Metabolic Heterogeneity of Eosinophils From Normal and Hypereosinophilic Patients

By S. H. Pincus, W. R. Schooley, A. M. DiNapoli, and S. Broder

Eosinophils, which may be associated with allergic, parasitic, or neoplastic disease, have a potent oxidative burst that may be activated by particulate or soluble stimuli. Eosinophils from normal persons and patients with hypereosinophilia were compared with respect to their ability to produce the active oxygen product, superoxide anion. Normal eosinophils produced large amounts of superoxide anion under resting conditions (0.53 ± 0.15 nmoles cyto-c/10^6 eos/hr) and when stimulated by preopsonized zymosan (0.85 ± 0.10 nmoles cyto-c/10^6 eos/hr) or phorbol myristate acetate (PMA) (2.38 ± 0.46 nmoles cyto-c/10^6 eos/hr). Considerable variation was observed in superoxide production by eosinophils from patients with hypereosinophilia. Eosinophils from a group of four patients with hypereosinophilia associated with neoplastic disease produced less superoxide anion than normal eosinophils when stimulated by preopsonized zymosan or PMA (p ≤ 0.05). Eosinophils from a group of five patients with other causes of hypereosinophilia produced more superoxide anion than normal eosinophils when stimulated by PMA (p ≤ 0.01). These studies demonstrate metabolic heterogeneity of eosinophils from patients with hypereosinophilia, and further emphasize that normal eosinophils and eosinophils from hypereosinophilic patients are not functionally equivalent.

Eosinophilia may be a marker of allergic, parasitic, or neoplastic disease. On occasion, it may be associated with bullous skin disease, systemic vasculitis, or hereditary immunologic disorders. These clinical observations have led to the theory that eosinophils function as effector cells by modulating immediate hypersensitivity reactions and by killing parasites. Recent experiments have confirmed that eosinophils can kill larval forms of Trichinella spiralis and schistosomula of Schistosoma mansoni and that eosinophils may influence immediate hypersensitivity reactions by release of histaminase and arylsulfatase, which inactivate slow-reacting substance of anaphylaxis.

Eosinophils are predominantly a tissue cell localized to the skin, respiratory tract, gastrointestinal tract, and female genital tract; they usually comprise only 2%-3% of the circulating leukocytes. Human experiments have been largely confined to studies of eosinophils obtained from the blood of patients with hypereosinophilia of diverse etiologies. These studies have shown that eosinophils are phagocytic cells with many properties similar to those of neutrophils. When eosinophils are activated by exposure to ingestible particles, such as latex beads or opsonized zymosan, or by soluble membrane activators (i.e., phorbol myristate acetate, PMA), a potent oxidative metabolic burst is initiated. There is an increase in oxygen consumption; active oxygen metabolites such as superoxide anion and hydrogen peroxide are generated and released from the cell; and the hexose-monophosphate shunt pathway of glucose metabolism is activated. Superoxide anion is frequently studied since it is the initial active oxygen species derived from the reduction of oxygen by a membrane-bound oxidase. In addition, superoxide anion may play an important role by mediating tissue damage in inflammatory immune complex diseases, by its release from activated mast cells, and by its involvement in radiation damage. Furthermore, superoxide anion may be bactericidal or may generate other bactericidal compounds such as hydroxyl radical or hydrogen peroxide through interaction with hydrogen peroxide or hydrogen ions, respectively.

A unique feature of the oxidative burst of eosinophils has been reported to be the sustained production of superoxide anion over periods of up to 3 hr, and this is subject to marked suppression by the addition of the peroxidase inhibitor, azide. Throughout these studies, the assumption has been that eosinophils obtained from hypereosinophilic patients are functionally equivalent to normal eosinophils.

The recently devised metrizamide method of eosinophil separation facilitates preparation of pure populations of eosinophils from both normal individuals and those with hypereosinophilia. The studies reported here were designed to evaluate the production of superoxide anion by normal eosinophils and to investigate the question of possible metabolic differences between eosinophils from normal and hypereosinophilic patients.

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philic patients. This article provides evidence that there are metabolic differences among eosinophils from patients with hypereosinophilia of diverse causes.

MATERIALS AND METHODS

Eosinophil Purification

Heparinized (A.H. Robbins Co., Richmond, Va.) venous blood was obtained from normal volunteers and patients with hypereosinophilia after obtaining appropriate informed consent. Routinely, 120–150 cc of blood was obtained from greater than 20 normal subjects who had no history of atopic disease, and 30–60 cc of blood was drawn from hypereosinophilic patients. The blood was diluted with an equal volume of 4.5% Dextran T-500 (Pharmacia Fine Chemicals, Piscataway, N.J.) and allowed to sediment at 37°C for 30 min. The leukocyte-rich plasma was removed, and the cells pelletted at 150 g. Leukocytes, 100–120 x 10⁶, were washed in Hank’s balanced salt solution (HBSS) and then were layered on discontinuous metrizamide (Nygaaard and Co., Oslo, Norway) gradients as described. Eosinophils were harvested from the 24/25% interface and/or the pellet. Since there was considerable individual variation, differential counts on the final preparation were performed for each experiment. Preparations usually contained greater than 90% eosinophils, the contaminating cells being neutrophils. The cells were washed and suspended in either HBSS or phosphate-buffered saline.

Heparinized blood from the two patients with Sézary syndrome was processed differently in order to remove lymphocytes. Blood was mixed with Ficoll-Hypaque and allowed to sediment at room temperature. After removal of the lymphocyte-rich layer, the remainder of the blood was mixed with an equal amount of 4.5% Dextran T-500 and sedimented for 45 min at room temperature (Pharmacia Fine Chemicals, Piscataway, N.J.). The eosinophils were recovered directly from the granulocyte-rich layer. In each experiment, purity was greater than 95%.

Superoxide Anion Production

Eosinophils were suspended in HBSS at a final concentration of 2 x 10⁶ cc. Leukocytes (10⁶) were added to 15 x 75 mm plastic test tubes containing 100 nmole of cytochrome-c (type VI, Sigma Chemical Co., St. Louis, Mo.) and where indicated, 1 µg/ml of phorbol myristate acetate (PMA) (Sigma Chemical Co.) or 0.5 mg of preopsonized zymosan (Schwartz-Mann Co., Orangeburg, N.Y.). Zymosan (10 mg) was opsonized with 1 ml of fresh-frozen pooled guinea pig serum and washed four times with HBSS, as previously described. Preliminary experiments showed that guinea pig serum was more effective in activating superoxide anion production than human AB serum. Incubations were terminated at the indicated times by rapidly cooling the cells to 4°C and pelleting the cells by centrifugation at 400 g for 5 min. Superoxide production was quantitated by measuring the reduction of cytochrome-c at 550 nm in a Gilford recording spectrophotometer (Gilford Instrument Laboratories, Inc., Oberlin, Ohio). Conditions were selected so that for each experiment, the additions of superoxide dismutase (0.05 mg/ml) (Sigma Chemical Co.) prevented the reduction of cytochrome-c.

Sodium azide (Fisher Chemical Co.) was added 10 min prior to the addition of cytochrome-c and stimuli. The two-tailed Student t test was used to evaluate statistical significance.

Measurement of Hexose-Monophosphate Shunt Activation

Activation of the hexose-monophosphate shunt pathway of glucose C-1 oxidation was measured by determination of ¹⁴CO₂ by minor modification of previously described technique. Briefly, 1⁰ purified eosinophils were incubated at 37°C for 20 min with or without stimuli (latex beads, 1.µ diameter, Dow Chemical, Midland, Mich. or PMA, 1.µg/ml). ¹⁴CO₂ was collected, counted, and the nmoles ¹⁴C-1 glucose metabolized/1⁰ eosinophils determined.

Patients

Patients were referred for study by other physicians. The sole criterion for inclusion in the study was a differential count revealing 10% greater eosinophils. Brief descriptions and the details of the leukocyte counts and purification are included in Table 1.

RESULTS

Superoxide Production by Normal Eosinophils

When normal human eosinophils from more than 20 different individuals were incubated under unstimulated (resting) conditions, there was little detectable superoxide anion production during the initial 20 min (Table 2). When the incubation period was increased to 60 min, there was a marked increase in the unstimulated production of superoxide anion. Both washed opsonized zymosan particles and PMA were effective stimulants of superoxide production, measured both at 20 min and 60 min. In general, PMA at a concentration of 1 µg/ml led to production of more measurable superoxide anion than preopsonized zymosan.

<table>
<thead>
<tr>
<th>No.</th>
<th>Purity</th>
<th>Age</th>
<th>Sex</th>
<th>Brief Clinical Description</th>
<th>Leukocytes/cu mm (% Eos)</th>
<th>Final Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>M</td>
<td>Ampicillin hypersensitivity reaction</td>
<td>15–20,000 (30%)</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>M</td>
<td>Hyper eosinophilic syndrome</td>
<td>14–19,000 (50%–72%)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>M</td>
<td>Hyper eosinophilic syndrome, probable eosinophilic leukemia</td>
<td>30,000 (40–60%)</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>M</td>
<td>Sézary syndrome</td>
<td>10,400 (55%)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>M</td>
<td>Hookworm infection</td>
<td>18,000 (25%)</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>F</td>
<td>Sézary syndrome</td>
<td>26,000 (61%)</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>Lymphoma or pseudolymphoma secondary to Dilantin</td>
<td>17,000 (25%)</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>M</td>
<td>Erythrodema, ulcerative colitis, sclerosing cholangitis, nephrotic syndrome</td>
<td>15–23,000 (15%–20%)</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>M</td>
<td>Clonorchus and schistosome infection</td>
<td>9,000 (10%)</td>
<td>98%</td>
<td></td>
</tr>
</tbody>
</table>

Patients 3, 4, 6, and 7 were included in group I (see text for details) and patients 1, 2, 5, 8, and 9 were included in group II.
Table 2. Superoxide Production by Normal Eosinophils

<table>
<thead>
<tr>
<th>Incubation Time</th>
<th>Resting</th>
<th>Preopsonized Zymosan</th>
<th>PMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 min</td>
<td>0.06 ± 0.04(18)</td>
<td>0.47 ± 0.09(20)</td>
<td>1.69 ± 0.34(15)</td>
</tr>
<tr>
<td>60 min</td>
<td>0.53 ± 0.15(12)</td>
<td>0.85 ± 0.10(13)</td>
<td>2.38 ± 0.45(12)</td>
</tr>
</tbody>
</table>

Results are the mean ± standard error, with the number of experiments performed in duplicate indicated in the parentheses. Eosinophils were prepared from normal peripheral blood by the metrizamide method. All incubations employed 10^6 eosinophils and, where indicated, 0.5 mg of preopsonized zymosan or 1 μg of PMA.

Superoxide production was dependent on cell concentration. As illustrated in Fig. 1, doubling the number of eosinophils doubled the superoxide production in the presence of preopsonized zymosan. When PMA (Fig. 2) was employed as the stimulus, superoxide production was not linearly dependent on cell concentration. Superoxide production by unstimulated eosinophils was directly dependent on cell number at all concentrations tested (Fig. 2). All subsequent experiments were performed employing 5 × 10^4 or 10^5 human eosinophils.

The production of superoxide anion was not linear with respect to time, as illustrated in Fig. 3. Rates of superoxide production were greatest within 10–30 min after an initial lag period, and plateaued with time. Though only representative experiments are illustrated, these findings were confirmed on at least 3 occasions employing both preopsonized zymosan and PMA as the stimulus.

Superoxide Production by Eosinophils From Hypereosinophilic Patients

Eosinophils from patients with hypereosinophilia of diverse etiology were prepared by metrizamide purification, and superoxide production was studied employing the standard laboratory conditions. When the data were examined, considerable heterogeneity was evident. However, the results seemed to fall into two groups, those that appeared similar to normal eosinophils and those that appeared much more active (Fig. 4). We then examined the cases to see if any clinical features could be used to divide these patients and facilitate data analysis. The patients were divided in two groups: those where the eosinophilia was associated with a neoplastic process (group I) and those where the eosinophilia was associated with another disease process (group II). Included in the first group were three patients with Sézary syndrome and eosinophilia, one patient with pseudolymphoma, and one patient with eosinophilic leukemia. Included in the second group, where the eosinophilia may have been more actively involved in the disease process, were one patient with a drug hypersensitivity reaction, two patients with parasitic disease, one patient with prednisone-responsive hypereosinophilic syndrome, and one patient with erythroderma and prednisone-responsive eosinophilia.

Using these groupings, there were clear-cut differ-
Fig. 3. The time course of superoxide production by normal human eosinophils. 10^6 normal eosinophils were incubated without stimulus (○), or with preopsonized zymosan (●) or PMA (□) under the standard laboratory conditions. Incubations were terminated at the indicated times. Results are the mean of duplicate values from a typical experiment and are expressed as the number of nmoles of cytochrome-c reduced/10^6 eosinophils.

ences between eosinophils from normal and hypereosinophilic patient (Fig. 5). Cells obtained from group I patients were significantly less active than normal eosinophils (p ≤ 0.05) when stimulated by zymosan or PMA and measured at 20 min. At 60 min, no significant differences were apparent. Unstimulated resting eosinophils produced equivalent amounts of superoxide anion at both time periods. Thus, these eosinophils appeared defective when studied during the initial phases of oxidative metabolism. By contrast, eosinophils from group II patients were equivalent when studied at 20 or 60 min under resting or zymosan-stimulated conditions. However, employing PMA, a much more potent stimulus, group II eosinophils were significantly more active than both normal and group I eosinophils at both 20 min (p ≤ 0.05) and 60 min (p ≤ 0.01). Thus, these cells appeared to have an enhanced oxidative response to potent stimulants. This was not due to sustained production of superoxide anion, since several experiments demonstrated that the rate of production declined after the initial 20 or 30 min (data not shown). In two cases (patients 2 and 8), studies were carried out on more than one occasion, and the results were consistent.

Hexose-Monophosphate Shunt Activation

The observed changes in superoxide production might be explained either by changes in the total amount of superoxide anion generated from molecular oxygen or by changes in the site of production of superoxide anion, which would effect the ability to be measured by the detecting system employed. For instance, if more superoxide anion were generated extracellularly or at a site other than the phagocytic vacuole, it might react more readily with cytochrome-c used in our assay. If increased production of superoxide anion were due to increased oxidative metabolism, this should be reflected in increased activation of the hexose-monophosphate shunt pathway of glucose oxidation. Release of 14CO2 from 14C-labeled glucose was studied under resting and stimulated conditions. Normal eosinophils (Table 3) oxidized 28.02 ± 11.5(5) nmole/10^7 eos/20 min of C-1 glucose under resting conditions; this was increased to 118.7 ± 22.8(4) nmole/10^7 eos/20 min by the addition of latex particles and to 273.4 ± 76.4(5) nmole/10^7 eos/20 min by the addition of PMA. Eosinophils obtained from 4 patients with hypereosinophilia were compared with normal eosinophils. When the data were combined, no significant differences between normal eosinophils and eosinophils from hypereosinophilic patients were noted. If the results were analyzed by dividing the patients into 2 groups, as had been done for analysis of superoxide anion, more differences were apparent. Eosinophils from patients in group I produced less 14CO2 under resting and stimulated conditions than normal eosinophils. However, the results were not statistically significant. Eosinophils from patients in group II produced equivalent amounts of 14CO2 under resting conditions or when stimulated by latex beads. There was an increase that was not statistically significant when PMA was employed as the stimulus. It is possible that if more patients were studied, the trends suggested by this data could have
Eosinophils from normal persons and patients with hypereosinophilia have been tested for possible metabolic differences. Resting normal eosinophils produced little superoxide anion. The resting values observed here were similar to those previously observed, though they are considerably less than those reported employing human peritoneal exudate eosinophils. These observations are contrary to reports that other aspects of oxidative metabolism are elevated in a resting state.

When eosinophils were exposed to particulate (preopsonized zymosan) or soluble stimuli (PMA), there was marked stimulation of superoxide anion production. Though production was linear with increasing cell number using preopsonized zymosan as a stimulus, this was not observed with PMA-stimulated cells. This might be due to cell crowding or interference with the assay of cytochrome-c. Although superoxide production increased with time, the rate of production sharply declined after the initial 30 min. There was a marked “lag” during the first 10 min, which has not been previously noted. Contrary to previous reports, no sustained elevation of superoxide production was noted.

Eosinophils from patients with hypereosinophilia of diverse causes also responded to membrane stimulation with the production of superoxide anion. Though...
patients and incubations were performed according to the standard laboratory procedure. Results are the mean ± standard error, with the number of experiments performed in duplicate or quadruplicate indicated in parentheses. Results for hypereosinophilic eosinophils were calculated inclusively, and as the subgroups described for superoxide anion production. Group I represents studies from patients 6 and 7, and group II from patients 8 and 9.

<table>
<thead>
<tr>
<th></th>
<th>Normal eosinophils</th>
<th>Hypereosinophilic eosinophils</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28.0 ± 11.5(6)</td>
<td>7.7 ± 2.0(4)</td>
<td>4.5 ± 0.2(2)</td>
<td>10.9 ± 1.9(2)</td>
</tr>
<tr>
<td>Latex</td>
<td>118.7 ± 22.8(4)</td>
<td>82.9 ± 65.8(4)</td>
<td>62.3 ± 19.9(2)</td>
<td>103.7 ± 16.4(2)</td>
</tr>
<tr>
<td>PMA</td>
<td>273.4 ± 76.4(5)</td>
<td>260.4 ± 87.2(4)</td>
<td>107.9 ± 79.6(2)</td>
<td>362.8 ± 136.8(2)</td>
</tr>
</tbody>
</table>

Eosinophils were prepared from normal persons and hypereosinophilic patients, and incubations were performed according to the standard laboratory procedure. Results are the mean ± standard error, with the number of experiments performed in duplicate or quadruplicate indicated in parentheses. Results for hypereosinophilic eosinophils were calculated inclusively, and as the subgroups described for superoxide anion production. Group I represents studies from patients 6 and 7, and group II from patients 8 and 9.

Table 3. Stimulation of the Hexose-Monophosphate Shunt

<table>
<thead>
<tr>
<th></th>
<th>Resting</th>
<th>Latex</th>
<th>PMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal eosinophils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose C-1 Oxidation (n mole glucose oxidized/10^7 eos/20 min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal eosinophils</td>
<td>28.0 ± 11.5(6)</td>
<td>118.7 ± 22.8(4)</td>
<td>273.4 ± 76.4(5)</td>
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<tr>
<td>Hypereosinophilic eosinophils</td>
<td>7.7 ± 2.0(4)</td>
<td>82.9 ± 65.8(4)</td>
<td>260.4 ± 87.2(4)</td>
</tr>
<tr>
<td>Group I</td>
<td>4.5 ± 0.2(2)</td>
<td>62.3 ± 19.9(2)</td>
<td>107.9 ± 79.6(2)</td>
</tr>
<tr>
<td>Group II</td>
<td>10.9 ± 1.9(2)</td>
<td>103.7 ± 16.4(2)</td>
<td>362.8 ± 136.8(2)</td>
</tr>
</tbody>
</table>

There was marked diversity in the amount of superoxide production, the results seemed to fall into two groups. By dividing the hypereosinophilic patients into two groups, clear-cut differences between eosinophils were noted. Three of our hypereosinophilic patients had eosinophilia related to neoplastic disease. Patient 3 apparently had an eosinophilic leukemia. Patients 4 and 6 had hypereosinophilia thought to be related to their cutaneous lymphoma. Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome) has now been shown to be malignant proliferation of T helper cells in certain cases. In these patients, these malignant cells might be elaborating factors stimulating eosinophil production. These patients were grouped along with the patient who had a pseudolymphoma, where again the eosinophilia may have been related to lymphocyte activation. These patients were identified as group I. The remainder of the patients were considered as a separate group (group II). In these cases, we reasoned that the eosinophil might be more actively participating in the disease process, be it allergic (drug hypersensitivity), parasitic, or idiopathic.

Using these groupings, differences became apparent. Eosinophils from the group I patients were deficient with respect to zymosan and PMA-activated superoxide production at early time periods. That this indeed represents an inability of the membrane to be activated by zymosan is suggested by the deficient zymosan-induced iodination (Pincus, unpublished data). A possible explanation is the deficiency of C3 receptors noted in eosinophils from some patients with hypereosinophilia. Unfortunately, we were unable to study the receptors in our particular patients. Another possible explanation is that these cells were functionally deactivated as a result of prior in vivo activation. Though eosinophils from hypereosinophilic patients may sometimes appear vacuolated and degranulated, only 1 of our patients (eosinophilic leukemia) had morphologically abnormal cells.

Eosinophils from group II patients had clearly elevated PMA stimulated superoxide production when compared to normal cells. The failure to find increased resting levels of superoxide production suggests that the cells were not activated in vivo, but rather had increased capacity to generate superoxide in response to soluble stimuli or that the superoxide production was more accessible to measurement. That this increased oxidative response is not due solely to the presence of eosinophilia is confirmed by the failure to find an increased oxidative response in eosinophils of Sézary patients. These observations strongly suggest that some reports of an increased oxidative metabolism of eosinophils might reflect the use of "activated" eosinophils from selected patients with hypereosinophilia.

The mechanism of the differences in superoxide production is not clear. No studies of oxygen consumption were performed. Though studies of the hexose-monophosphate shunt were performed with eosinophils from four patients, the small numbers of subjects and the variability of normal eosinophils preclude any statistically significant conclusions. If the trends observed were confirmed by further studies, they indicate that the differences observed in some hypereosinophilic patients may reflect less active oxidative metabolism. The eosinophils of patients in group II appeared more nearly similar to normal eosinophils, and thus apparent increases in superoxide anion production might possibly represent differences in sites of production that would facilitate measurement by our extracellular system.

Our report further suggests that in certain disease states, eosinophils may be functionally adapted, presumably reflecting their biologic role. Heterogeneity of eosinophil populations has been suggested on the basis of receptor studies; some patients have been noted to have increased Fc receptors and others deficient C3 receptors. Reports of increased killing of schistosomula by eosinophils derived from patients with eosinophilia also support the concept of functional modification. Additionally, studies of human neutrophils have demonstrated subpopulations with different functional properties. It is of interest that in
experimental schistosomiasis, T-cell-derived products can modulate eosinophil function through increased migration of eosinophils and enhanced egg destruction.\textsuperscript{18,19} Thus, the concept of functional modification of eosinophils in various disease states has other supporting evidence. How these differences relate to the biologic role of the eosinophil is highly speculative. These studies additionally emphasize the importance of using normal and not abnormal cells in studies of eosinophil function.

ACKNOWLEDGMENT

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