Susceptibility of Monocytes to Lymphokine-Activated Killer Cell Lysis: Effect of Granulocyte-Macrophage Colony-Stimulating Factor and Interleukin-3

By Julie Y. Djeu, Raymond Widen, and D. Kay Blanchard

Cultured human monocytes have been shown to be susceptible to lysis by autologous lymphokine-activated killer (LAK) cells. To determine factors that might modulate the sensitivity of monocytes to lysis, we cultured adherent peripheral blood leukocytes (PBL) in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin-3 (IL-3) since these cytokines have been reported to affect both functional and physical characteristics of monocytes. Both recombinant human GM-CSF and IL-3 were found to significantly enhance the susceptibility of monocytes to lysis by LAK cells in a dose-dependent manner, with GM-CSF being slightly more effective. In a kinetics study, the lysability of monocytes increased after two days of incubation with either cytokine, with maximal susceptibility occurring after four to six days of culture. The effects of GM-CSF and IL-3 appeared to be specific for monocytes since culture of either nonadherent cells or granulocytes, which are normally resistant to LAK-mediated lysis, did not induce sensitivity. While the effects of GM-CSF and IL-3 have been shown to be synergistic in some cases, they did not act synergistically to induce monocyte susceptibility to LAK lysis. In cold target experiments, cytokine-treated monocytes reciprocally blocked lysis, suggesting that similar target structures were modulated with either factor. FACS analysis and sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) demonstrated comparable modulation of surface antigens with either GM-CSF or IL-3. Thus, these cytokines can serve to augment susceptibility of monocytes to LAK cells, emphasizing the complex interactions that occur in the immune system.

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ity of monocytes to LAK lysis, and thus provide clues to the antigenic structure(s) on monocytes recognized by LAK cells, we cultured human monocytes in the presence of GM-CSF and IL-3. The present study demonstrates that these cytokines render monocytes significantly more susceptible to LAK lysis than monocytes cultured in medium alone.

MATERIALS AND METHODS

Preparation of human leukocytes. Leukocyte buffy coats, obtained from normal volunteers at the Southwest Florida Blood Bank, were diluted 1:2 in phosphate buffered saline (PBS) (M.A. Biologics, Walkersville, MD) and layered on 10 mL of Ficoll-Hypaque solution (Pharmacia, Piscataway, NJ). After centrifugation at 400 g for 20 minutes at room temperature, the band of peripheral blood leukocytes (PBL) at the interphase was collected and washed twice with PBS. PMN were collected by aspirating the band of cells lying on the surface of the RBC pellet. RBC were lysed by the addition of sterile distilled water for 20 seconds followed by 10 x 10^6 cells to a final concentration of 1 x 10^6 cells. The washed PBL and PMN were suspended in RPMI 1640 medium (GIBCO Laboratories, Grand Island, NY) containing 5% heat-inactivated human AB serum (Flow Laboratories, McLean, VA), 10 mmol/L glucose, 100 U/mL penicillin, 100 mg/mL streptomycin, 5 mmol/L HEPES buffer (GIBCO), and 5 x 10^-4 mol/L 2-mercaptoethanol (Sigma Chemical Co, St Louis), and will subsequently be referred to as complete medium. Plasticware was purchased from COSTAR (Cambridge, MA). Recombinant human GM-CSF (specific activity of 4 x 10^9 colony-forming units [CFU] per milligram of protein) and recombinant human IL-3 (sp act, 4 x 10^5 cfu/mg) were very generous gifts from ImmuneX Corp, Seattle.

Preparation of monocytes. PBL were allowed to adhere to tissue culture flasks for one hour at 37°C. Nonadherent cells (NAC) were recovered by vigorous washing of the flasks with warm medium, and the adherent cells were cultured for one to seven days with fresh medium, as previously described. Adherent cells were then washed twice with PBS and added to effector cells at 10^6 cells/mL in 5 to 10 mL of the indicated cytokine-treated and untreated monocyte target cells. Cells were then indirectly labeled with fluorescein-conjugated goat anti-mouse Ig and analyzed on the FACSscan flow cytometer (Beckton-Dickinson, Mountain View, CA). Reagents were obtained from Beckton-Dickinson, unless specified. Anti-HLA-A,B,C antibodies were obtained from AMAC, Inc (Westbrook, ME) and FcgRI (clone 32.2). FcgRII (clone IV-3), and FcgRIII (clone 3G8) were a generous gift from Dr M.W. Fanger (Dartmouth Medical School, Hanover, NH).

SDS-PAGE analysis of monocyte membrane proteins. For each cytokine, 5 x 10^6 monocytes were treated as described, washed in PBS, and suspended in suspension medium containing 50 mmol/L Tris-HCl, pH 8.0, with 0.1 mmol/L PMSF and 1 mmol/L EDTA. Cells were sonicated using a Branson sonicator at 40% maximal energy with three 10-second bursts. Cells were confirmed to be lysed by examination using trypan blue exclusion. Membranes were collected and washed twice with centrifugation at 17,000 g at 4°C in the disruption medium. The membranes were then solubilized by incubation at 4°C for one hour in a buffer containing 10 mmol/L Tris-HCl, pH 7.8, 140 mmol/L NaCl, 10 mmol/L CHAPS, and 0.1 mmol/L PMSF and 1 mmol/L EDTA as protease inhibitors. Particulate debris was removed by centrifugation at 16,000 g for ten minutes and the supernatants were treated with SDS and 2-mercaptoethanol as described. Proteins were separated by electrophoresis on a 10% acrylamide slab gel and were visualized by staining with 0.25% Coomassie blue. Membrane preparations from identical numbers of cells from each treatment were examined both for induction of novel proteins as well as differences in the expression of existing antigens.

Measurement of cytotoxicity. A five-hour 3Cr-release assay was used to measure the cytotoxicity of IL-2-activated LGL against autologous cytokine-treated or untreated monocytes. Monocytes were labeled with 400 μCi of sodium [3Cr] chromate (Amersham Corp, Arlington Heights, IL) for two hours in 0.5 mL of medium, as described for fresh tumor targets. The cells were then washed twice and incubated an additional 30 minutes in 5 mL of medium. Target cells were then washed twice more and then added to effector cells at 5 x 10^6 cells/well, resulting in effector:target ratios ranging from 20:1 to 2.5:1 in a final volume of 0.2 mL in each well. After five hours incubation at 37°C, the culture supernatants were harvested by removing 0.1 mL of the fluid to be counted in a gamma counter. Maximum isotope incorporated was determined by counting target cells alone, and spontaneous release was measured by counting supernatants of targets incubated with medium alone. The percentage of specific lysis was calculated by the formula: [(experimental cpm – spontaneous cpm)/maximal cpm incorporated] x 100. All determinations were done in triplicate. The SEM of all assays was calculated and was typically 5% of the mean or less. Lytic units (LU) were calculated and were defined as the number of effector cells required to lyse 20% of 5 x 10^6 target cells. Paired t tests were performed to determine significant differences between the lysis of cytokine-treated and untreated monocyte target cells.

RESULTS

FACS analysis of cytokine-treated monocytes. To determine the effects of GM-CSF and IL-3 on the phenotype of treated monocytes, FACS analysis was performed on IL-3- and GM-CSF-treated and untreated monocytes using a panel of monoclonal antibodies that identify various monocyte and macrophage antigens. The results are shown in Fig 1 and 2. After incubation with GM-CSF or IL-3, monocytes had a higher expression of HLA-DR, which is an indication of the activation status of monocytes. On the other hand, expression of HLA-A,B,C, which is MHC class I antigen,
Fig 1. FACS analysis of monocytes. I. MHC antigens. Monocytes were cultured in medium alone or in the presence of 1,000 U/mL of GM-CSF or IL-3 for four days before being stained with the indicated monoclonal antibodies for FACS analysis. Control graphs represent analysis of monocytes with the indirect stain, FITC-labeled goat anti-mouse antibodies, alone. Abscissa is the number of cells counted and the ordinate is the intensity of stain as measured by relative fluorescence units (RFU). (x indicates mean RFU).

was slightly decreased after incubation with either cytokine. As seen in Fig 2, the expression of Leu M5, which is a tissue macrophage marker, is markedly enhanced, indicating that both GM-CSF and IL-3 induced differentiation of monocytes to macroage-like cells in culture. Also the expression of all three Fc-gamma receptors were likewise enhanced. These receptors bind different forms of monomeric and oligomeric IgG and appear to play a critical role in triggering effector functions of human monocytes. Thus, GM-CSF and IL-3 appeared to similarly modulate several of the differentiation markers and class I and II MHC antigens on monocyte/macrophages.

Dose response to GM-CSF and IL-3. In preliminary experiments using a variety of cytokines to determine their effects on the susceptibility of monocytes to lysis by autologous LAK cells, we found that monocytes, cultured for three days in the presence of 1,000 units of GM-CSF per milliliter, were more sensitive to LAK lysis than monocytes cultured in medium alone. To further examine this effect, various dilutions of GM-CSF were added to monocyte cultures, incubated for four days, and the cells were assessed for their susceptibility to LAK lysis in a five-hour 51Cr-release assay. Recombinant human IL-3 was also assessed for its effect since this cytokine has similar properties as GM-CSF. The results are shown in Fig 3. Monocytes cultured in medium with 1,000 U/mL of GM-CSF or IL-3 were significantly more sensitive to lysis than monocytes cultured in medium alone, with as little as 10 U/mL eliciting some response. The induction of maximal sensitivity to lysis occurred after treatment of monocytes with 1,000 to 3,000 U/mL of GM-CSF or IL-3, with GM-CSF being slightly, though not significantly, more efficient.

Finally, cytokine-treated monocytes were not lysed by fresh LGL or LGL that had been incubated in medium alone without IL-2 (data not shown). Thus, IL-2 was required to induce LAK activity against IL-3- or GM-CSF-treated monocytes and cytokine treatment did not render monocytes susceptible to spontaneous NK activity associated with fresh LGL.

Kinetics of cytokine-mediated effects on monocytes. To determine the period of incubation with GM-CSF or IL-3 required to induce enhanced susceptibility, experimental cultures of monocytes were incubated for six days and 1,000 U/mL of GM-CSF or IL-3 was added at various times during their culture. As shown in Fig 4, monocytes that had been cultured in the presence of either cytokine for four to six days acquired maximal sensitivity to LAK lysis. Monocytes cultured for six days in medium alone or to which GM-CSF or IL-3 was added for the last day of incubation did not demonstrate increased susceptibility. Thus, at least two days of incubation with either cytokine was required to induce sensitivity. Monocytes appeared to respond more rapidly to GM-CSF than IL-3 although levels of susceptibility after six days of stimulation with these factors were similar.

Specificity of the effect of GM-CSF and IL-3. Since both cytokines are known to modulate functional activity and differentiation of both monocytes and granulocytes, the effect of GM-CSF and IL-3 on the susceptibility of granulocytes to LAK lysis was of interest. We have previously reported that granulocytes were not susceptible to LAK-mediated lysis, in contrast to monocytes, but treatment with GM-CSF or IL-3 might alter this resistance. The results in Table 1 indicate that treatment of granulocytes with 1,000 U/mL of GM-CSF or IL-3 did not render these
cells susceptible to lysis, even after three days of incubation. It should be noted that the viability of cytokine-treated and untreated granulocyte suspensions was 85% or greater after incubation. To further define the specificity of the effects of GM-CSF and IL-3, NAC, which were recovered after plastic adherence of PBL to remove monocytes, were also incubated with either cytokine for three days. As shown, both treated and untreated NAC were resistant to LAK-mediated lysis.

Cold-target inhibition of LAK activity. In an effort to examine the mechanism of lysis of cytokine-treated monocytes, cold-target inhibition studies were performed. Unlabeled cells were added to cytotoxicity assays to determine whether competition occurred with radiolabeled target cells for recognition sites on LAK effector cells. As shown in Fig 5, unlabeled monocytes effectively blocked the lysis of radio-labeled, untreated monocytes, but only minimally blocked the lysis of cytokine-treated monocytes. Cold GM-CSF-treated monocytes were found to successfully compete with all targets tested, including IL-3-treated monocytes. Likewise, cold IL-3–treated monocytes comparably blocked the lysis of GM-CSF– or IL-3–treated monocytes and untreated monocytes.

Lack of synergy between GM-CSF and IL-3. Since IL-3 and GM-CSF synergize with respect to their ability to induce colony formation from bone marrow the possibility that these cytokines synergistically enhance the susceptibility of monocytes to LAK lysis was examined. Monocytes
Fig 3. Dose response of monocytes to GM-CSF and IL-3. Monocytes were incubated for four days in the presence of the indicated concentration of either GM-CSF (○) or IL-3 (●) before being used as targets for LAK cells. The mean ± SEM of triplicate determinations is shown. Asterisks indicate statistically significant (P < .05) determinations compared with control target cells cultured in the absence of GM-CSF or IL-3.

Fig 4. Time response to cytokine treatment. Monocytes were incubated for six days and 1,000 U/mL of GM-CSF (○) or IL-3 (●) were added at various times during culture. Days of incubation indicates length of time that monocytes were incubated in the presence of cytokines during the six-day culture. Asterisks indicate statistically significant (P < .05) determinations compared with control target cells cultured in the absence of GM-CSF or IL-3 (0 days of incubation).

Table 1. Specificity of Effect of GM-CSF and IL-3

<table>
<thead>
<tr>
<th>Target</th>
<th>Treatment</th>
<th>% Specific Lysis + SEM at E:T Ratios of:</th>
<th>20:1</th>
<th>10:1</th>
<th>5:1</th>
<th>LU/10⁶ Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocyte</td>
<td>None</td>
<td>12.7 ± 1.5</td>
<td>9.1 ± 1.0</td>
<td>5.2 ± 0.5</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>20.1 ± 1.5</td>
<td>13.2 ± 0.7</td>
<td>8.4 ± 0.7</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-3</td>
<td>19.4 ± 1.9</td>
<td>15.0 ± 0.9</td>
<td>9.7 ± 0.5</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>NAC</td>
<td>None</td>
<td>-0.9 ± 0.8</td>
<td>-1.4 ± 0.5</td>
<td>-2.5 ± 1.0</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>-0.6 ± 0.4</td>
<td>2.4 ± 0.6</td>
<td>-1.2 ± 0.3</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-3</td>
<td>2.2 ± 0.9</td>
<td>1.3 ± 0.4</td>
<td>1.4 ± 0.5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>PMN</td>
<td>None</td>
<td>-0.7 ± 0.3</td>
<td>-4.3 ± 1.1</td>
<td>1.9 ± 0.4</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
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<td>-2.9 ± 1.1</td>
<td>-2.6 ± 0.9</td>
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<tr>
<td></td>
<td>IL-3</td>
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<td>0.8 ± 0.7</td>
<td>-4.3 ± 2.0</td>
<td>&lt;2</td>
<td></td>
</tr>
</tbody>
</table>

Cells were incubated with the indicated cytokine at 1,000 U/mL for three days before their use as target cells for LAK cells. Shown is a representative experiment of four that were performed with similar results.
Fig 5. Cold-target inhibition. The indicated monocytes were labeled with $^{81}$Cr and used as targets for LAK cells. Cold, unlabeled monocytes were added to the wells of cytotoxicity assays in the indicated I:T ratios and were assessed for their ability to competitively inhibit lysis of the respective radiolabeled targets. For each target, the percent inhibition by control monocytes (○), monocytes + GM-CSF (●), and monocytes + IL-3 (▲) was assessed. The E:T ratio was held constant at 20:1. Monocytes were cultured for four days in medium alone or in the presence of 1,000 U/mL GM-CSF or 1,000 U/mL of IL-3 before assay.

were incubated for four days in the presence of sub-optimal concentrations of both cytokines and assessed for their sensitivity to LAK cells. As seen in Table 2, the effect of GM-CSF and IL-3 was additive instead of synergistic. The combination of 1 or 10 U/mL of either cytokine resulted in minimally detectable induction of sensitivity, while 100 U/mL of either GM-CSF or IL-3 as a positive control was capable of rendering monocytes significantly more susceptible to lysis. These results suggest that both cytokines act in a similar manner on monocyte susceptibility.

**SDS-PAGE analysis of monocyte membranes.** Since GM-CSF and IL-3 were found to enhance the lysability of monocytes, the possibility that these cytokines modulated a putative target structure(s) on monocytic target cells was explored. FACS analysis of cytokine-treated monocytes indicated the up-regulation of several monocyte-linked surface antigens, and to further examine membrane proteins of treated and untreated cells, SDS-PAGE was performed. For each treatment, membranes from an equivalent number of cells were solubilized and electrophoresed. As shown in Fig 6, the intensity of Coomassie blue stain in the GM-CSF- and IL-3-treated membranes exceeded that of untreated monocytes, with some of the bands appearing disproportionately darker. This correlated with FACS analysis of all of the surface markers assessed in that intensity of each were

| Table 2. Effect of IL-3/GM-CSF Combinations on Monocyte Susceptibility |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| GM-CSF (U/mL) | IL-3 (U/mL) | % Specific Lysis ± SEM at E:T Ratios of: |
| 20:1 | 10:1 | 5:1 | LL/10^7 Cells |
| 0 | 0 | 16.3 ± 1.3 | 9.7 ± 1.0 | 4.7 ± 0.4 | 43 |
| 1 | 0 | 15.9 ± 0.3 | 12.6 ± 0.8 | 6.4 ± 0.6 | 51 |
| 10 | 0 | 18.7 ± 1.1 | 13.1 ± 0.6 | 7.5 ± 0.8 | 64 |
| 0 | 1 | 16.9 ± 1.2 | 10.6 ± 1.7 | 6.6 ± 0.8 | 50 |
| 0 | 10 | 20.1 ± 0.3 | 15.0 ± 0.7 | 7.1 ± 1.0 | 73 |
| 1 | 1 | 14.5 ± 1.4 | 11.7 ± 1.5 | 6.2 ± 0.5 | 46 |
| 1 | 10 | 20.0 ± 1.1 | 12.8 ± 0.8 | 10.1 ± 1.9 | 76 |
| 10 | 1 | 18.3 ± 0.3 | 13.0 ± 0.7 | 6.5 ± 1.0 | 62 |
| 10 | 10 | 21.5 ± 0.7 | 13.3 ± 0.2 | 9.6 ± 0.4 | 97 |
| 100 | 0 | 29.6 ± 2.5 | 23.1 ± 0.4 | 14.7 ± 0.6 | 262 |
| 100 | 100 | 27.1 ± 1.2 | 21.0 ± 1.0 | 12.9 ± 0.7 | 215 |

Monocytes were incubated with the indicated cytokine at the indicated concentration for four days before use as target cells for LAK effector cells. Shown is a representative experiment of three that were performed with similar results.
increased. In addition, novel bands appeared in the cytokine-treated monocytes, particularly within the high molecular weight range. Thus, the effect of IL-3 and GM-CSF on surface proteins of monocytes was twofold; some were expressed at a higher level than in untreated cells, and some novel molecules were also detected.

DISCUSSION

Our recent identification of normal human monocytes as LAK targets has prompted us to define conditions that can modulate the susceptibility of these cells to lysis. The reason for defining parameters for modulation of target cell sensitivity is twofold: (1) to find means to protect monocytes from LAK-mediated lysis, and (2) to shed some light on the nature of the monocyte surface structure(s) that form the ligand(s) for LAK recognition. Because monocytes are known to be differentiated by a number of cytokines including interferons (IFNs) and CSF, and such differentiation is usually accompanied by alteration in cell surface antigen expression, we tested the ability of these cytokines to alter monocyte susceptibility to LAK lysis. We observed that either enhanced or decreased regulation of monocyte sensitivity could be achieved, depending on the cytokine used. We first reported that culture of monocytes with IFN-gamma induced resistance to LAK lysis. Induction of resistance was detectable with as little as 10 U/mL of recombinant human IFN-gamma, and the kinetics of induction was rapid, with resistance appearing within two hours of IFN-gamma exposure. Once resistance was induced, the inability of treated monocytes to be lysed by LAK cells lasted at least three days even in the absence of IFN.

In the present study, we report that GM-CSF and IL-3 have the opposite effect on monocytes, with susceptibility significantly increased after two days of culture in the presence of these cytokines. Peak susceptibility was reached after four to five days of culture in 1,000 U/mL of either CSF. These conditions coincided with the kinetics and the presence of these cytokines. Peak susceptibility was reached after two days of culture in the presence of CSF. This is also true of lymphocytes and HLA-DR on human monocytes in a four-day culture in the presence of human AB serum. Our own analysis of surface markers induced by IL-3 or GM-CSF using flow cytometric techniques has confirmed that IL-3 can induce the same types of increases in the surface antigens of monocytes as can GM-CSF, ie, MHC class II, FcRs, and Leu M5. Because of the similarities between IL-3 and GM-CSF in parallel induction of monocyte/macrophage surface antigens and susceptibility to LAK lysis, it appears that IL-3 acts via the same mechanism as GM-CSF and may maturate monocytes among the same pathway. This speculation is supported by the similarities in proteins appearing in cytokine-treated monocyte surface membranes as demonstrated by SDS-PAGE. Additionally, the lack of synergy between IL-3 and GM-CSF in the induction of monocyte susceptibility to LAK lysis tends to suggest a common pathway in response to these factors. Interestingly, the class I MHC expression of monocytes decreased during culture with GM-CSF or IL-3 in our hands. In other studies, decreased MHC expression was correlated with augmented NK susceptibility of target cells, although a direct causal link has not been firmly established. Regardless, the correlation between decreased class I MHC expression and enhanced susceptibility to lysis can be extended to human monocytes treated with these cytokines.

Further analysis of the monocyte/macrophage target structure(s) recognized by LAK cells was performed by cold-target inhibition assays. GM-CSF-treated monocytes blocked the lysis of both treated and untreated monocyte targets. In parallel, IL-3-treated monocytes were similarly effective in their ability to serve as cold targets. Normal, untreated monocytes could block LAK lysis, but to a much lesser degree against cytokine-treated monocytes. These results suggest that IL-3 and GM-CSF either (1) upregulate the expression of a target structure on normal monocytes, or (2) induce the expression of a novel antigen that is also recognized by LAK cells. Either explanation is possible since FACS analysis and SDS-PAGE have indicated that both effects occur after treatment of monocytes with GM-CSF or IL-3. Thus, the putative target structure may be a normal differentiation antigen that is enhanced by IL-3 and GM-CSF or a new antigen that is induced de novo. Further study is required to answer these questions and may lead to a better understanding of target structures on tumor or allogeneic target cells.

The clinical relevance of enhanced susceptibility of CSF-treated monocytes to LAK lysis may be of considerable interest. While CSF have been reported to alleviate the leukopenias associated with AIDS, chemotherapy, and the myelodysplasias, the relationship between CSF and other biological response modifiers is not known. One side-effect of
IL-2/LAK adoptive immunotherapy is severe anemia, often accompanied by leukopenia, indicating an involvement in hematopoiesis. Using bone marrow cultures, IL-2 was shown to directly inhibit GM-CSF-induced colony formation, and in other studies, IL-2-activated PBL also suppressed G-M colony formation. While these LAK cells had low direct cytolytic activity against normal bone marrow cells, incubation with CSF may render these cells very sensitive to lysis, much like the response seen with monocytes. Thus, further studies are required to clearly define cytokine interactions, particularly with regard to clinical trials using multiple biological response modifiers.

REFERENCES


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Susceptibility of monocytes to lymphokine-activated killer cell lysis: effect of granulocyte-macrophage colony-stimulating factor and interleukin-3

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