Reports that interleukin-8 (IL-8) induces the infiltration of neutrophils followed by T-cells into injection sites led us to postulate that by stimulation of neutrophil degranulation IL-8 may cause the release of factors with chemoattractant activity for T-lymphocytes. Extracts of human neutrophil granules were chromatographed to isolate and purify T-lymphocyte chemoattractant factors. Two major peaks of T-cell chemotactic activity were purified by C18 reversed phase high pressure liquid chromatography (HPLC). The first peak was resolved further by C4 reversed phase HPLC and identified by N\(^2\)-terminal amino acid sequence analysis to contain defensins HNP-1, HNP-2, and HNP-3. Purified defensins HNP-1 and HNP-2 (kindly provided by Dr. R. I. Lehrer, UCLA) were also potent chemoattractants for human T-cells, while HNP-3 was inactive. The second peak of T-cell chemoattractant activity was also further purified to homogeneity by C4 reversed phase HPLC and identified by N\(^2\)-terminal sequence analysis as CAP37/azurocidin, a protein with sequence homology to serine proteases. 0.1–100 ng of defensins and 1.0–100 ng/ml CAP37 were able to stimulate in vitro T-cell chemotaxis. Neutrophil activating factors, i.e. IL-8, phorbol 12-myristate 13-acetate/ionomycin, and formylmethionylleucylphenylalanine each induced the release of CAP37 and defensins from neutrophil granules. Subcutaneous administration of defensins or CAP37/azurocidin into BALB/c mice resulted in a moderate neutrophil and mononuclear cell infiltration by 4 h, which was greater by 24 h at the site of injection. Additionally, subcutaneous injection of defensins into chimeric huPBL-SCID mice resulted in significant infiltration by human CD3\(^+\) cells within 4 h. These results identify the antimicrobial proteins, CAP37/azurocidin and defensins HNP-1 and HNP-2, as potent neutrophil-derived chemoattractants for T-cells. These proteins represent primordial antimicrobial peptides which may have evolved into acute inflammatory cell-derived signals that mobilize immunocompetent T-cells and other inflammatory cells.

Immunologically induced inflammatory responses are multistep processes involving the production of various chemotactic factors resulting in the orchestrated recruitment of neutrophils, mast cells, monocytes, and T-cells. The chemokine (1, 2) IL-8,\(^1\) a potent chemoattractant and activator of neutrophils, is produced by many cell types including neutrophils (3, 4), monocytes (5, 6), eosinophils (7), and endothelial cells (8). Two receptors for IL-8 have been cloned and belong to the family of seven transmembrane G protein-coupled receptors (9, 10). Signaling through these receptors induces a number of biochemical and biological events including the mobilization of intracellular calcium (11), changes in adhesion (12), respiratory burst (13), degranulation, and enzyme release from neutrophils (6, 11, 14, 15).

IL-8 has also been reported to be an in vitro and in vivo chemoattractant for T-cells (16). Furthermore, we have demonstrated that subcutaneous injection of human IL-8 into human T-cell-engrafted SCID mice causes an initial infiltration of murine neutrophils by 4 h into the site of injection, which is followed by a marked infiltration of human T-cells by 72 h (17). This delayed infiltration of human T-cells suggested that IL-8 may recruit T-cells indirectly, perhaps by stimulating the release of T-cell chemotactic factors by activated neutrophils. This hypothesis was tested by incubating purified peripheral blood neutrophils with a number of degranulating agents, including IL-8, and resulted in the release of T-cell chemotactic activity into the supernatants within 2 h. This led us to detect, purify, and identify several T-cell chemotactic factors from extracts of neutrophil granules.

**MATERIALS AND METHODS**

Reagents—Rabbit anti-human CAP37 antisera was prepared by immunization with purified CAP37/azurocidin in Freund’s adjuvant (both the CAP37 and antisera were kindly provided by Dr. A. Pereira of the University of Oklahoma). Purified defensins and rabbit anti-defensin antisera were kindly gifts from Dr. R. I. Lehrer, UCLA.

T-cell Preparations—Human peripheral blood enriched in mononuclear cells or lymphocytes was obtained from normal donors by leukapheresis (National Institutes of Health Clinical Center, Department of Transfusion Medicine, Bethesda, MD). The blood was centrifuged through Ficoll-Hypaque at 800 \(\times\) g for 30 min. The peripheral blood mononuclear cells at the interface were washed twice with PBS and centrifuged through an isosmotic Percoll gradient as described to remove monocytes. Human T-cell enrichment columns (R&D Systems, Minneapolis, MN) were then used according to the manufacturer’s instructions to rapidly purify the T-cells using high affinity negative selection. This isolation procedure typically yields greater than 90% purity.

\(^1\)The abbreviations used are IL, interleukin; PBS, phosphate-buffered saline; HPLC, high pressure liquid chromatography; PAGE, polyacrylamide gel electrophoresis; FMLP, formylmethionylleucylphenylalanine; PMN, polymorphonuclear cell.
CD3+ T-cells. The cells were resuspended in chemotaxis medium (RPMI 1640 containing 1% bovine serum albumin and 25 mm HEPEs).

Chemotaxis Assay—T-lymphocyte migration was assessed using a 48-well microchemotaxis chamber (NeuroProbe, Cabin John, MD) as reported (18). 25 µl of the sample to be tested (diluted in chemotaxis medium) was placed in the lower compartment, and 50 µl of cell suspension (10^6 cells ml^-1) was placed in the upper compartment. The two compartments were separated by a polycarbonate filter (5-µm pore size) coated with 10 µg/ml collagen type IV overnight at 4°C. The apparatus was incubated at 37°C for 3 h in humidified air with 5% CO2. At the end of the incubation period the filter was removed, fixed, and stained with Leukostat (Fisher). The number of cells per high power field that migrated through the filter was counted by light microscopy. The results are expressed as the mean ± S.D. value of the migration in triplicate samples and are representative of at least three experiments. The statistical significance of the number of cells migrating in response to stimuli versus control medium was calculated using the Student’s t test.

Neutrophil Granule Preparations—Human neutrophils were isolated from granulocyte packs obtained from the Department of Transfusion Medicine. Briefly, erythrocytes were removed by sedimentation with 1.5% dextran. Mononuclear cells were centrifuged on a Ficoll-Hypaque cushion, and the residual erythrocytes were removed by hypotonic lysis. The neutrophils were resuspended in PBS, counted, and assessed for viability. Following a wash with PBS, the neutrophils were resuspended in disruption buffer (0.25 M sucrose and 10 mm HEPEs, pH 7.4, containing 4 µM EGTA). Neutrophils were lysed by nitrogen cavitation, and granule fractions were separated on Percoll gradients (19). The cells were equilibrated at 450 g for 20 min in a nitrogen bomb and lysed by dropwise release. Nuclei and cell debris were removed by centrifugation at 600 × g for 10 min. The supernatant was layered over 48% Percoll and centrifuged at 29,000 rpm for 26 min. The Percoll gradient was fractionated, and the fractions were assessed for granule enzymes and T-cell chemotactic activity. Granule fractions were pooled and recentrifuged at 35,000 rpm for 3 h. The granules were recovered as a white flocculent material just above the Percoll pellet. At this point aliquots of the granule-containing fraction were made and stored at -70°C until further use.

Purification of T-cell Chemotactic Activity—Neutrophil granules (0.5 ml) were lysed by freeze-thawing (three times) in 3 ml of 0.1% trifluoroacetic acid containing 2 M NaCl. The suspension was centrifuged for 15 min at 800 × g of 1 ml of clarified supernatant was applied to a C18 reversed phase HPLC column. The first peak of activity was reversed phase HPLC and eluted with a linear gradient of acetoni- trile (- -). The absorbance was monitored at 206 nm. Protein-containing fractions were tested for T-cell chemotactic activity using the microchamber assay, hpf, high power field.

Identification of Chemoattractant Proteins—Fractions containing chemotactic activity were pooled, lyophilized, redissolved in Buffer A, and applied to a C4 reversed phase HPLC column (4.6 × 250 mm, Bio-Rad, RP-304). Proteins were eluted with a linear gradient of 0–90% Buffer B (0.05% trifluoroacidic acid in acetonitrile) over 60 min at a flow rate of 1 ml min^-1 (Fig. 1). Absorbance at 206 nm was monitored as a measure of protein concentration. Collected fractions were lyophilized and assayed for chemotactic activity.

Identification of Chemoattractant Proteins—Fractions containing chemotactic activity were pooled, lyophilized, redissolved in Buffer A, and applied to a C4 reversed phase HPLC column (4.6 × 250 mm, Bio-Rad, RP-304). Proteins were eluted with a linear gradient of 0–90% Buffer B over 60 min at a flow rate of 0.5 ml min^-1 (Figs. 2 and 3). Fractions with activity were analyzed by SDS-PAGE (20) and used for automatic sequence analysis on an Applied Biosystems sequencer model 477A. The presence of cysteine residues was inferred from the absence of detectable amino acid.

Release of Granule Contents—Neutrophils (2 × 10^6 ml^-1) suspended in AIM-V medium (Life Technologies, Inc.) were incubated at 37°C in 6-well plates that had been coated with fibronectin or vascular-cell adhesion molecule-1. Exocytosis was initiated by addition of the appropriate stimulus, and the media was collected and used for the supernatant. Lactoferrin and adhesion molecule-1. Exocytosis was initiated by addition of the appropriate stimulus and stopped by centrifugation and removal of the supernatant. Lactoferrin and adhesion molecule-1. Exocytosis was initiated by addition of the appropriate stimulus and stopped by centrifugation and removal of the supernatant.

FIG. 1. Partial purification of neutrophil granule-derived T-cell chemotactic factors by reversed phase HPLC. Acid- and salt-extracted proteins from neutrophil granules were loaded on a C18 Radial-Pak HPLC column and eluted with a linear gradient of acetonitrile (- -). The absorbance was monitored at 206 nm. Protein-containing fractions were tested for T-cell chemotactic activity using the microchamber assay, hpf, high power field.

Identification of Defensins as T-cell Chemotractants—Human neutrophil granule proteins were extracted by repeated freeze-thawing in a solution of high salt and acid pH. These granule extracts yielded a T-cell chemotactic activity that was concentrated and partially purified by C18 reversed phase HPLC chromatography. This resulted in two major peaks of chemotactic activity (Fig. 1). The proteins with chemotactic activities were further resolved by chromatography on a C4 reversed phase HPLC column. The first peak of activity was purified to apparent homogeneity (Fig. 2), appearing as a single band that migrated with an apparent molecular mass of approximately 3 kDa on Tris-Tricine SDS-PAGE (23). NH2-terminal sequence analysis of the preparation revealed the presence of the related sequences (Table I) corresponding to defensin HNP-1 (50% of the material), HNP-2 (30%), and HNP-3 (20%). The fact that 1) we detected only defensin sequences by sequence analysis, 2) no impurities were detected by silver staining, and 3) amino acid analysis of our preparation corresponds well with amino acid composition of defensins (data not shown) suggests that our preparation consisted of at least 95% pure defensins.

The T-cell chemotactic activity of homogeneous preparations of neutrophil-derived HNP-1, HNP-2, and HNP-3 (kindly provided by Dr. R. I. Lehrer, UCLA) were compared with our preparations. The dose response to individual HNP-1, HNP-2 was practically identical to that of our preparation containing a mixture of HNP-1, HNP-2, and HNP-3 (Fig. 3). Checkerboard analysis of our HNP-1 and HNP-2 showed that their effect was chemotactic rather than chemokinetic (data not shown). HNP-3, which differs from HNP-1 only by substitution of aspartate for the amino-terminal alanine, was not able to stimulate T-cell chemotaxis. It has been proposed that HNP-3 is a precursor of HNP-2 (24) and proteolytic removal of the amino-terminal aspartate residue converts the inactive HNP-3 into chemotactically active HNP-2 (24). While serum proteins have been reported to inhibit the antimicrobial activity of defensins (24), both HNP-1 and HNP-2 retained in vitro chemo-
tactic activity for human T-cells in the presence of 10% human serum (data not shown).

Identification of CAP37/Azurocidin as T-cell Chemotactants—The second major peak of T-cell chemotactic activity (Fig. 1) was also further purified using the same C4 reversed phase HPLC column. In this case T-cell chemotactic activity co-eluted with a major protein peak corresponding to a homogeneous 30-kDa band on Tris/glycine SDS-PAGE (Fig. 4). Amino-terminal sequence analysis identified this protein as CAP37 (cationic antimicrobial protein of molecular mass 37 kDa), also known as azurocidin (Table I). By amino acid analysis, our preparation of CAP37/azurocidin corresponded well with the known amino acid composition of CAP37/azurocidin. In addition, upon sequence analysis of our preparation we detected no other sequence except CAP37/azurocidin. These facts indicate that our preparation must be at least 95% pure. CAP37/azurocidin is a previously identified azurophilic granule protein with sequence homology to the serine protease family and has potent oxygen-independent bactericidal activity (25, 26). Sequencing of the polypeptide eluting just before CAP37/azurocidin revealed it to be a lysozyme that does not induce T-cell chemotaxis. CAP37 was chemotactic from 1.0 to 100 ng/ml, which is comparable in molar concentration with the range of defensin activity (Fig. 3). In addition, preparations of purified as well as recombinant human CAP37/azurocidin (kindly provided to us by Dr. A. Pereira) were equally potent chemoattractants for human T-cells (data not shown).

IL-8-stimulated Release of Defensins from Neutrophils—Experiments were performed to ascertain that defensins and CAP37/azurocidin would be released into the extracellular environment by appropriate stimuli. Neutrophils exposed to IL-8 could be shown to degranulate with the release of lactoferrin and β-glucuronidase (27). The release of defensins following degranulating stimuli was examined by concentration of the culture supernatants and quantitative detection of the defensins released using a Western blot assay (Fig. 5) (28). We established by scanning of the Western blots that IL-8 released about 10% of the total content of defensins in the granules of 2 × 10⁶ neutrophils, while FMLP released 17% and phorbol 12-myristate 13-acetate/ionomycin 23% of the total content of defensin in the granules. The addition of cytochalasin increased the degranulating effect of IL-8 only minimally to 13% of the total and did not effect FMLP release. Tumor necrosis factor-α has also been shown to have a synergistic effect on IL-8-stimulated degranulation (27). Similarly, as determined by Western blotting, IL-8 also induced the release of CAP37/azurocidin, which is also contained in the azurophilic granules (data not shown).

In Vivo Inflammatory Effects of Human Defensins and CAP37/Azurocidin in Mice—BALB/c mice were injected subcutaneously with 1 μg of the defensin or CAP37/azurocidin preparations. After 4 or 24 h the injection site was excised, and the extent and types of cells infiltrating the site were examined histologically. Within 4 h of injection the defensin and CAP37/azurocidin each resulted in infiltration by PMNs and mononuclear cells in the dermis and subcutaneous tissues (Table I). This is in contrast to a single 1-μg injection of recombinant human IL-8, which produced a marked infiltration of PMNs by 4 h with little mononuclear cell infiltration (17). By 24 h, 4 h after a second injection at the same site, an even greater infiltration of PMNs and mononuclear cells was elicited by defensins as well as CAP37/azurocidin. Doses of 10 and 100 ng of defensins and CAP37 also induced neutrophil and mononuclear cell infiltrates at 24 h. Thus, human defensins and CAP37/azurocidin are capable of inducing considerable local murine neutrophil and mononuclear cell infiltration. Immunohistochemical studies of sites of defensin injection in chimeric huPBL-SCID mice were performed to establish whether there were T-cells in the infiltrate (22). A single injection of 1 μg of defensins (HNP-1 and HNP-2) within 4 h resulted in the infiltration by low to modest numbers of human CD3+ T-lymphocytes in four of six mice examined (Table III). In contrast, the sites of PBS injection in six control mice did not contain any human CD3+ T-cells. These in vivo results support the in vitro evidence that defensins are T-cell chemoattractants.

**DISCUSSION**

The results presented in this report demonstrate that neutrophils are an important source of factors chemotactic for T-lymphocytes. The polypeptides derived from neutrophil granules were identified as T-cell chemotactic factors: defensins NP-1 and -2 and CAP37/azurocidin. Defensins are a family of small (29–30 amino acids, approximately 3.5 kDa) cationic antimicrobial proteins (24) whose structure is stabilized by three conserved disulfide bridges, including one disulfide that cyclizes the protein by linking the carboxy-terminal cysteine to the amino-terminal ultimate (HNP-2) or penultimate (HNP-1, HNP-3) cysteine (29). Indeed the defensins HNP-1, HNP-2 and HNP-3 differ by only a single NH₂-terminal amino acid. Ap-

**Table I**

Identification of the T-cell chemotactic proteins by amino-terminal sequences analysis

| Defensin   | Amino-terminal sequence |
|------------|-------------------------|
| HNP-1      | ACYCRIPIACIAGERRYGTClQYGR|LWAFCC |
| HNP-2      | CYCRIPACIAGERRYGTClQYGR|LWAFCC |
| HNP-3      | DCYCRIPIACIAGERRYGTClQYGR|LWAFCC |
| CAP37/azurocidin | TVGGKRAPRQPFPFLASIQNGRHFCGGALIHARFVMTAA... |
approximately 25–30% of the human azurophilic granule protein consists of defensins. It has been estimated that up to 3–5 pg of defensins can be released by each neutrophil. They are believed to be released into the phagocytic vesicle of the neutrophil and into the medium (30) where they contribute to the respiratory burst-independent cytotoxic killing of microbes. The cytotoxic effect of defensins occurs at micromolar concentrations and is thought to be due to their ability to form numerous transmembrane channels that permeabilize lipid bilayers of microorganisms. Even though their amino acid sequences are virtually identical, HNP-3 does not kill Candida albicans (31) whereas HNP-1 and HNP-2 have been reported to have this activity. HNP-3 also lacked T-cell chemotactic activity, but cleavage of the amino-terminal aspartate residue can convert it into active HNP-2.

CAP37/azurocidin, like defensins, was previously identified as a neutrophil granule protein also with antimicrobial activity at micromolar concentrations (32). Structurally, CAP37 belongs to the serine protease superfamily and has 45% sequence identity with human neutrophil elastase; however, due to replacements of crucial amino acids at the active site, CAP37/azurocidin is inactive as a protease (26). It is unlikely that there are any other T-cell chemotactic peptides present that we have not detected in the neutrophil granule extracts because the defensins and CAP37 are major protein constituents of neutrophil granules and are chemotactic at low (nanomolar) concentrations.

Both the defensins HNP-1 and HNP-2 and CAP37/azurocidin have been reported to chemotact monocytes (35, 36). How-
Defensins and CAP37/Azurocidin Attract T-cells

...showing that BALB/c mice injected subcutaneously with 1.0-μg injections of defensins or CAP37/azurocidin developed mononuclear cells as well as neutrophilic infiltrates by 4 h. This prediction that defensins and CAP37/azurocidin are potent in vitro T-cell chemoattractants...

### Table III

| Animal no. | Treatment | CD3+ cells |
|------------|-----------|------------|
| 21102-1    | PBS (1×)  | —          |
| 21102-2    | PBS (1×)  | —          |
| 21103-1    | PBS (1×)  | —          |
| 21103-2    | PBS (1×)  | —          |
| 21104-1    | PBS (1×)  | —          |
| 21104-2    | PBS (1×)  | —          |
| 21108-1    | Defensin (1×) | 2F*       |
| 21108-2    | Defensin (1×) | 2MF*      |
| 21109-1    | Defensin (1×) | 2MF*      |
| 21110-1    | Defensin (1×) | —        |
| 21110-2    | Defensin (1×) | 1F*       |

*The presence of infiltrating mast cells was noted.

...ever, we have repeatedly been unable to detect any monocyte or neutrophil chemotaxis with doses of 1–1000 ng/ml defensins. The report that defensins chemoattract human monocytes is based on assays of the leading front of mononuclear cells migrating into a filter (35). It is difficult to identify cells lodging in a filter, and this may have led to a misidentification of the migrating mononuclear cell type. Our assay method more readily permits the identification of cells adhering to the underside of polycarbonate filters as T-cells. In the case of our preparations of natural CAP37/azurocidin and the purified and recombinant CAP37 (provided by Dr. A. Pereira, we also could not detect significant monocyte chemotaxis (chemotaxis index ≤ 1.5). Perhaps this is based on technical discrepancies in our assays, or possibly tissue macrophages express more receptors for CAP37 than do human peripheral monocytes. However, we have identified another protein present in the chromatography fractions of the neutrophil granule extracts as having monocyte chemoattractant activity but not T-cell chemoatactic activity. This protein migrates very closely to CAP37/azurocidin and may therefore have been a contaminant of CAP37 preparations that attract monocytes.2 Our data indicate that defensins and CAP37/azurocidin are potent in vitro T-cell chemoattractants.

Because defensins account for 25–30% of the neutrophil granule protein content, they may serve as a major source of T-cell chemoattractant whose release is under the control of neutrophil activators such as IL-8. Although serum proteins effectively inactivate the antimicrobial activity of defensins, their in vitro chemotactic activity is not impaired by the presence of 10% fetal calf serum (data not shown). This predicts that defensins can deliver a T-lymphocyte activating signal at the distance from a site of acute inflammation where they originate. This prediction was borne out by our experiments showing that BALB/c mice injected subcutaneously with 1.0-μg injections of defensins or CAP37/azurocidin developed mononuclear as well as neutrophilic infiltrates by 4 h. By 24 h the number of accumulated neutrophils and mononuclear cells was markedly increased even in response to lower 10- or 100-ng doses. The infiltration by neutrophils and mononuclear cells was not predicted by the in vitro assays. It is possible that defensins and CAP37/azurocidin initiate a cascade of proinflammatory signals in vivo resulting in the recruitment of neutrophils and monocytes. The inflammatory response may be a result of the tissue-damaging effects of these microbialid agents, although necrosis became evident only at 24 h in response to the 1000-ng dose. In the case of the defensins, immuno-...
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