Human Interleukin-5 (IL-5) Regulates the Production of Eosinophils in Human Bone Marrow Cultures: Comparison and Interaction With IL-1, IL-3, IL-6, and GMCSF

By Elaine J. Clutterbuck, Elizabeth M.A. Hirst, and Colin J. Sanderson

Recombinant human interleukin-5 (rHL-5), in either liquid or semi-solid cultures, selectively induced eosinophil production from normal human bone marrow, with no activity on other cell lineages. The time course of eosinophil production induced by murine IL-5, rHL-3, and rH granulocyte-macrophage colony stimulating factor (GMCSF) was similar to rHL-5. The rate of eosinophil maturation in vitro was independent of the stimulating cytokine, mature eosinophils being produced after 4 to 5 weeks in liquid culture with each of these cytokines. The eosinophils produced in response to each cytokine were morphologically indistinguishable, and had the ultrastructural features of maturity except that the electron-dense material in the granules had not formed into crystalline cores. Neither rHL-1 nor rHL-6 alone, or in combination with rHL-5 or rHL-3, induced eosinophil differentiation or proliferation under the conditions used. rHL-3 and rHGMCSF induced more eosinophil colonies than rHL-5. rHL-5 had an additive, not synergistic, effect on eosinophil colony production when combined with either rHL-3 or rHGMCSF, suggesting that rHL-5 stimulates a smaller and possibly different population of eosinophil progenitors. However, rHL-5 induced the greatest eosinophil production in liquid cultures, suggesting that although it may act on a smaller population of precursors, it is able to stimulate more proliferative steps than either rHL-3 or rHGMCSF.

OSINOPHILIA is commonly seen in patients with helminth infections and certain allergic conditions. The eosinophilia is often an isolated abnormality, occurring without a coincident increase in neutrophils or macrophages, suggesting that the regulation of eosinophil production is independent of other cell lineages.

Murine eosinophil differentiation factor (EDF), now called interleukin-5, stimulates the production of eosinophils from human bone marrow although at low specific activity. Although no native source of an analogous human factor has been identified, the gene for human IL-5 has been cloned and expressed using mIL-5 cDNA as a probe. Preliminary data have shown that this recombinant material is capable of supporting the production of human eosinophils in vitro. Two other recombinant human (rh) factors, IL-3 and granulocyte-macrophage colony stimulating factor (GMCSF), stimulate the production of eosinophils in addition to neutrophils and macrophages from human bone marrow. There is evidence that they act early in the neutrophil and macrophage differentiation pathways, and it is possible that they could also be involved at an early stage of eosinophil production.

This study attempts to define the roles of rHL-5, rHL-3, and rHGMCSF in the production and morphology of eosinophils in vitro. rHL-1 and rHL-6 were also tested because they have been shown to activate the production of hematopoietic growth factors by accessory cells, and to interact with early murine progenitors.

MATERIALS AND METHODS

Cytokines. rHL-5 (1.4 x 10^6 U/mL) was purified from the culture supernatant of COS 7 cells transfected with the rHL-5 gene as previously described. One unit of activity was defined as the amount required to stimulate half-maximal human eosinophil production after 21 days in liquid culture (determined by linear regression of log transformed data). Conditioned medium from the T-cell hybrid NIMP-TH-1 was used as the source of murine (m) IL-5. rHGMCSF (3.4 x 10^6 U/mL) was kindly provided by Biogen (Cambridge, MA); rHL-3 (COS supernatant) and rHL-6 (1 x 10^6 B-cell assay dilution U/mg protein, 335 µg protein/m/L) were a gift of Dr G.G. Wong (Genetics Institute); and rHL-1α (>10^7 thymocyte mitogenesis U/mg protein, 100 ng/mL) was a gift from Dr S. Gillis (Immunex Corp, Seattle). Preliminary experiments established the optimal final dilutions of the cytokines to be 1:1,000 rHL-3, rHL-6, rHGMCSF; 1:2,000 rHL-5; 1:10 rHL-5 and 0.1 ng/mL rHL-1.

Human bone marrow cells. Human bone marrow was obtained from normal patients (peripheral blood eosinophil count less than 3%), donating marrow primarily for allotransplantation at The Royal Free Hospital and Hammersmith Hospital, London. Marrow was collected in accordance with a protocol approved by the Ethics Committees of both hospitals. Mononuclear cells were obtained by centrifugation over Ficoll Paque (1.077 g/mL) (Pharmacia Fine Chemicals, Uppsala, Sweden), and resuspended at 10^6 cells/mL in RPMI 1640 containing 15% FCS.

Liquid culture. The cultures were performed as previously described. Briefly, 10^6 marrow mononuclear cells were cultured with 10 µL of diluted stimuli in 0.1 mL at 37°C in humidified 5% CO2 in air. Fifty microliters of the supernatant was replaced weekly with fresh medium containing 5 µL of the appropriate stimulus. After the culture period indicated in the text, the cells were resuspended, counted with a Coulter Counter, and differential cell counts performed on cytocentrifuge preparations. These were stained with: 0.1% Luxol Fast Blue in urea-saturated 70% ethanol and Harris’ acidified hematoxylin, May-Grünwald Giemsa, or Congo Red and Harris’ acidified hematoxylin. Cell viability was assessed by trypan-blue exclusion.
described by Strath et al.14 and on human cultures by a modified technique described elsewhere.3

Semisolid culture. Mononuclear cells were incubated at 2 x 10⁶/mL in RPMI containing 15% FCS, 0.33% Bacto-agar (Difco Laboratories, Detroit), and diluted stimuli as specified in the text at 37°C in 5% CO₂ in air for 14 days.21,22 Whole cultures were methanol-fixed and stained with either Luxol Fast Blue and Harris' acidified hematoxylin or Congo Red and Toluidine Blue. Eosinophil clusters (groups of more than two cells) and colonies (clusters of more than 40 cells) of all cell types were counted.

Electron microscopy. Cells cultured in the liquid assay in the presence of optimal concentrations of cytokines were fixed with 1% paraformaldehyde, 1.25% glutaraldehyde in 0.1 mol/L sodium cacodylate buffer, pH 7.25, followed by 1% osmium tetroxide in the same buffer, and then 1% aqueous uranyl acetate. After dehydrating with absolute ethanol they were embedded in araldite and post-stained with uranyl acetate and Reynolds' lead citrate.

Statistics. Results are expressed as the mean ± 1 SD of three replicates unless stated otherwise in the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. When omitted from the text. 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In contrast, by day 21 in liquid culture the number of eosinophils induced by optimal doses of rhIL-5 (6.8 ± 0.9 × 10⁶/mL) were always greater than by rhIL-3 (2.9 ± 1.5 × 10⁶/mL) or rhGMCSF (2.3 ± 1.3 × 10⁶/mL, mean of three experiments). Representative data are shown in Fig 3.

rhIL-1 and rhIL-6 have no demonstrable direct effect on hematopoietic activity. Liquid cultures containing either rhIL-1 or rhIL-6 were not significantly different from controls (data not shown). Neither cytokine induced eosinophil colonies, although each increased the number of GM colonies in one of three experiments (Table 2).

Comparison of the time course of eosinophil production. Table 1 summarizes the action of rhIL-5 on bone marrow from ten donors. When cultured in RPMI and FCS alone, cells of the neutrophil and monocyte lineages were progressively lost. After 3 weeks in culture only macrophages and lymphocytes remained viable. Eosinophil production induced by rhIL-5 was first detectable after seven days, and

<table>
<thead>
<tr>
<th>Expt Stimulus</th>
<th>Colony Type†</th>
<th>E</th>
<th>GM</th>
<th>Mφ</th>
<th>GME</th>
<th>N</th>
</tr>
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<tr>
<td>1 None</td>
<td>1.5 ± 1.5 µL</td>
<td>12.5 ± 1.5</td>
<td>1.0 ± 0.5</td>
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<td>0</td>
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<td>IL5 5.5 ± 1.5 µL</td>
<td>11 ± 2</td>
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<td>IL3 15.5 ± 0.5 µL</td>
<td>29.5 ± 2.5 µL</td>
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<td>12.5 ± 1.5 µL</td>
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<td>GMCSF 3 ± 2</td>
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<td>4 ± 0</td>
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<tr>
<td>2 None</td>
<td>0.3 ± 0.5 µL</td>
<td>1 ± 1</td>
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<tr>
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<td>2.5 ± 0.5</td>
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<td>IL6 0</td>
<td>4 ± 1</td>
<td>1.5 ± 0.5</td>
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<tr>
<td>3 None</td>
<td>24 ± 12</td>
<td>0.8 ± 0.4</td>
<td>1.6 ± 1.1</td>
<td>31 ± 12</td>
<td>0</td>
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<tr>
<td>IL5 32 ± 9 µL</td>
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<td>GMCSF 97 ± 6 µL</td>
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<td>13 ± 4</td>
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<tr>
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<td>2 ± 0</td>
<td>23.5 ± 8</td>
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Data are representative of three separate experiments. *Full titration curves were carried out with each factor. Only representative data from optimal dilutions are shown. †Number of colonies per culture (8 × 10⁵ cells). Results are expressed as mean ± 1 SD of duplicate cultures. ‡Indicates a value significantly greater than controls (P < .05). Abbreviations: E, eosinophil; GM, neutrophil granulocyte-macrophage; Mφ, macrophage; GME, neutrophil granulocyte-macrophage-eosinophil; N, neutrophil colony.

Table 2. Effect of the Panel of Cytokines on Colony Production

![Fig 1. Dose response of eosinophil production by rhIL-5 on human and murine bone marrow. Maximal responses in the different assays were human liquid culture eosinophil production (C), 8 × 10⁵ eosinophils/mL; semisolid culture (E), 33 colonies; human (L) and murine (A) eosinophil peroxidase assays A₅₄₀ nm 1.94, 50% end points were 1:49, 1:2884 χ 1:22430, and 1:1797, respectively. Mean ± 1 SD duplicate cultures.](image1)

![Fig 2. Dose response of colony production by rhIL-3 and rhGMCSF. Control cultures supported 10.5 ± 2 neutrophil granulocyte-macrophage (GM) colonies but no eosinophil (E), neutrophil (M), macrophage (M), or mixed GM-E colonies. N and M colonies were not stimulated and are not plotted. Maximal responses were for rhGMCSF, 26 ± 1 GM, 39 ± 1 M, 17 ± 3 GME colonies; for rhIL-3, 18.5 ± 4 GM, 76 ± 3 E, and 31 ± 1 GME colonies. Mean ± 1 SD duplicate cultures.](image2)
Each panel represents data from a different bone marrow donor. rhIL-3 and rhGMCSF at optimal dilution has a similar time course.

REGULATION OF HUMAN EOSINOPHILS BY CYTOKINES

Fig 3. Eosinophil production in liquid culture by rhIL-5, mIL-5, rhIL-3, and rhGMCSF at optimal dilution has a similar time course. Each panel represents data from a different bone marrow donor.

reached a peak after 21 days, when 50% to 86% of the total cells were eosinophils. Eosinophils remained the predominant cell type when cultures were maintained for a further 4 weeks. Although the absolute eosinophil count fell, those remaining were more than 95% viable by trypan blue exclusion.

The time course of eosinophil production by mIL-5, rhGMCSF, and rhIL-3 was similar to that of rhIL-5 (Fig 3). As eosinophil production by all these factors was generally maximal after 21 days in culture, this time point was used when comparing the interaction between the panel of cytokines.

Factors affecting eosinophil clusters. The effect of optimal doses of the cytokines on eosinophil clusters (inclusive of colonies) is shown in Table 3. The absolute numbers of eosinophil clusters and colonies (Table 4) formed in response to the same cytokine varied significantly (P < .001) between donors, but this variation did not affect the actions or interactions of the cytokines. rhIL-5 did not significantly alter the total cluster number either alone or in combination with any of the other cytokines (Table 3), but it did increase the size of the clusters. In six separate experiments, 93% (range 70% to 100%) of clusters present in control cultures (marrow cultured in RPMI/FCS alone) contained less than 20 eosinophils, and none had more than 30 cells. In the presence of rhIL-5 only 23% (9% to 38%) of clusters contained less than 20 cells, 29% (14% to 41%) between 20 and 40 cells, and 48% (21% to 77%) were colonies of more than 40 cells.

rhIL-3 and rhGMCSF increased eosinophil cluster numbers by twofold to sixfold, but rhIL-1 and rhIL-6 had no significant effect. In one experiment rhIL-6 induced a small (10% to 40% increase, but this effect was not observed in two other experiments and analysis of the full data failed to show a significant effect of rhIL-6 (P > .02).

Interaction between rhIL-5 and the other cytokines. The interactions of the cytokines with rhIL-5 on eosinophil colony formation in four experiments is shown in Table 4. In all the experiments, the effect of coculturing an optimal dose of rhIL-5 with either rhIL-3 or rhGMCSF was to increase the numbers of eosinophil colonies supported by either rhIL-3 or rhGMCSF alone. The interaction was additive, not synergistic, and was also observed when suboptimal doses of rhIL-3 or rhGMCSF were cocultured with an optimal dose of rhIL-5 (Fig 4A). rhIL-5 did not affect the numbers of eosinophil clusters (Table 3) or other colony types stimulated by the other cytokines (data not shown).

There is also an additive effect of rhIL-5 when combined with rhIL-3 in liquid culture (Fig 4B). However, this interaction was not seen when rhIL-5 was combined with rhGMCSF: eosinophil production was the same as that in cultures containing rhIL-5 alone. Moreover, rhGMCSF did not enhance eosinophil production in cultures already containing rhIL-5 and rhIL-3.

Neither rhIL-1 nor rhIL-6 altered the production of eosinophils induced by rhIL-5 or rhIL-3 in either liquid (data not shown) or semisolid cultures (Tables 3 and 4).

Morphologic features of eosinophils cultured in vitro. Whether induced by rhIL-5, rhIL-3, or rhGMCSF, eosinophils at 14 days of culture had the typical light microscopic appearance of promyelocytes. Thereafter they progressively developed the features of myelocytes, and then metamyelocytes, until more than 80% of the eosinophils were of mature morphology after 5 weeks in culture.

These light-microscopic observations were confirmed by electron microscopy. Day 14 eosinophil promyelocytes induced by rhIL-5 were from 13 to 21 μm in diameter, with characteristic eccentrically placed globular nuclei with diffuse chromatin and prominent nucleoli (Fig 5A). There were numerous dilated cisterna of the endoplasmic reticulum (ER), prominent Golgi zones, and numerous large mitochondria. The immature granules appeared as membrane-limited

| Table 3. Effect of Cytokines on the Frequency of Eosinophil Clusters |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                   | None            | rhIL-3          | rhGMCSF         | rhIL-1          | rhIL-6          | rhIL-1 + rhIL-3  | rhIL-6 + rhIL-3  |
| Donor             |                 |                 |                 |                 |                 |                 |                 |
| 1                 | 54              | 55              | 219             | 212             | 79              | 67              | 62              | 59              |
| 2                 | 19              | 27              | 53              | 69              | 44              | 48              | 27              | 35              | 26              | 34              | 90              | 74              |
| 3                 | 70              | 85              | 209             | 229             | 135             | 35              | 81              | 94              | 99              | 247             | 278             |
| 4                 | 56              | 100             | 353             | 316             | 288             | 231             | 128             | 141             | 86              | 92              | 288             | 362             | 233             | 237             |

Data are the number of clusters after culture of 8 x 10^4 cells for 14 days with optimal dilutions of the cytokines. The mean of duplicate cultures are quoted. 1 SD was 5% to 15% of the mean.

Results of analysis of variance (NS, not significant): Donor (P < .001); rhIL-5 (NS); Cytokine (P < .001) due to rhIL-3 (P < .01), rhGMCSF (P < .05), rhIL-1 (NS), and rhIL-6 (NS).
vacuoles partially filled with flocculent electron-dense material. Most of these granules (Fig 5B) were spherical and quite large (1.3 ± 0.3 μm in diameter).

After 3 weeks the eosinophils had developed into characteristic myelocytes. The nuclei were kidney shaped, granules smaller (0.3 to 1 μm in diameter) and completely filled with homogeneous electron-dense material with cores and peripheries of different densities, although a few vacuolar granules remained (Fig 5C, D). The Golgi zones and ER were still active and mitochondria frequent.

The mean dimensions of mature cells present after 5 weeks in culture were 8 to 11 μm (Fig 5E). Their nuclei were bi- or tri-lobed, devoid of nucleoli with condensed peripheral chromatin connected by thin chromatin strands. There were minimal nondilated cisterna of ER and general loss of Golgi zones. The granules were small (0.1 to 0.9 μm in diameter), but continued to have electron dense cores with less dense matrices. No “secondary” granules with crystalline cores were seen (Fig 5F). Eosinophils produced by other cytokine combinations were morphologically indistinguishable, and in none of the preparations were crystalline cores present (Fig 6).

**DISCUSSION**

We demonstrate that rhIL-5, rhIL-3, and rhGMCSF all stimulate eosinophil production in both liquid and semisolid bone marrow cultures, but only rhIL-5 is selective for the eosinophil lineage. It has been reported that IL-5 induced mixed eosinophil/basophil and eosinophil/erythroid colonies in addition to pure eosinophil colonies in human bone marrow cultures. In 13 separate experiments we found that rhIL-5 acts specifically on the eosinophil lineage at all concentrations. All the colonies supported by rhIL-5 were composed entirely of cells staining as eosinophils, no mixed colonies were present, and rhIL-5 did not affect other cell lineages in liquid cultures.

These results reveal similarities between eosinophil production and the regulation of the neutrophil lineage. Neutrophils can be stimulated nonselectively by rhIL-3 and rhGMCSF, and selectively by granulocyte CSF. rhIL-5 is the analogous selective cytokine for the eosinophil lineage. Furthermore, there is a similarity in the concentration requirements for rhIL-3 and rhGMCSF toward the individual lineages. The optimal concentration for neutrophil colonies is higher than for mixed colony types, and a similar pattern is now shown for eosinophil colony production (Fig 2).

The time course of eosinophil maturation induced by each of the three cytokines was similar, and morphologically mature eosinophils were produced in the absence of other factors. These data do not support the claim that maturation of eosinophils may require factors other than IL-5.

These experiments showed a peak of eosinophil production at 3 weeks, with mature eosinophils not developing until after 4 to 5 weeks in culture. Although our studies with murine cultures have not been so detailed, the persistence in culture of eosinophils with “doughnut” nuclei suggest that final

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### Table 4. Effect of Cytokines on the Frequency of Eosinophil Colonies

<table>
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<tr>
<th>Cytokine</th>
<th>+/−rhIL-5</th>
<th>rhIL-3</th>
<th>rhGMCSF</th>
<th>rhIL-1</th>
<th>rhIL-6</th>
<th>rhIL-1 + rhIL-3</th>
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Data are the number of colonies after culture of 8 × 10⁴ cells for 14 days with optimal dilutions of the cytokines. The mean of duplicate cultures are quoted. 1 SD was 5% to 15% of the mean.

Results of analysis of variance (NS, not significant): Donor (P < .001), rhIL-3 (P < .01), Cytokine (P < .001) due to: rhIL-3 (P < .001), rhGMCSF (P < .05), rhIL-1 (NS), and rhIL-6 (NS).
maturation may be delayed in that system as well. This appears to contrast with the rapid appearance of mature eosinophils in vivo. Eosinophilia appears 1 to 2 weeks after ingestion of food infested with *Trichinella spiralis* and peaks at the end of the third week.²⁸ Herion²⁹ and Stryckmans³⁰ suggested a mean marrow transit time of nine days and a postmitotic transit time of 2.5 days in normal subjects and patients with eosinophilia. While this difference is not understood, margination from tissue pools also contributes to blood eosinophilia in vivo, and so the kinetics are not directly comparable. It is also interesting to note that although maturation may be delayed in vitro, development of functional activity is not.²³

It has been postulated from observations of marrow aspirates²²,²³ that dense "primary" eosinophil granules in myelocytes result from condensation of the flocculent contents of the membrane-lined vacuoles present in promyelocytes. Primary granules were then thought to develop into the smaller "secondary" granules usually seen in circulating mature eosinophils, which have crystalloid cores. We have followed the differentiation of granules and confirm that primary granules first appear as vacuoles containing flocculent material. Like Scott and Horn,³³ we did not see dense material resembling granule matrix in the Golgi lamellae. Although the vacuoles occasionally resembled adjacent areas of dilated ER, the origin of these granules remains unclear.

The granules present in the mature cells were similar in size to mature secondary granules (0.45 ± 0.17 μm),³⁴,³⁵ but none of the cytokines produced granules with classical crystalline cores. A few had lamellae parallel to the granule surface, which might be an early stage of crystallization.³⁶ The crystalloid core of mature granules contains major basic protein (MBP),³⁷,³⁸ and MBP is present in the granules of eosinophil myelocytes induced in vitro by both rhIL-5 and rhIL-3.³⁷ As these eosinophils exhibit normal functional activity,² it is possible that this "abnormal" appearance of
In an attempt to unravel the activity of these different cytokines, their ability to induce eosinophils in liquid and semisolid cultures was assessed. It should be noted that the same medium is used in both systems, the only differences being the presence of agar in the semisolid medium and the number of cells (liquid, $10^7/100 \mu L$; semisolid, $2 \times 10^7/400 \mu L$). Because of donor to donor variation, we have tested the different cytokines with marrow from at least three different patients and performed multiple variant statistical analysis before testing for differences between the cytokines by paired $t$ tests.

Semisolid cultures allow assessment of numbers of individual precursors (number of eosinophil clusters) and their proliferative potential (size of cluster), with colonies being defined as large clusters containing more than 40 cells. Liquid cultures allow estimation of the total number of eosinophils produced.

rhIL-5 does not cause an increase in the small number of eosinophil clusters present in control cultures. This, the transience of the eosinophil production in vitro described here and previously, and the observation that murine IL-5 does not support eosinophil colony formation by spleen cells from mice pretreated with 5-fluoro-uracil, suggests that rhIL-5 has little or no effect on the commitment of stem cells to the eosinophil lineage. This therefore differs from the effects of rhIL-3 or rhGMCSF, which do increase the number of eosinophil clusters (Table 3).

rhIL-5 causes eosinophil proliferation, increasing the size of the clusters with a significant proportion being defined as colonies. However, both rhIL-3 and rhGMCSF stimulate the production of more colonies than rhIL-5. This would suggest that rhIL-5 is active on a smaller pool of precursors than either rhIL-3 or rhGMCSF. In contrast, rhIL-5 stimulates the production of more eosinophils in liquid cultures than either rhIL-3 or rhGMCSF. These contrasting data from the two different culture systems are quite clear and appear to indicate that while rhIL-5 may act on fewer precursors than rhIL-3 or rhGMCSF, it might cause more proliferative steps in liquid culture and so produce more eosinophils.

Apart from the suggestion, discussed above, that rhIL-5 may not be active on the production of committed eosinophil progenitors from stem cells, these experiments do not address early stages of differentiation. While rhIL-3 and rhGMCSF increase the total cluster numbers compared with control cultures, this increase may result from existing precursor cells, which do not proliferate in either control or rhIL-5-containing cultures. Cytokine coculture experiments revealed that rhIL-5 enhanced the eosinophil production induced by the other cytokines (numbers in liquid culture and colonies), again without altering the total cluster numbers. In all cases, eosinophil production was only increased to the sum of that induced by the individual factors alone; i.e., the interaction between rhIL-5 and the other cytokines was additive, not synergistic. These data suggest that rhIL-5 acts on a subpopulation of eosinophil precursor cells. The additive effect of rhIL-5 on colony numbers suggests that within the total cluster-forming population rhIL-3 and rhIL-5 act on different colony-forming populations. IL-1 and IL-6 act synergistically with other cytokines on
early murine progenitors, but there are no previous reports on the effect of rhIL-6 specifically on either murine or human eosinophilopoiesis. We demonstrate that neither rhIL-1 nor rhIL-6 stimulate eosinophil production from unfractionated human marrow, either alone or in combination with rhIL-3 or rhIL-3.

The role of cytokines in the production of eosinophilia is not clear. Further experiments are being carried out with sequential culture of the different cytokines to assess their activity in the generation of eosinophil progenitor cells.

However, there remains an unsolved paradox. If rhIL-3 or rhGMCSF play a significant role in the production of eosinophils, how is eosinophilia achieved without a concomitant increase in neutrophils and macrophages? rhIL-5 can provide the biological specificity, but seems unable to generate its own precursors.

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Human interleukin-5 (IL-5) regulates the production of eosinophils in human bone marrow cultures: comparison and interaction with IL-1, IL-3, IL-6, and GMCSF

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