We investigated the effects of stem cell factor (SCF) on the migration of murine bone marrow hematopoietic progenitor cells (HPC) in vitro using a modification of the checkerboard assay. Chemotactic and chemokinetic activities of SCF on HPC were evaluated by the numbers of HPC migrated on positive and negative gradients of SCF, respectively. On both positive and negative gradients of SCF, HPC began to migrate after 4 hours incubation, and their numbers then increased time-dependently. These results indicated that SCF functions as a chemotactic and chemokinetic agent for HPC. Analysis of types of colonies derived from the migrated HPC showed that SCF had chemotactic and chemokinetic effects on all types of HPC. When migrating activities of other cytokines were examined, interleukin (IL)-3 and IL-11 also affected the migration of HPC, but the degrees of each effect were lower than that of SCF. The results of the present study demonstrated that SCF is one of the most potent chemotactic and chemokinetic factors for HPC and suggest that SCF may play an important role in the flow of HPC into bone marrow where stromal cells constitutively produce SCF.

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**Materials and Methods**

**Cell preparation.** Female BDF mice, 10 to 15 weeks old, were obtained from Shizuoka Experimental Animal Center (Shizuoka, Japan). Bone marrow cells were flushed from femurs into α-medium (Flow Laboratories, Rockville, MD) using 26-gauge needles. Packed cells after centrifugation were treated for 3 minutes at room temperature with lysis solution containing 0.15 mol/L ammonium chloride, 0.014 mol/L sodium bicarbonate, and 0.1 × 10^{-3} mol/L disodium ethylenediamine tetraacetate acid for hemolysis of red blood cells, and washed three times with α-medium by centrifugation at 1,000×g for 30 seconds. The marrow cells were enriched for progenitors by density gradient separation and immunomagnetic selection using monoclonal antibodies with a modification of the technique described previously (hereafter referred to as Lin cells). Moreover, Lin cells were stained with fluorescein isothiocyanate (FITC)-conjugated antimouse Ly6A/E (clone D7, Sca-1) (Pharmergen, San Diego, CA) and the positive population was sorted by a FACSVantage (Becton Dickinson, Mountain View, CA) as described previously (hereafter referred to as Lin'Sca-1' cells). Anti-CD45R/B220 (RA3-6B2), CD4 (RM4-5), CD8 (53-6.72), Gr-1 (RB6-8C5), and TR119 (TER-119) were purchased from Pharmergen. Mac-1 (M1/70.15.1) was purchased from Serotec (Oxford, UK). Immunomagnetic beads (Dynabeads M-450, coated with sheep antirat IgG) were purchased from Dynal A/S (Oslo, Norway).

**Hematopoietic growth factors and antibody.** Murine recombinant-(r)SCF was a generous gift from Dr Junji Nakao (Laboratory of Molecular Genetics, The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan), and was prepared by expressing a cDNA for murine SCF in yeast cells, followed by further purification, according to the method described previously. Human IL-1α was generously provided by Dr Yoshikazu Hirai, Otsuka Pharmaceutical Research Institute, Tokyo, Japan.
Fig 1. Time course of the migration of bone marrow nucleated cells (BMNC) (A) and hematopoietic progenitor cells (HPC) (B) induced by SCF. A total of $3 \times 10^6$ BMNC placed in the upper compartment were incubated for various times (4 to 48 hours) and 100 ng/mL SCF was placed in the lower compartment (positive gradient) (B) or the upper compartment (negative gradient) (A). Control experiments (absence of SCF in both lower and upper compartment) were also performed (A). Results represent the mean ± SD of the numbers of migrated progenitor cells in triplicate cultures. A significant decrease ($P < .02$) in number of migrated BMNC was observed at 12 hours incubation in the negative gradient experiment in comparison with the control (A). Significant migration of HPC ($P < .05$) was observed in positive and in negative gradient experiments after 8 or 24 hours incubation, respectively, in comparison with controls (B). In addition, numbers of migrated HPC were significantly increased in positive gradient in comparison with negative gradient experiments ($*P < .05$, $tP < .02$, and $*P < .005$).

Co, Ltd (Tokushima, Japan). Specific activity of IL-1α was determined as $2 \times 10^7$ U/mg by the lymphocyte activation assay. Murine rIL-3 was a generous gift from Dr Atsushi Miyajima (DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, CA). Human rIL-6 (Ajinomoto Co, Inc, Kawasaki, Japan) was synthesized by *Escherichia coli* expressing a cDNA for human IL-6 followed by further purification to a specific activity of $3.6 \times 10^6$ U/mg, as estimated using the IL-6-responsive human B lymphoblastoid cell line SKW6-CL4. Human rIL-8 was generously provided by Dr Kouji Matsushima, Cancer Research Institute, Kanazawa University (Kanazawa, Japan). Human rIL-11 (Genetics Institute Inc, Cambridge, MA) expressed in *Escherichia coli* was purified to a specific activity of $2.44 \times 10^6$ U/mg. Murine rGM-CSF, with a specific activity of $5 \times 10^6$ U/mg, was kindly provided by Sumitomo Pharmaceutical Co (Hyogo, Japan). Human rG-CSF, with a specific activity of $1 \times 10^6$ U/mg, was provided by Chugai Pharmaceutical Co (Tokyo, Japan). Highly purified human urinary macrophage colony-stimulating factor (M-CSF), with a specific activity of $2 \times 10^6$ U/mg, was kindly provided by Green Cross Co (Osaka, Japan). Human rEpo (a specific activity of 150,000 U/mg), produced by Chinese hamster ovary cells transfected with a cDNA encoding human Epo, was kindly provided by Kirin-Brewery Co, Ltd (Tokyo, Japan). ACK2 was kindly provided by Dr Shin-ichi Nishikawa, Department of Pathology, Institute for Medical Immunology, Kumamoto University Medical School, Kumamoto, Japan. This monoclonal antibody (IgG2b), made by immunizing rats with murine IL-3-dependent cultured mast cells, recognizes the extracellular domain of KIT and can block blood cell formation in long-term bone marrow culture and inhibit colony growth by SCF on HPC of normal mice.

Assay of chemotaxis and chemokinesis. Chemotaxis and chemokinesis of HPC were assayed by a modification of the checkerboard assay described by Zigmond and Hirsch for the study of neutrophils. One hundred and fifty microliters of cell mixture containing $3 \times 10^5$ murine bone marrow nucleated cells (BMNC), α-medium, 5% fetal calf serum (FCS) (Hyclone Laboratories, Inc, Logan, UT), 1% crystallized deionized bovine serum albumin (BSA) (Calbiochem, San Diego, CA), and $1 \times 10^{-3}$ mol/L 2-mercaptoethanol (ME) (Eastman Organic Chemicals, Rochester, NY) was placed in the upper compartment of a Costar Transwell cell culture chamber 6.5 mm in diameter (no. 3421, Costar, Cambridge, MA) separated by a polycarbonate membrane filter (5.0 μm pore size) from a lower compartment containing 0.9 mL of medium. Various concentrations of cytokines were added to the medium in the lower compartment (positive gradient of cytokines) or the upper compartment (negative gradient of cytokines).
Chemotactic and chemokinetic effects of SCF on HPC. We first examined the time course of the migration of BMNC and HPC induced by SCF. When 100 ng/mL of SCF was added to the lower or upper compartment to generate a positive or negative gradient, respectively, the numbers of mobilized nucleated cells including lymphocytes and immature granulocytes were not significantly different between the two types of gradient, and approximately half to two thirds of the maximum number of mobilized cells had already migrated by 4 hours incubation. We found no stimulatory effects of SCF on the migration of total nucleated cells (Fig 1A). On the other hand, HPC began to migrate at 4 hours incubation whether on a positive or negative gradient of SCF, and their numbers then increased time-dependently (Fig 1B).

The number of migrated HPC on the positive gradient of SCF was greater than that on the negative gradient after 8 hours incubation (Fig 1B). In the absence of SCF, the number of migrated HPC decreased after 24 hours incubation (Fig 1B). These observations suggested that SCF functioned both as a chemotactic and chemokinetic agent for HPC, although the initiation of their migration was delayed as compared with that of other BMNC.

Types of colonies derived from the migrated HPC shown in Fig 1B were analyzed. Table 1 summarizes the proportions of each type in the colonies derived from HPC migrated on positive and negative gradients of SCF at 12 and 48 hours incubation. All types of colonies were observed in the clonal cultures of BMNC migrated on both positive and negative gradients. These results suggested that SCF has chemotactic and chemokinetic activities on all types of HPC, although immature HPC containing multi- and oligopotent cells appeared to migrate more readily than mature HPC containing bi- and monopotent cells.

Effects of SCF on proliferation and survival of HPC. Several investigators have reported the effects of SCF on the proliferation and survival of HPC. Therefore, in the assay system used in the present study for HPC-chemotactic and chemokinetic activity, it is possible that HPC may have proliferated in the presence of SCF or died in the absence of
MIGRATING ACTIVITY OF SCF ON MURINE HPC

Table 2. Assessment of Survival of Murine Hematopoietic Progenitor Cells

<table>
<thead>
<tr>
<th>Incubation Period (h)</th>
<th>Addition of SCF (ng/mL)</th>
<th>Hematopoietic Progenitor Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Immature</td>
</tr>
<tr>
<td>Experiment 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>23.7 ± 5.1</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>6.0 ± 1.7*</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>13.7 ± 5.1</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>16.0 ± 2.6</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>16.3 ± 1.5</td>
</tr>
<tr>
<td>24</td>
<td>1,000</td>
<td>14.3 ± 2.5#</td>
</tr>
<tr>
<td>Experiment 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>18.3 ± 7.1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>16.3 ± 4.0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>16.7 ± 3.8</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>14.0 ± 1.7</td>
</tr>
<tr>
<td>24</td>
<td>100</td>
<td>13.0 ± 5.0</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
<td>2.3 ± 0.6†</td>
</tr>
<tr>
<td>100</td>
<td>1.11 ± 1.9</td>
<td>31.3 ± 2.4</td>
</tr>
</tbody>
</table>

After incubation in medium containing various concentrations of SCF, aliquots of cell suspensions corresponding to originally 3 × 10^6 murine BMNC were assayed by clonal cell culture to count numbers of hematopoietic progenitor cells. Data represent the mean ± SD of the numbers of progenitor cells in triplicate cultures. Immature and mature progenitor cells are described in Materials and Methods. Significant decreases in comparison with original number of progenitor cells are shown, as well as significant increases in comparison with original number of progenitor cells.

* P < .01.
† P < .001.
‡ P < .10.
§ P < .05.
¶ P < .001.
# P < .10.
** P < .05.

SCF during incubation. To examine these possibilities, cell suspensions containing various concentrations of SCF were incubated for 4 to 48 hours. After various incubation periods, numbers of immature and mature HPC in the suspensions were assayed by clonal cell culture (Table 2). In the presence of more than 10 ng/mL SCF, the numbers of immature and mature HPC did not change during 24 hours incubation. However, at 48 hours, the number of mature HPC increased to approximately 1.8-fold, whereas that of immature HPC did not change (Exp. 1). In the absence of SCF, both immature and mature HPC were maintained for at least 12 hours, but their numbers then decreased (Exp. 2). These results are in accordance with previous reports that SCF supports the proliferation and survival of HPC, and suggest that the decrease in the number of HPC after 24 hours incubation in the control experiment in Fig 1B may be partially caused by their death in the absence of SCF, and that the numbers of HPC within 12 hours incubation are not affected by the activity of SCF on the proliferation and survival of HPC.

Confirmation of chemotactic and chemokinetic activities of SCF on HPC. To confirm the effects of SCF on the migration of HPC, we first performed a checkerboard assay with varying concentrations of SCF added to the lower (positive gradient) or upper compartment (negative gradient) at 12 hours incubation (Table 3). The numbers of immature and mature HPC migrated on positive gradient increased dose-dependently on the concentration of SCF added to the lower compartment, and reached a plateau at 10 ng/mL. The numbers of immature and mature HPC migrated on negative gradient also increased dose-dependently on the concentration of SCF added to the upper compartment, reaching a plateau at 100 ng/mL.

Secondly, to exclude the possibility that the observed effects on HPC migration were due to contaminants such as endotoxins etc., a specific antibody to the extracellular domain of KIT was included in our assay system. Briefly, increasing concentrations of ACK2 were added to the upper compartment containing 3 × 10^5 BMNC with the positive or negative gradient of 5 ng/mL SCF. ACK2 dose-dependently inhibited chemotactic and chemokinetic activities of SCF on HPC at concentrations of 0.1 to 100 μg/mL (Fig 2). The addition of purified rat IgG2b (10 and 100 μg/mL) to the upper compartment as a control had no inhibitory effect on either chemotactic or chemokinetic activities of SCF on HPC (data not shown).

Thirdly, to eliminate the possibilities of indirect SCF effects via other cell populations containing unseparated bone marrow cells for migrating activities on HPC, Lin Sca-1^+ cells separated from murine BMNC were used for migration experiments. Thirty-three percent of Lin Sca-1^+ cells were colony-forming HPC and about two thirds of these were immature HPC (data not shown). As shown in Table 4, SCF acted as a chemotactic and chemokinetic agent for purified HPC, as well as for HPC containing unseparated BMNC. These findings clearly demonstrated that SCF has not only chemotactic but also chemokinetic effects on HPC.

Chemotactic and chemokinetic activities of other cytokines on HPC. Other cytokines were screened for their chemotactic and chemokinetic activities on murine HPC. The numbers of HPC migrated after 12 hours incubation on positive and negative cytokine gradients were counted and compared with that of HPC migrated in the control chamber containing no cytokines in both lower and upper compartments. The concentrations of each cytokine used in this screening were optimal for clonal cell culture: murine rIL-3, 200 U/mL; murine rGM-CSF, 30 ng/mL; human rIL-6, 100 ng/mL; human rIL-11, 100 U/mL; human rG-CSF, 100 ng/mL; human IL-1α, 100 ng/mL; human rIL-8, 80 ng/mL; human M-CSF, 2,000 U/mL; and human rEpo, 2U/mL. The results are summarized in Table 5. Only IL-3 and IL-11 showed effects on the migration of HPC, although their effects were less than that of SCF. The effects of IL-3 and IL-11 were then examined in more detail using the checkerboard assay. IL-3 exhibited chemotactic and chemokinetic activity on both immature and mature HPC, as well as SCF (Table 6). In contrast, IL-11 exhibited chemotactic...
activity on immature HPC, but chemotactic activity on mature HPC and chemokinetic activity on immature and mature HPC were not observed (Table 7).

DISCUSSION

Our previous studies demonstrated that potential HPC were easily identified from mononuclear cells cultured with various cytokines based on characteristics of cell size, ceaselessly changing shape and migratory ability observed under an inverted microscope. These results suggest that HPC have not only random mobility, but also chemotactic and chemokinetic activities in response to some cytokines. To clarify this, we examined the effects of various cytokines on chemotaxis and chemokinesis of HPC using a checkerboard assay system.

In this study, we examined the effects of SCF on the migration of murine HPC using a modification of the checkerboard assay. The number of HPC that migrated on stimulation by SCF increased in a time-dependent manner from 4 to 48 hours incubation, although the initiation of the migration of HPC was delayed as compared with that of other BMNC including lymphocytes and immature granulocytes, and the numbers of HPC migrating on positive gradients of SCF were greater than those on negative gradients after 8 hours incubation. The anti-KIT extracellular domain monoclonal antibody ACK2 inhibited chemotactic and chemokinetic activities of SCF on HPC. Furthermore, SCF also showed chemotactic and chemokinetic activity for Lin"Sca-1" cells, as well as for HPC containing unseparated BMNC. These results clearly indicated that murine SCF directly functioned as a chemotactic and chemokinetic factor on murine HPC. It is known that murine and human HPC express KIT on their cell surfaces. Since analysis of colony types derived from migrated HPC demonstrated that SCF could induce migration of all types of HPC, SCF induces the migration of HPC via binding to KIT and subsequent signal transduction. Katayama et al reported recently that expression of KIT on murine primitive dormant HPC was lower than that on later actively cycling HPC. Because our clonal culture system could not detect primitive dormant HPC, further experiments are needed to clarify the differences in chemotactic and chemokinetic activity of SCF between KIT-low and KIT-high populations of HPC with blood cell formation in long-term bone marrow culture.

IL-3 and IL-11 also affected the migration of HPC, although their effects were weaker than that of SCF. Interestingly, the effect of IL-3 resembled that of SCF, while IL-11 acted in a manner different to both of these agents. SCF and IL-3 showed chemotactic and chemokinetic activity on both immature and mature HPC. IL-11 had chemotactic, but not chemokinetic activity, on immature HPC, and neither chemotactic nor chemokinetic activity on mature HPC. Yasuzumi et al reported recently that SCF and IL-11 did not exhibit chemotactic activity for HPC in contrast with the results of the present report. This discrepancy may have been caused by differences in the assay systems used: their assay, using Boyden's chambers separated by cellulose nitrate filters with 5 μm pore size, was performed with only a 3-hour incubation, and in our assay system, HPC began to migrate after a 4-hour incubation.

Administration of cytokines including G-CSF, GM-CSF, IL-3 plus GM-CSF, and SCF produces increases in number of circulating HPC in the peripheral blood. One explanation for this phenomena is that these cytokines...
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Increasing concentrations of ACK2 were added to the upper compartment containing 3 × 10⁶ BMNC with positive (A) or negative (B) gradient of 5 ng/mL SCF. Control experiments (absence of SCF in both lower and upper compartments) were also performed. Migrated HPC were expressed by subtraction of control experiments. Therefore, although the peripheralization of HPC induced by SCF or IL-3 may be partially achieved by ACK2, G-CSF and GM-CSF did not. Therefore, although the peripheralization of HPC induced by SCF or IL-3 may be partially achieved by ACK2, G-CSF and GM-CSF did not.

A number of reports have indicated multiple functions of SCF in hematopoiesis. SCF can interact with other synergistic factors to stimulate proliferation and differentiation of HPC indications that mast cells expressing KIT adhere to stromal cells that possess the transmembrane form of SCF on their surface. In addition to these functions, we have demonstrated that mast cells expressing KIT adhere to stromal cells that possess the transmembrane form of SCF on their surface.}

Each of the cytokines was added to the upper compartment containing 3 × 10⁶ murine BMNC or to the lower compartment of the chamber. Chemotaxis is shown by the latter experiment and chemokinesis by the former. Presence and absence of each cytokine in the upper and lower compartments are indicated by + or −, respectively (upper/lower). Data represent the mean ± SD of the numbers of migrated progenitor cells in triplicate cultures incubated for 12 hours. Immature and mature progenitor cells are described in Materials and Methods. Significant increases in comparison with medium alone are shown.

<table>
<thead>
<tr>
<th>Cytokine and its Concentration</th>
<th>Addition of Cytokine</th>
<th>No. of Migrated Progenitor Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>−/−</td>
<td>260 ± 46</td>
</tr>
<tr>
<td>SCF (100 ng/mL)</td>
<td>−/+</td>
<td>726 ± 32*</td>
</tr>
<tr>
<td>IL-3 (200 U/mL)</td>
<td>−/+</td>
<td>354 ± 19†</td>
</tr>
<tr>
<td>GM-CSF (10 ng/mL)</td>
<td>−/+</td>
<td>355 ± 26†</td>
</tr>
<tr>
<td>IL-6 (100 ng/mL)</td>
<td>−/+</td>
<td>289 ± 82</td>
</tr>
<tr>
<td>IL-11 (100 U/mL)</td>
<td>−/+</td>
<td>192 ± 101</td>
</tr>
<tr>
<td>G-CSF (100 ng/mL)</td>
<td>−/+</td>
<td>205 ± 32</td>
</tr>
<tr>
<td>IL-1α (100 ng/mL)</td>
<td>−/+</td>
<td>163 ± 46</td>
</tr>
<tr>
<td>IL-8 (80 ng/mL)</td>
<td>−/+</td>
<td>414 ± 68†</td>
</tr>
<tr>
<td>M-CSF (2,000 U/mL)</td>
<td>−/+</td>
<td>171 ± 22</td>
</tr>
<tr>
<td>Epo (2 U/mL)</td>
<td>−/+</td>
<td>203 ± 43</td>
</tr>
<tr>
<td></td>
<td>−/+</td>
<td>227 ± 86</td>
</tr>
<tr>
<td></td>
<td>−/+</td>
<td>173 ± 45</td>
</tr>
<tr>
<td></td>
<td>−/+</td>
<td>153 ± 47</td>
</tr>
<tr>
<td></td>
<td>−/+</td>
<td>272 ± 25</td>
</tr>
<tr>
<td></td>
<td>−/+</td>
<td>162 ± 18</td>
</tr>
<tr>
<td></td>
<td>−/+</td>
<td>190 ± 30</td>
</tr>
<tr>
<td></td>
<td>−/+</td>
<td>115 ± 39</td>
</tr>
</tbody>
</table>

Fig 2. Inhibitory effects of ACK2 on chemotactic (A) and chemokinetic (B) effects of SCF on hematopoietic progenitor cells (HPC). In addition to these functions, we have demonstrated that mast cells expressing KIT adhere to stromal cells that possess the transmembrane form of SCF on their surface. In addition to these functions, we have demonstrated that mast cells expressing KIT adhere to stromal cells that possess the transmembrane form of SCF on their surface. In addition to these functions, we have demonstrated that mast cells expressing KIT adhere to stromal cells that possess the transmembrane form of SCF on their surface.
in hematopoiesis, and provide us with a model of a successful bone marrow transplantation. After intravenous injection, KIT-positive HPC may migrate to bone marrow along a positive gradient of SCF (or other cytokines) and adhere to bone marrow stromal cells via binding of KIT on HPC to the transmembrane form of SCF on stromal cells (or receptor for adhesion molecules on HPC to corresponding molecules on stromal cells). After adhesion, SCF (or other cytokines) may support survival, proliferation, and differentiation of HPC.

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Chemotactic and chemokinetic activities of stem cell factor on murine hematopoietic progenitor cells

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