). In all cases, the E:T ratio (hot target) was maintained at 50:1. If the effector cell (plus antibody) could not distinguish between the cold and hot target cells, then the concentration of cold target was increased. As shown in the SB plus anti-SB system, when cold SB targets were added, the apparent cytotoxicity was reduced from 44.2 (no cold) to 12.1% (16:1, cold/hot), representing 72.6% inhibition of cytotoxicity and indicating that the cold and hot targets were recognized by the ADCC mechanism as being similar. When cold SB targets were added to the SB-LTA plus anti-LTA system, no significant suppression of cytotoxicity was detected (<10%). However, when cold LTA-SB targets were added, almost 82% suppression of the homologous system was observed. These findings indicated that (via the antibody) the effector cells were being directed to the LTA epitope present on the surface of the target cell.

Other target cells. To show that this targeting phenomenon was not unique to SB cells, CEM cells and CRBC were tested in the same system (Table 7). In all cases, there was marked specificity for the LTA epitope regardless of the target cell employed.

DISCUSSION

A well-defined role for ADCC in human disease has not yet been clearly established. It has been proposed as a putative pathologic mechanism in numerous diseases having autoimmune components, including systemic sclerosis (3, 22), type 1 diabetes (26), systemic lupus erythematosus (19, 21), and allograft rejection (7). Impairment of ADCC is a common feature of autoimmune connective tissue disorders (6). In addition, this mechanism has been receiving considerable interest as a cellular defense mechanism against malignancy. For example, elevated cytotoxic activity is seen in patients with urinary bladder carcinoma (4). There are numerous reports implicating ADCC as an antimicrobial mechanism. After natural infection with respiratory syncytial virus, ADCC activity in nasopharyngeal secretions against the virus are observed as early as 3 days after the onset of clinical symptoms (9). ADCC activity against influenza virus-infected target cells can be detected after natural infection or immunization with live attenuated vaccine (5). ADCC mechanisms against *Salmonella typhimurium* (18) and meningococcal infections (28) have also been described.

TABLE 6. Inhibitory effect of unsensitized, unlabeled target cells on anti-SB and anti-LTA ADCC[a]

Category	Cold target cells[b]	% Cytotoxicity (% inhibition)[c] at cold/hot target cell ratio of:					
		No cold cells	1:1	2:1	4:1	8:1	16:1
SB + anti-SB		1.3					
SB + anti-SB + E	SB	44.2	35.4 (19.9)	32.5 (26.5)	26.2 (40.7)	22.6 (48.9)	12.1 (72.6)
SB-LTA + anti-LTA		2.4					
SB-LTA + anti-LTA + E	SB	80.3	82.9 (−1.0)	85.1 (−5.9)	73.9 (7.9)	74.5 (7.2)	78.7 (1.9)
SB-LTA + anti-LTA + E	SB-LTA	80.3	62.3 (22.4)	54.8 (31.7)	33.1 (60.5)	21.2 (73.6)	14.7 (81.7)

[a] Standard assay conditions as described in the text were used. PBMC were employed as effector cells at an E:T ratio of 50:1. Results are the mean of four experiments.
[b] Unlabeled target cells were added at various ratios to ^{51}Cr-labeled target cells. E:T ratios were based on labeled target cells.
[c] Inhibition of ^{51}Cr release by cold targets was based on the categories containing only labeled (no cold) target cells.

TABLE 7. Comparison of LTA-sensitized CEM cells and CRBC with LTA-SB[a]

Antibody	% Cytotoxicity for target cells					
	SB	LTA-SB	CEM	LTA-CEM	CRBC	LTA-CRBC
Anti-SB	45.6	21.6	8.3	6.4	11.4	13.1
Anti-CEM	5.9	7.9	49.9	30.2	5.6	5.3
Anti-CRBC	1.2	3.5	6.8	5.3	72.9	28.1
Anti-LTA	1.1	71.5	2.1	53.5	0.6	39.4

[a] Standard assay conditions as described in the text were used. PBMC were employed as effector cells at an E:T ratio of 100:1. Results of five experiments.

ADCC may be especially important in infections at the mucosal level, since such areas tend to be rich in immunoglobulin G and secretory immunoglobulin A but quite deficient in complement. Adhesion to mucosal surfaces is the primary event in colonization by many pathogens. Thus, a cell-mediated mechanism that can function in the absence of complement but is facilitated by the presence of immunoglobulin G and immunoglobulin A could function as a significant antimicrobial mechanism at the primary focus of infection. However, ADCC may also result in the bystander killing of host cells sensitized by either the adherent bacteria or their products and substituents. For example, LTAs have been shown to produce local immunotoxic reactions.

We examined the ability of ADCC effector cells to kill LTA-coated mammalian cells. ADCC is quite specific and sensitive to the presence of LTA (<1 ng). Currently, we are testing ADCC effector activity against specific microorganisms and their subcellular components in the presence of sera from patients to establish a role in specific human disease. ADCC may provide an avenue by which to understand the course of a variety of bacterial infections, especially the delayed sequelae. It may be useful in understanding tissue damage associated with the presence of chronic low-grade infection. An example is periodontal disease, in which inflammation and tissue damage are associated with changes in the levels or qualities of plaque microorganisms with minimal apparent change, in many cases, of systemic parameters of immunity to these microorganisms (14). ADCC effector cells have been demonstrated in the gingival crevices (29) of periodontal patients. Since the antibodies to most of the plaque microorganisms are ubiquitous, a change in the sensitizing dose of a plaque microorganism would lead to the targeting of the ADCC mechanisms to the tissue.

We confirmed the observation that PMN effector cell populations did not normally kill mammalian cell targets but found that they did become efficient killers when those targets were coated with LTA. The significance of this observation is not clear at this time; however, it probably relates to the nature of the recognition of the target by the PMN, which is perhaps related to antigen density on the target cell surface. Since the PMN is commonly the first scavenger at the scene of a bacterial infection, antimammalian cell ADCC activity might tend to be quite detrimental to the host. Coating of the target by bacterial substances may fool the PMN into unleasing a misguided armament of destruction against the host. This phenomenon remains to be further elucidated.

In summary, the adherence of bacterial subcomponents or the bacteria themselves to host tissues may lead to the targeting of immune effector mechanisms to these tissues with hypersensitivity reactions occurring. ADCC-mediated effector activity would be expressed in the presence of low levels of antibody and would be favored in parts of the body, such as mucosal surfaces, where complement levels are low. Further evaluation of this model of targeted hypersensitivity is warranted to understand its role in chronic infection and the delayed sequelae of acute infection.

ACKNOWLEDGMENTS

We thank A. J. Wicken for generously providing the *L. fermentum* LTA reference standard, Luann M. Martel and Michael Freedland for their excellent technical assistance, and Neal Van Poperin for editorial assistance.

This research was supported by U.S. Public Health Service grants DE02731, DE05723, and DE05916 from the National Institutes of Health.

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