Role of Cell-Cell Communication in Inhibiting Butyric Acid-Induced T-Cell Apoptosis

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We have previously demonstrated that human gingival fibroblasts rescue butyric acid-induced T-cell apoptosis via proinflammatory cytokines such as interleukin 6 (IL-6) and IL-11, which are produced by fibroblasts stimulated with butyric acid. In this study, we determined if T-cell adhesion to human gingival fibroblasts influenced the susceptibility of T cells to butyric acid-induced apoptosis. We have shown that the number of Jurkat T cells adherent to gingival fibroblasts (Gin-1 cells) was significantly increased by the addition of butyric acid. All Jurkat cells that adhered to Gin-1 cells remained viable, while the nonadherent Jurkat cells dropped into apoptosis. The increase in T-cell adhesion to fibroblasts was also observed when Jurkat cells, but not Gin-1 cells, were pretreated with butyric acid. The expression levels of CD44, very late antigen 2 (VLA-2) and VLA-5 but not of leukocyte-function-associated antigen 1 (LFA-1) and VLA-4 on Jurkat cells were increased following treatment with butyric acid. Furthermore, pretreatment of butyric acid-sensitized Jurkat cells with monoclonal antibodies against CD44, VLA-2, and VLA-5, but not LFA-1 and VLA-4, followed by coculture with Gin-1 cells inhibited T-cell adhesion to fibroblasts and increased apoptosis of nonadherent T cells after coculture of gingival fibroblasts and Jurkat cells. These results indicate that T-cell adherence to fibroblasts is enhanced by butyric acid and that butyric acid-induced T-cell apoptosis is down-regulated by T-cell adhesion to gingival fibroblasts through an interaction with the adhesion molecules CD44, VLA-2, and VLA-5 expressed on T cells stimulated with butyric acid.

Adult periodontitis is a chronic, destructive disease involving host inflammatory responses to gram-negative bacteria. Recent studies have suggested an association between human periodontal disease and certain systemic disorders, such as diabetes mellitus, pneumonia, heart disease, and preterm birth (35). Certain bacteria, including Porphyromonas, Prevotella, and Fusobacterium spp., are important in the pathogenesis of periodontal disease (34). These periodontopathogens produce a variety of virulence factors, such as proteases, lipopolysaccharides, fimbriae, and butyric acid.

Butyric acid has been shown to inhibit in vitro cell growth by favoring cell cycle arrest and promoting differentiation of normal as well as transformed cells (2). Butyric acid also induces apoptosis in a number of cancer cells (13, 23). It has previously been shown that butyric acid induces apoptosis of murine and human T and B cells via mechanisms that are dependent on caspase-3, caspase-8, and caspase-9 and that are Fas independent (17–19). Furthermore, it was recently reported that butyric acid-induced apoptosis is mediated by reactive oxygen species synthesis in mitochondria and ceramide production, followed by c-Jun N-terminal kinase activation in the mitogen-activated protein kinase cascade in Jurkat cells (20). Emerging evidence indicates that the bacterial modulation of apoptosis is an important part of pathogenesis (4). Specific pathogens or their extracellular products may directly induce the apoptosis of host cells (37). The pathways that regulate apoptosis are complex, with a network of survival and death regulatory molecules working in a delicate balance to achieve a proper response (9, 10, 31). It has been reported that resistance to apoptosis may result from an aberrant regulation of extracellular survival signals delivered by extracellular matrix (ECM), cell-cell interactions, and growth factors (6, 15, 30).

Cell-cell interactions play an important role in pathological conditions where cells that are normally located in different compartments come in close proximity to each other. In inflamed periodontal lesions, dense lymphocytic infiltrations are usually observed in the extravascular periodontal connective tissue, adjacent to gingival fibroblasts. Previous studies have revealed that activated lymphocytes could adhere to gingival fibroblasts via CD44-hyaluronate, leukocyte-function-associated antigen 1 (LFA-1), intracellular adhesion molecule 1, and very late antigen (VLA) integrins in vitro (24, 25). Adhesion molecules can initiate intracellular signaling. Signal transduction pathways are no longer thought of as linear sequences of biochemical modifications but, rather, as networks with several levels of complexity. These networks are triggered by extracellular ligands that interact with a range of cell surface receptors, and part of the complexity lies in the organization of these receptors. Several cell adhesion molecules, which include the integrins and cadherins, have been implicated in the formation of complexes that are composed of extracellular ligands, receptor tyrosine kinase, and cytoskeletal proteins (14). The picture that is emerging of how such multicomponent complexes are formed and regulated provides new insights into how components of ECM can influence cell behavior.

The aims of the present study were to examine the effects of cell-to-cell interactions on butyric acid-induced T-cell apoptosis and to elucidate the role of surface signals on T cells in modulating butyric acid-induced T-cell apoptosis. We report
here that the interactions between gingival fibroblasts and butyric acid-pretreated T cells prevented butyric acid-induced T-cell apoptosis. Furthermore, we provide evidence that the interaction of gingival fibroblasts with CD44, VLA-2, and VLA-5 expressed on T cells stimulated with butyric acid enhanced the rescue of T cells from apoptosis.

MATERIALS AND METHODS

Reagents. Highly purified butyric acid was purchased from Sigma (St. Louis, Mo.). SYTOX green was purchased from Molecular Probes (Eugene, Ore.). Solutions of 5 mM butyric acid were diluted in Dulbecco’s modified Eagle medium (Gibco Laboratories, Grand Island, N.Y.) and adjusted to pH 7.2 with sodium hydroxide.

Cells. The human gingival fibroblast cell line Gin-1 was obtained from the American Type Culture Collection (Manassas, Va.) and maintained and expanded in complete medium consisting of 25 mM HEPES-buffered Dulbecco’s modified Eagle medium supplemented with 10% fetal calf serum, penicillin (100 U/ml), streptomycin (100 µg/ml), and 2 mM l-glutamine. The human T-lymphoma Jurkat cell line was kindly provided by Fujisaki Cell Center Hayashibara (Okayama, Japan). The cells were cultured at 37°C in a moist atmosphere of 5% CO2 in a complete medium consisting of RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum, 2 mM l-glutamine, penicillin (100 U/ml), and 0.05 mM 2-mercaptoethanol.

Adhesion of Jurkat cells to Gin-1 cell monolayer. Cover glasses (Matsunami, Osaka, Japan) were fitted into 24-well culture plates (Nunc, Rochester, N.Y.) and pretreated with BD Cell-Tak to immobilize cells (Becton Dickinson Labware, Lincoln Park, N.J.) at a concentration of 0.11 mg/ml for 30 min at room temperature, according to the manufacturer’s protocol. Gin-1 cells were plated onto BD Cell-Tak-treated cover glasses at a concentration of 106 cells per well in 500 µl of complete medium and were preincubated for 20 h. Jurkat cells (10⁶ cells/well) suspended in complete medium were then overlaid on the Gin-1 cell monolayer and incubated with 5 mM butyric acid for a maximum of 2 h. After removal of the floating Jurkat cells from the cultures, the adherent cells were washed twice with RPMI 1640 medium, and then the number of Jurkat cells nonadherent or adherent to Gin-1 cells was counted by using a phase-contrast microscope (BX50; Olympus, Tokyo, Japan) with the aid of an eyepiece micrometer (24-mm square; Olympus). For the adhesion inhibition assay, Jurkat cells were pretreated with 5 mM butyric acid for 2 h and then were treated with monoclonal antibodies (MAbs) against human CD44, LFA-1, VLA-2, VLA-4, and VLA-5 for 30 min. Jurkat cells (10⁶ cells/well) suspended in complete medium were then overlaid onto the Gin-1 cell monolayer and incubated for 1 h.

Detection of apoptosis. Jurkat cells (5 × 10⁶ cells per well) suspended in complete medium were then overlaid on the Gin-1 cell monolayer and incubated with 5 mM butyric acid for 21 h. After incubation, nonadherent Jurkat cells and Jurkat cells adherent to Gin-1 cells were fixed in 3% paraformaldehyde and phosphate-buffered saline (PBS) for 20 min at room temperature. The cells were then permeabilized with PBS containing 0.1% Triton X-100 (Sigma) for 5 min at room temperature, stained with SYTOX green (2.5 µM in PBS; nuclear staining) for 10 min at room temperature (32), and mounted with 2.5% diazobicyclooctanone (Sigma) solution. Cells were examined under a confocal laser scanning microscope (LSM510; Zeiss, Heidelberg, Germany), and apoptotic cells were identified by the presence of chromatin condensation and/or nuclear fragmentation.

Flow cytometric apoptosis assay. To measure the annexin V binding and propidium iodide (PI) staining of Jurkat cells, cells (10⁴) were harvested and stained with fluorescein isothiocyanate (FITC)-labeled annexin V and PI (Molecular Probes) as specified by the supplier. Briefly, Jurkat cells (10⁴) in 1 ml of medium were cultured as indicated for 21 h, washed, and then stained with PI and annexin V-FITC in annexin binding buffer and analyzed with CellQuest software (BD Biosciences, San Jose, Calif.) by FACS Calibur within 1 h. Data from 10⁶ cells were analyzed for each sample.

Gel electrophoresis. The nonadherent and adherent cells were resuspended in 400 µl of hypotonic lysis buffer (0.2% Triton X-100, 10 mM Tris, 1 mM EDTA [pH 8.0]) and centrifuged for 15 min at 13,800 × g (27). Half of the supernatant, containing small DNA fragments, was treated with an equal volume of absolute isopropanol alcohol and 0.5 M NaCl to precipitate the DNA and was then stored at −20°C overnight. After centrifugation, at 13,800 × g for 15 min, the pellet was washed with 200 µl of 70% ethanol and allowed to dry at room temperature. The DNA was then resuspended in 12 µl of TE solution (10 mM Tris-HCl, 1 mM EDTA [pH 7.4]) plus 3 µl of loading buffer (50% glycerol, 1% Triton X-100, 1% sodium bromide, and 1% xylene cyanol) at 37°C for 20 min and then electrophoresed for 1 h in a 1.7% agarose gel containing 0.7 µg of ethidium bromide per ml. The gels were photographed under UV transillumination.

Flow cytometry analysis. Jurkat cells (10⁶) in 1 ml of medium were cultured for 2 h with or without 5 mM butyric acid. The cells were then harvested and stained with FITC-labeled anti-human CD44, LFA-1, VLA-2, VLA-4, and VLA-5 MAbs or with an isotype control (mouse immunoglobulin G1 and immunoglobulin G2) (Becton Dickinson) for 30 min at 4°C. After being washed in PBS, the samples were analyzed with a FACS Calibur apparatus within 1 h. Data from 10⁶ cells were analyzed for each sample.

Statistics. Multiple-group comparisons were made with a one-way analysis of variance, followed by post hoc intergroup comparisons made by using the Bonferroni-Dunn test. Where appropriate, Student’s t test was used to assess the statistical significance of differences between two groups.

RESULTS

Effect of butyric acid on Jurkat cell adhesion to the Gin-1 cell monolayer. To initially examine the effect of butyric acid on the adhesion of Jurkat cells to the Gin-1 cell monolayer, Jurkat and Gin-1 cells were cocultured in the presence or absence of 5 mM butyric acid. The number of Jurkat cells that adhered to gingival fibroblasts increased in a time-dependent manner following the addition of butyric acid (Fig. 1B). After a 120-min incubation, the number of Jurkat cells adherent to fibroblasts in butyric acid-treated cocultures was 3.1-fold higher than in untreated cocultures (Fig. 1A and B). In order to determine how butyric acid facilitates cytoadherence between Jurkat cells and Gin-1 cells, Jurkat or Gin-1 cells were pretreated with 5 mM butyric acid for 2 h and then cocultured with Gin-1 or Jurkat cells, respectively, for 1 h. The interaction between Gin-1 cells that were pretreated with butyric acid and Jurkat cells showed a similar amount of adherence as that seen with untreated Gin-1 and Jurkat cells (Fig. 1C). However, a significant increase was seen in cytoadherence between Gin-1 cells and Jurkat cells that were pretreated with butyric acid, compared to the interaction between untreated Jurkat and Gin-1 cells. These results indicate that butyric acid facilitates the cytoadherence of Jurkat cells to Gin-1 cells but not of Gin-1 cells to Jurkat cells.

Analysis of Jurkat cells that adhere to Gin-1 cells. Based on our initial findings, we next examined the viability of Jurkat cells in the presence of 5 mM butyric acid. In these studies, the DePsipher assay was used, followed by confocal laser scanning analysis, which showed healthy cell mitochondria as red and apoptotic cell mitochondria as green. Jurkat cells that adhered to Gin-1 cells in the presence of 5 mM butyric acid stained red, while nonadherent cells stained green (Fig. 2A). Furthermore, when we tested the adherent and nonadherent cells by using SYTOX green nuclear staining, we confirmed that >98% of the nonadherent cells and <2% of adherent cells were apoptotic (Fig. 2B). The escape of adherent cells from apoptosis was further confirmed by electrophoresis of fragmented DNA (Fig. 2C). Low-molecular-weight DNA fragments extracted from the Jurkat cells that were nonadherent to Gin-1 cells in the presence of 5 mM butyric acid showed typical oligonucleosomal ladders. In contrast, negligible cleavage of DNA into nucleosomal fragments was seen with untreated Jurkat cells and Jurkat cells that adhered to Gin-1 cells in the presence of 5 mM butyric acid. These results indicate that butyric acid contributes to the survival of Jurkat cells that adhered to Gin-1 cells.
Effect of butyric acid treatment on the expression of adhesion molecules on Jurkat cells. Since butyric acid increased the cytoadherence of Jurkat cells to Gin-1 cells and the viability of adherent Jurkat cells, we next examined which adhesion molecules were expressed on Jurkat cells following exposure to butyric acid. Specifically, we examined the effect of butyric acid on the expression of CD44, VLA-2, VLA-4, VLA-5, and LFA-1. Jurkat cells normally express very low levels of CD44 (2.2%), VLA-2 (1.0%), VLA-5 (0.3%), and LFA-1 (0.2%) and a very high level of VLA-4 (99.4%). However, following incubation of Jurkat cells with 5 mM butyric acid for 2 h, an increase in the expression of CD44 (19.2%), VLA-2 (4.0%), and VLA-5 (5.1%) was observed (Fig. 3). The expression of CD44 was significantly increased 2 h after the addition of 5

FIG. 1. Effect of butyric acid on Jurkat cell adhesion to the Gin-1 cell monolayer. Jurkat cells were directly cocultured with Gin-1 cells in the presence or absence of 5 mM butyric acid for 30, 60, and 120 min. The numbers of Jurkat cells adherent to Gin-1 cells were counted by using a phase-contrast microscope (A and B). In other experiments, Jurkat or Gin-1 cells were pretreated with 5 mM butyric acid for 2 h and then cocultured with Gin-1 or Jurkat cells, respectively, for 1 h. The numbers of Jurkat cells adherent to Gin-1 cells were counted by using a phase-contrast microscope. The results are expressed as the means ± standard errors of the means (error bars) of three different experiments with triplicate cultures. Values that were significantly different from those of corresponding negative controls at $P < 0.01$ are indicated by asterisks.
mM butyric acid, while LFA-1 and VLA-4 expression levels were unchanged (0.2% for LFA-1 and 99.6% for VLA-4). Similar results were obtained with Jurkat cells that were cocultured with Gin-1 cells in the presence of butyric acid (data not shown). These results indicate that butyric acid induced the expression of the adhesion molecules CD44, VLA-2, and VLA-5 on Jurkat cells.

MAbs against adhesion molecules inhibit T-cell adhesion to fibroblasts and increase T-cell apoptosis. To examine whether the adhesion molecules expressed on butyric acid-stimulated T cells were involved in T-cell adhesion to fibroblasts, we next examined whether MAbs against CD44, VLA-2, and VLA-5 inhibited the cytoadherence between T cells and fibroblasts (Fig. 4A). The adherence of untreated Jurkat cells to Gin-1 cells was only slightly inhibited by MAbs against the adhesion molecules CD44 (11.4%), VLA-2 (9.0%), and VLA-5 (16.6%) and against all of them together (24.3%). However, in the presence of butyric acid T-cell adhesion to Gin-1 cells was inhibited by 27.5, 18.2, and 25.4% by MAbs to CD44, VLA-2, and VLA-5, respectively. Furthermore, a combined effect was recognized when the MAbs were used together as a group (42.5% inhibition). The addition of anti-LFA-1 and anti-VLA-4 MAbs did not have any effect on butyric acid-treated and untreated Jurkat cell adherence (data not shown). We additionally examined whether MAbs against CD44, VLA-2, and VLA-5 increased the apoptosis of nonadherent T cells after coculture of gingival fibroblasts and Jurkat cells. After treatment with MAbs, apoptosis of the nonadherent T cells was accelerated as the result of the blocking of cytoadherence between T cells and Gin-1 cells (Fig. 4B). These results suggest that the expression of adhesion molecules on Jurkat cells induced by butyric acid were involved in T-cell adherence to fibroblasts and T-cell survival.

**DISCUSSION**

Human chronic periodontitis is usually characterized by an infiltration of inflammatory cells into the periodontal connective tissues (22, 28, 33). T lymphocytes are known to play an important role in modulating local immune responses in periodontal lesions (12, 28). Since most T cells that penetrate periodontal lesions are adjacent to gingival fibroblasts, it is worth considering how these two cell types interact. Therefore, we assessed the role of gingival fibroblasts in the regulation of butyric acid-induced T-cell death by using a direct cell-to-cell interaction system. On the basis of previous studies showing that 13.3 to 26.8 mM butyric acid was detected in culture filtrates from *Porphyromonas gingivalis*, *Prevotella loescheii*, and *Fusobacterium nucleatum* (16), along with previous findings showing that butyric acid concentrations in subgingival plaque from a periodontitis site could reach 14.4 to 20 mM (17; C. Naleway, H. Chou, T. Manos, C. Goodman, P. Robinson, and R. Singer, Abstr. 18th Annu. Int. Assoc. Dent. Res. Meet., San Francisco, Calif., abstr. no. 121, 1989) and that its concentration in periodontal pockets has been shown to correlate with the severity of periodontal disease (3), butyric acid can be recognized as an important virulence factor of these periodontopathogens. Therefore, in the present study, cells were cultured with 5 mM butyric acid, while LFA-1 and VLA-4 expression levels were unchanged (0.2% for LFA-1 and 99.6% for VLA-4). Similar results were obtained with Jurkat cells that were cocultured with Gin-1 cells in the presence of butyric acid (data not shown). These results indicate that butyric acid induced the expression of the adhesion molecules CD44, VLA-2, and VLA-5 on Jurkat cells.

**FIG. 2.** Analysis of Jurkat cells that adhere to Gin-1 cells. Jurkat cells were directly cocultured with Gin-1 cells in the presence of 5 mM butyric acid. The viability of Jurkat cells that were adherent or nonadherent to Gin-1 cells was examined by DePsipher assay (A) or SYTOX green nucleic acid staining (B), followed by confocal laser scanning microscopy. The results are expressed as the means ± standard errors of the means (error bars) of three different experiments with triplicate cultures. Values that were significantly different from those of corresponding negative controls at P < 0.01 are indicated by asterisks. The viability of Jurkat cells that were adherent or nonadherent to Gin-1 cells was also examined by agarose gel electrophoresis of DNA extracted from Jurkat cells (C). Lane U, unadhered T cells; lane A, adhered T cells.
butyric acid, which induced a maximal increase in DNA fragmentation after 21 h of culture (20).

In this study, cytoadherence between Jurkat T cells and gingival fibroblasts was significantly increased by the addition of butyric acid. This enhanced cytoadherence between Jurkat cells and Gin-1 cells occurred when Jurkat cells but not Gin-1 cells were pretreated with butyric acid. Thus, butyric acid facilitates cytoadherence via an effect on Jurkat cells but not on Gin-1 cells.

Interestingly, when we examined the viability of T cells following treatment with butyric acid by using the DePsipher assay, SYTOX green nuclear staining, and fragmented DNA analysis, the nonadherent cells dropped into apoptosis, whereas almost all Jurkat cells adherent to Gin-1 cells were alive. These results indicate that T-cell apoptosis induced by butyric acid was down-regulated by direct cell-cell communication between Jurkat cells and gingival fibroblasts.

Other examples that apoptosis can be evaded by cell-cell contact have been reported. For instance, epithelial cells require contact with ECM to inhibit detachment-induced apoptosis (11). Neutrophil (polymorphonuclear cell) contacts with an endothelial monolayer down-regulates spontaneous polymorphonuclear cell apoptosis (36). Further, it was reported that cell-cell adhesion of bone marrow stromal cells with my-
FIG. 4. MAbs against adhesion molecules inhibit adhesion of Gin-1 cells to Jurkat cells and increase apoptosis. Jurkat cells were pretreated with 5 mM butyric acid for 2 h and then treated with MAbs against CD44, VLA-2, and VLA-5 for 30 min. The Jurkat cells were then added to a monolayer of Gin-1 cells and incubated for 1 h (A) or 21 h with 5 mM butyric acid (B). In panel A, the numbers of Jurkat cells adherent to Gin-1 cells were counted by using a phase-contrast microscope. The results are expressed as the means ± standard errors of the means (error bars) of three different experiments with triplicate cultures. Values that were significantly different from those of corresponding negative controls at P < 0.01 are indicated by asterisks. In panel B the viability of Jurkat cells nonadherent to Gin-1 cells was examined by surface binding of annexin V. Results shown are representative of three independent experiments.
cloma cells is involved in the protection of myeloma cell apoptosis (26). Since pretreatment of Jurkat cells with butyric acid significantly increased their cytoadherence to Gin-1 cells and the viability of the adherent Jurkat cells, we postulated that stimulation with butyric acid resulted in a change in the distribution of surface molecules on Jurkat cells. We further postulated that the increase in the expression of surface molecules on Jurkat cells was involved in the cytoadherence to fibroblasts and the signals to Jurkat cell survival.

In this study, after Jurkat cells were treated with butyric acid, we observed increases in the expression of CD44, VLA-5, and VLA-2 (in order of increase, greatest to least). In addition, increases in the expression of VLA-2, CD44, and VLA-5 (in order of increase, greatest to least) on Jurkat cells were also observed when Jurkat cells were cocultured with fibroblasts in the presence of butyric acid (data not shown). Furthermore, the treatment of butyric acid-sensitized Jurkat cells with anti-CD44, anti-VLA-2, and anti-VLA-5 MAbs significantly suppressed T-cell adhesion to fibroblasts and increased apoptosis of nonadherent T cells after coculture of gingival fibroblasts and Jurkat cells. Previous studies have indicated that CD44 and β-integrins are related to cytoadherence. For instance, cross-linking of CD44 with MAbs enhanced VLA-5-dependent adhesion of human cord blood CD34+ cells to fibronectin (1). VLA-5 also mediates human chondrocyte adhesion to cartilage (21). The CD44-hyaluronate interaction has been shown to participate in the adherence of T lymphocytes to gingival fibroblasts (25). Furthermore, the stimulation of CD44 on osteoblastic cells amplifies their adhesion to monocytes (through intracellular adhesion molecule 1 and vascular cell adhesion molecule 1) (7). Recently, cell adhesion molecules, once believed to function primarily in tethering cells to extracellular ligands, have now been recognized as having broader functions in cellular signaling cascades. CD44 adds new aspects not only by establishing specific transmembrane complexes but also by organizing the signaling cascade through association with the actin cytoskeleton (29) and the antiapoptotic effect (8). βeta-1 integrin-mediated adhesion also influences cell survival and prevents programmed cell death (5). Therefore, our results suggest that the adhesion molecules CD44, VLA-2, and VLA-5 expressed on T cells stimulated with butyric acid are involved in T-cell adherence to fibroblasts, which is followed by T-cell survival. However, because the results of fluorescence-activated cell sorter analysis did not fully support the effects of MAbs on the cytoadherence between T cells and fibroblasts and on apoptosis, it is possible that the expression rates of the adhesion molecules on T cells do not always correlate with their binding capacities. Furthermore, the partial effect of MAbs on cytoadherence and apoptosis suggests that a factor other than the adhesion molecules we used in this study may be involved in these activities. It is also possible that adherence and apoptosis may involve different signaling pathways at different phases of cell activities or cell cycles besides the phenomenon that we described here.

In conclusion, our study demonstrates for the first time that the survival of T cells exposed to butyric acid is primarily maintained by direct cell adhesion to fibroblasts. Furthermore, our findings suggest that the interaction of CD44, VLA-2, and VLA-5 with their ligands can rescue butyric acid-induced Jurkat cell apoptosis.

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