Interleukin-6 induces demargination of intravascular neutrophils and shortens their transit in marrow

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Received 28 April 2000; accepted in final form 21 July 2000

Suwa, Tatsushi, James C. Hogg, Dean English, and Stephan F. van Eeden. Interleukin-6 induces demargination of intravascular neutrophils and shortens their transit in marrow. Am J Physiol Heart Circ Physiol 279: H2954–H2960, 2000.—Recombinant human interleukin-6 (IL-6) causes both a thrombocytosis and leukocytosis. The thrombocytosis is caused by an accelerating thrombopoiesis, but the mechanism of the leukocytosis is unknown. This study was designed to determine the relative contributions of marrow stimulation and intravascular demargination to the IL-6 induced neutrophilia. IL-6 (2 μg/kg), administered intravenously to rabbits, caused a biphasic neutrophilia with an initial peak at 3 h and a second peak at 9 h. Using the thymidine analog 5′-bromo-2′-deoxyuridine (BrdU) to label dividing polymorphonuclear leukocytes (PMNs) in the bone marrow, we showed that IL-6 treatment mobilizes PMNs from the marginated pool into the circulating pool at 2–6 h with a decrease in L-selectin expression on PMNs and also accelerates the release of PMNs from the postmitotic pool in the bone marrow at 12–24 h. We have concluded that IL-6 causes a biphasic neutrophilia wherein the first peak results from the mobilization of PMNs into the circulating pool from the marginated pool and the second peak results from an accelerated bone marrow release of PMNs.

INTERLEUKIN-6 (IL-6) is a 26-kDa cytokine with pleiotropic activities in both the immune and hematopoietic systems. It is produced in response to inflammatory stress and is one of the major regulators of the acute-phase response (8, 15). Elevated blood levels have been implicated in the pathogenesis of sepsis, acute respiratory distress syndrome (4), and multiorgan failure (12) as well as in chronic inflammatory conditions such as rheumatoid arthritis (21). IL-6 has also been implicated in the pathogenesis of acute and chronic vascular diseases because of its ability to stimulate the production of prothrombotic factors such as fibrinogen (24) and its platelet enhancing properties (3, 15).

IL-6 is produced by different cell types that include T cells, macrophages, and fibroblasts and mediates a wide variety of biological activities (10, 20). It enhances differentiation and proliferation of multipotential hematopoietic progenitors in vitro (11, 20, 25). It stimulates the clonal growth of granulocyte and macrophage progenitor cells (18) and the multipotential hematopoietic progenitors (11) in synergy with IL-3 in spleen cells culture. IL-6 produced by stromal cells in the bone marrow induces the proliferation and differentiation of hematopoietic cells in the marrow microenvironment (9). Therefore, IL-6 produced either in the bone marrow (9) or at distant sites and released into the systemic circulation could have a profound effect on the production and the kinetics of polymorphonuclear leukocytes (PMNs).

Several studies have reported that a single intravenous injection of IL-6 causes a thrombocytosis by stimulating thrombopoiesis (14, 22, 28), an effect with potential therapeutic potential. IL-6 also causes a leukocytosis characterized by a rapid neutrophilia (28). The present study was designed to determine the mechanisms of this neutrophilia, specifically, the contribution of marrow release of PMNs and the behavior and clearance of PMNs from the circulation by using a novel technique that was developed in our laboratory (2, 17, 26). This approach allowed us to both quantitate the effect of IL-6 on the transit time of PMNs through the bone marrow and measure their clearance from the circulating blood and reentry into the circulation from the marginated pool.

MATERIALS AND METHODS

Animals. This study was approved by the Animal Experimentation Committee of the University of British Columbia and was based on 41 female New Zealand White rabbits with an average weight of 2.2 ± 0.2 kg.

Experimental Design

Effect of IL-6 on transit time of PMNs through bone marrow. 5′-Bromo-2′-deoxyuridine (BrdU; 100 mg/kg; Sigma Chemical, St. Louis, MO) was infused into rabbits through the marginal ear veins at a concentration of 10 mg/ml in sterile saline over a period of 15 min. Twenty-four hours later, recombinant human IL-6 (2 μg/kg; lot no. 118H0227, purity >97%, endotoxin <0.1 ng/μg IL-6; Sigma) was infused through the marginal ear veins (n = 6), and control rabbits (n = 4) received an equivalent volume of saline. In this study, the costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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a dose of 2 μg/kg of IL-6 was selected on the basis of dose-response studies (22) in rabbits that produce circulating IL-6 levels similar to those in major stress such as surgery (1, 30). Blood samples (2.0 ml) were obtained from the central ear artery just before the BrdU, IL-6, or saline injection and at 0.5, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120, 144, and 168 h after the IL-6 or saline injection. Blood (1 ml) was collected in tubes containing EDTA for leukocyte counts, and an additional 1 ml was collected in tubes containing acid-citrate dextrose (ACD) for the detection of BrdU-labeled PMNs. Fentanyl (20 μg/kg) and droperidol (1 mg/kg) were administered by subcutaneous injection as sedation at each time point of blood collection.

**Effect of IL-6 on margination and demargination of PMNs.** Donor rabbits (n = 5) received an intravenous injection of BrdU (25 mg/kg) for 7 days following a protocol that labels ~80% of PMNs in donor’s blood with BrdU (2, 17). Whole blood from the donors containing BrdU-labeled PMNs was transfused to serum-compatible recipients (15 ml/kg with ACD) via the marginal ear vein over a 15-min period. One hour after this blood transfusion, the recipients received either IL-6 (2 μg/kg, n = 5) or saline (n = 5) intravenously. This time point was selected on the basis of previous studies from our laboratory that showed that BrdU-labeled PMNs reached a steady state ~1 h after transfusion (2). Blood samples were obtained just before IL-6 or saline injection and at 1, 2, 4, 6, 12, 24, and 36 h after IL-6 or saline injection.

**Leukocyte Counts**

Total white blood cell (WBC) counts were determined on a model SS80 Coulter Counter (Coulter Electronics, Hialeah, FL). Differential counts were obtained by counting 100 leukocytes in randomly selected fields of view on Wright’s-stained blood smears, and 100 PMNs were evaluated in randomly selected fields of view to determine the changes in the number of segmented and nonsegmented PMNs (band cells).

**Immunocytochemical Detection of BrdU-Labeled PMNs**

Blood collected in ACD was used to obtain leukocyte-rich plasma (LRP). Erythrocytes in the ACD blood sample were allowed to sediment for 25–30 min after the addition of an equal volume of 4% dextran (average molecular weight 162,000; Sigma) in PMN buffer. The resulting LRP was cytospun onto 3-aminopropryl triethoxysilane-coated slides by cytocentrifugation at 180 g with a Cytospin 2 (Shandon Scientific, Runcorn, UK) for 5 min. The cytospun specimens were air dried and stained using the alkaline phosphatase and anti-alkaline phosphatase (APAAP) method (2, 5) to determine the fraction of the BrdU-labeled PMNs in each specimen (2) and calculate the transit of cells through the bone marrow as previously described (26) in detail. All slides were coded and examined by investigators without knowledge of the group or sampling time, fields were selected in a randomized fashion, and 200 cells were evaluated per specimen.

**Transit Time of PMNs Through Bone Marrow**

BrdU-labeled PMNs were divided into three groups according to the intensity of nuclear staining (G1–G3) with the use of an arbitrarily designated grading system as previously described (26). Briefly, G3 cells represent myeloid cells that were in their last division in the mitotic pool when exposed to BrdU, G2 cells represent those that were in the middle, and G1 cells represent those that were in their first division. This system allowed us to calculate the transit time of cells in the different pools of the marrow. The transit times were calculated from the appearance of BrdU-labeled PMNs in the circulation over time and corrected for the disappearance of cells in the circulation with the use of a previously measured half-life ($t_{1/2}$) of 4.5 h (2).

**Disappearance of Donor BrdU-Labeled PMNs From Circulating Pool**

The number of BrdU-labeled PMNs in the circulation of each recipient was expressed as a fraction ($\%PMN$) of the total number of labeled PMNs originally infused corrected for the calculated blood volume ($V_b$) of the recipient as

$$\%PMN = \frac{PMN_{circ}}{PMN_{inf}} \times \frac{PMN_{inf} \times fraction PMN_{BrdU-recipient}}{PMN_{BrdU-infused} \times 100}$$

where $PMN_{circ}$ is the number of PMNs per milliliter of circulating blood multiplied by the calculated blood volume (ml), fraction $PMN_{BrdU-recipient}$ is the fraction of circulating PMNs that are BrdU-labeled in the recipient, and $PMN_{BrdU-infused}$ is the total number of BrdU-labeled PMNs infused into the recipient from the donor.

**Flow Cytometry**

Blood collected in EDTA tubes was used to immunolabel circulating PMNs for the presence of surface L-selectin and CD18 with a commercially available kit (Coulter Clone, Coulter Electronics) using a whole blood method. Use of this method could avoid possible cell activation associated with purification of PMNs (32). The anti-L-selectin monoclonal antibody (mAb) DREG-200 (kind gift of Dr. E. C. Butcher, Stanford University, School of Medicine, Stanford, CA) or the anti-CD18 mAb 60.3 (kind gift of Dr. J. Harlan, University of Washington, Seattle, WA) were used, and the PMNs were labeled, as previously described (13). Analysis gates for PMNs were selected from typical forward- and side-angle light scattering, and a total of 3,000 cells/specimen were evaluated using a Profile Epics 2 flow cytometer (Coulter Electronics). Results are expressed as mean fluorescence intensity.

**Evaluation of Myeloid Cells in Bone Marrow**

To evaluate the acute effect of IL-6 on the cells in the bone marrow, 26 rabbits were killed at 24 h after treatment separately from those in the BrdU study. At 24 h after IL-6 (2 μg/kg; n = 8) or saline (n = 8) injection and 168 h after IL-6 (2 μg/kg; n = 6) or saline (n = 4) injection, all of the rabbits were killed with an overdose of pentobarbitone sodium. Bone marrow was harvested from both femurs by carefully removing the cortical bone of the femur, and marrow smear slides were prepared. Differential counts of myeloid or erythroid cells were performed on precoded May-Gruenwald-Giema-stained slides, and at least 500 cells/smear were counted using standard morphologic criteria (28).

**Statistical Analysis**

All values are expressed as means ± SE. Analysis of variance (ANOVA) for repeated measures was used for continuous data. The effect of multiple comparisons was corrected using the Bonferroni method. Transit times of BrdU-labeled PMNs and the differentiation of bone marrow cells were compared between IL-6 and control groups using Students t-test, and statistical significance was defined as a P value <0.05.
RESULTS

Effect of IL-6 on Release of PMNs From Bone Marrow

Leukocytes in circulation. Figure 1 shows that WBC, PMNs, and band cell counts were similar at baseline in both control and experimental groups and that IL-6 caused a biphasic leukocytic response characterized by a rapid increase in WBC counts that peaked 3 h after IL-6 increase (P < 0.05), with a temporary decrease at 6 h followed by a second increase at 9 h (Fig. 1A). A similar response was observed for PMNs [from 3.8 ± 0.1 × 10^9 cells/l at baseline to 7.0 ± 0.2 × 10^9 cells/l at 3 h (P < 0.05), 5.9 ± 0.1 × 10^9 cells/l at 6 h, and 6.6 ± 0.1 × 10^9 cells/l at 9 h], with a return to baseline values by 48 h (Fig. 1B). The percentage of nonsegmented PMNs (band cells) increased from 4.0 ± 0.4% at baseline to 8.5 ± 0.6% at 9 h (P < 0.05) and returned to the baseline values by 24 h (Fig. 1C). The circulating band cell counts followed the same pattern [from 1.5 ± 0.2 × 10^8 cells/l at baseline to 5.8 ± 0.5 × 10^8 cells/l at 9 h (P < 0.05)], with a return to baseline values by 36 h (Fig. 1D). WBC, PMNs, and band cell counts remained unchanged in the control group.

Release of BrdU-labeled PMNs into circulation. Figure 2 shows the appearance of BrdU-labeled PMNs in the circulation after the bolus injection of BrdU. BrdU-labeled PMNs appeared in the circulation at 24 h after labeling of the bone marrow and then rapidly rose and peaked at 24–36 h (IL-6 group) and at 48 h (control group). The number of BrdU-labeled PMNs in the peripheral blood of IL-6-treated animals was higher at 9, 12, and 24 h compared with that in blood of control animals (Fig. 2A, P < 0.05). Figure 2B shows highly stained BrdU-labeled PMNs (G3 cells), and Fig. 2C shows weakly stained BrdU-labeled PMNs (G1 cells). G3 cells peaked at 36 h in the control group and at 24 h in the IL-6 group. The earlier peak of BrdU-labeled PMNs in the IL-6 group was mostly due to the earlier release of these G3 cells. The curves for the percentage of BrdU-labeled PMNs were similar to the curves for the numbers of BrdU-labeled PMNs (data not shown). Figure 3 shows the accumulative number of all BrdU-labeled PMNs and G1 cells in the circulation (using daily measurements) over the study period. The data show that IL-6 treatment causes an increase in the pool of BrdU-labeled PMNs (P < 0.01) in the bone marrow and that this increase was mainly due to an increase in G1 cells (P < 0.01).

Table 1 shows that the transit time of the total population of BrdU-labeled PMNs through the bone
marrow was shortened by IL-6 ($P < 0.01$). This was due mainly to a reduction in the transit time through the postmitotic pool ($P < 0.01$).

**Mobilization of BrdU-Labeled PMNs From Marginated Pool**

*Circulating PMN counts.* Figure 4 shows the data from the animals that received BrdU-labeled PMNs from donor animals. The IL-6 group showed the same biphasic response in PMN counts as that shown in Fig. 1 with no response in the saline-treated control group. Figure 4B shows that, when BrdU-labeled PMNs reached steady state between the circulating and margined cells within the vascular space, the circulating blood contained $38.9 \pm 1.7\%$ of the infused BrdU-labeled PMNs in the experimental group and $40.2 \pm 1.0\%$ of those in the control group. After IL-6 treatment, the percentage of the transferred BrdU-labeled PMNs from donor animals.

### Table 1. PMN transit time through bone marrow

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>All PMNs (h)</th>
<th>G3 (h)</th>
<th>G2 (h)</th>
<th>G1 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>4</td>
<td>100.1 ± 2.7</td>
<td>60.3 ± 2.5</td>
<td>92.5 ± 5.0</td>
<td>118.4 ± 4.5</td>
</tr>
<tr>
<td>IL-6</td>
<td>6</td>
<td>84.2 ± 2.2*</td>
<td>45.5 ± 2.0*</td>
<td>70.5 ± 1.7*</td>
<td>107.9 ± 2.9*</td>
</tr>
</tbody>
</table>

All values are means ± SE; $n = \text{no. of experiments}$. All PMN, total transit time of all BrdU-labeled PMNs; G1–G3, transit time of different subpopulations of BrdU-labeled PMNs, where G3 represents transit time of PMNs through postmitotic pool; IL-6, interleukin-6. *$P < 0.01$ vs. saline-treated rabbits.
PMNs in the circulating blood increased in the experimental group by 2 h and remained above control values from 2 to 6 h \( (P < 0.05) \) (Fig. 4B). The rate of disappearance of BrdU-labeled PMNs from the circulation as measured from the slopes of these curves between 4 and 36 h was 4.75 h in the IL-6 group and 4.88 h in the control group \( (P > 0.05) \).

**Distribution of PMNs between marginated and circulating pools.** Figure 5 shows the calculated (17) total and marginated pools of BrdU-labeled PMNs in the intravascular space. Eighty-six percent of the total BrdU-labeled PMNs transferred from the donor animals remained intravascular just before IL-6 treatment. Fifty-five percent of these cells had entered the marginated pool, and forty-five percent were in the circulation. The decrease in the total number of cells in the vascular space was calculated by using the \( t_{1/2} \) of BrdU-labeled PMNs. After IL-6 treatment, the proportion of BrdU-labeled PMNs in the circulating pool increased from 45% to 67% (2 h) and 75% (4 h) with a corresponding decrease in the percentage of marginated cells. This indicates that IL-6 caused a major shift from the marginated to the circulating pool over this period.

**Effect of IL-6 on L-Selectin and CD18 Expression on PMNs in Circulation**

IL-6 decreased the mean fluorescence intensity of L-selectin on circulating PMNs at 3–12 h (Fig. 6A, \( P < 0.01 \)). The maximum effect was seen at 6 h after IL-6 treatment, and L-selectin levels were back to pretreatment levels at 24 h (Fig. 6A). CD18 expression was also measured as a marker of cell activation, but it did not change with IL-6 treatment (Fig. 6B).

**Effect of IL-6 on Myeloid Cells in Bone Marrow**

The bone marrow differential counts performed 24 h and 168 h after IL-6 and saline-treatment are shown in Table 2. At 24 h after IL-6 treatment, the percentage of myeloblasts and promyelocytes were approximately double that of the control group \( (P < 0.05) \). However, there was no measurable change in the number of mature neutrophils or other cell lines. The differential counts at 168 h between IL-6- and saline-treated rabbits were similar.

**DISCUSSION**

The biphasic neutrophilia following a single intravenous injection of IL-6 was first reported by Ulich and colleagues (28) in rats. These workers showed that IL-6 induced myeloid proliferation in the bone marrow, suggesting that the marrow stimulation is an important reason for the neutrophilic response following IL-6 treatment. The present study confirms this finding in
on circulating PMNs (16). The reduction in L-selectin expression is accompanied by a decrease in L-selectin levels demargination of PMNs (17) and that this demargination (27). We previously showed that steroids cause a rapid decrease in L-selectin levels, which peak 2 h after the administration of IL-6. IL-6 treatment was also associated with an increase in the size of marrow pools (Fig. 3), particularly the mitotic pool (Fig. 3B) that is supported by the increase in myeloblasts and promyelocytes observed 24 h after IL-6 treatment (Table 2). These data suggest expansion of the mitotic pool to replenish the loss from the postmitotic pool that occurs as an acute effect of IL-6 treatment. This effect of IL-6 on early myelocytes extends them by showing that the proliferative effect of IL-6 disappeared 1 wk after IL-6 treatment (Table 2).

The bone marrow response observed in these studies could be due to either a direct effect of IL-6 on the bone marrow or secondary effects of other mediators released by IL-6. The magnitude of change in PMN transit times and the increase in the size of the bone marrow pool of myeloid cells induced by IL-6 (Table 2) are greater than those produced by glucocorticoids (17). Other cytokines such as granulocyte colony-stimulating factor (G-CSF) induce IL-6 production (6, 19), but there are no reports of IL-6 inducing the release of G-CSF or other hematopoietic growth factors to account for this prominent marrow response to IL-6. Therefore, we suspect that IL-6 exerts an important effect of IL-6 treatment or a secondary effect related to an increase in circulating corticosteroids, and we postulate that it may play an important role in the demargination induced by IL-6. Alternatively, the demargination that we observed could be due to a change in deformability of PMNs because PMN deformability is one of the major determinants of PMN sequestration in the pulmonary microcirculation (29, 31).

We have used the nonisotopic thymidine analog BrdU to calculate bone marrow transit times based on a defined population of dividing myeloid progenitors being labeled in the bone marrow following a bolus injection of the tracer. This study shows that a single injection of IL-6 shortened the PMN transit time to a degree that is comparable to the effect of an inflammatory stimulus such as pneumococcal pneumonia (26).

Interleukin-6 induces an acute phase response that includes stimulation of the hypothalamic-pituitary-adrenal axis, resulting in a threefold increase in cortisol levels, which peak 2 h after the administration of IL-6 (27). We previously showed that steroids cause a rapid demargination of PMNs (17) and that this demargination is accompanied by a decrease in L-selectin levels on circulating PMNs (16). The reduction in L-selectin expression on circulating PMNs at 3–12 h. The maximum effect was seen at 6 h after IL-6 treatment, and L-selectin levels were back to pretreatment levels at 24 h.

Our data show that the first peak in circulating PMNs following IL-6 treatment is due to the mobilization of PMNs from the marginated pool (Figs. 4 and 5), and the lack of a band cell response or release of BrdU-labeled PMNs during this period confirms that the initial peak is not related to the bone marrow response. Furthermore, this demargination cannot be attributed to hemodynamic factors because IL-6 has little or no effect on hemodynamics (7).

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Table 2. Effect of IL-6 on differentiation of bone marrow

<table>
<thead>
<tr>
<th>Cells</th>
<th>1 day</th>
<th>7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline (n = 8)</td>
<td>IL-6 (n = 8)</td>
</tr>
<tr>
<td>Myeloid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>2.4 ± 0.2</td>
<td>4.4 ± 0.2*</td>
</tr>
<tr>
<td>Promyelocytes</td>
<td>1.3 ± 0.1</td>
<td>2.6 ± 0.1*</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>7.6 ± 0.6</td>
<td>6.4 ± 0.4</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>4.3 ± 0.4</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>Band cells</td>
<td>3.1 ± 0.3</td>
<td>4.1 ± 0.6</td>
</tr>
<tr>
<td>Segmented cells</td>
<td>19.0 ± 0.9</td>
<td>17.4 ± 0.7</td>
</tr>
<tr>
<td>Other</td>
<td>10.0 ± 0.7</td>
<td>5.4 ± 0.6</td>
</tr>
<tr>
<td>Lymphoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>19.0 ± 0.7</td>
<td>17.5 ± 0.6</td>
</tr>
<tr>
<td>Erythrocyte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoblasts</td>
<td>31.9 ± 1.0</td>
<td>37.6 ± 1.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.4 ± 0.2</td>
<td>1.6 ± 0.3</td>
</tr>
</tbody>
</table>

All values are means ± SE. *P < 0.05 vs. saline-treated rabbits.
primary effect on the bone marrow by releasing PMNs from the postmitotic pool and inducing accelerated myeloid turnover in the mitotic pool.

The data reported here show that IL-6 causes a rapid neutrophilia by mobilization of PMNs from the marginated pool into the circulating pool and a delayed neutrophilia by the release of PMNs from the bone marrow. We postulate that these effects of IL-6 on the bone marrow and the intravascular marginated pool of PMNs are critically important in mounting an appropriate host response, but they may also be detrimental in conditions such as septicemia and multiorgan failure, in which an excessive inflammatory response causes tissue damage.

We gratefully acknowledge Jennifer Hards and Beth Whalen for technical assistance. This work was supported by a grant from the Medical Research Council of Canada (Grant No. 4219) and the Toxic Substance Research Initiative.

REFERENCES


