Induction of the Erythropoietin Receptor Gene and Acquisition of Responsiveness to Erythropoietin by Stem Cell Factor in HML/SE, a Human Leukemic Cell Line*

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HML/SE is a cytokine-dependent cell line established from childhood acute megakaryoblastic leukemia. Granulocyte-macrophage colony-stimulating factor (SCF) alone could stimulate proliferation of HML/SE cells, however interleukin-3, interleukin-6, granulocyte colony-stimulating factor and thrombopoietin could not. Although erythropoietin (EPO) alone stimulated neither proliferation nor differentiation of HML/SE cells, it did stimulate proliferation of HML/SE cells and production of hemoglobin in the presence of SCF. SCF activated the human EPO receptor promoter and induced EPO receptor gene expression. Given these results, we speculate that HML/SE cells acquired responsiveness to EPO via the EPO receptor induced by SCF. Mutation analysis of putative transcription factor binding sites in the human EPO receptor promoter suggested that Sp1, rather than the GATA-1 binding site, contributed to the induction of the hEPO gene. Although it is well documented that hematopoietic stem cells and primitive progenitors require both an early-acting cytokine and a lineage-specific cytokine to differentiate to a certain lineage, related mechanisms are not well understood. HML/SE may serve as an excellent model system to analyze functions of early-acting cytokine SCF and lineage-specific cytokine EPO related to proliferation and differentiation of hematopoietic stem cells.

Proliferation and differentiation of hematopoietic stem/progenitor cells are modulated by cytokines such as interleukin-3 (IL-3),1 granulocyte-macrophage colony-stimulating factor (GM-CSF), stem cell factor (SCF), interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF), erythropoietin (EPO) (1, 2), and thrombopoietin (TPO) (3). Hematopoietic cytokines can be classified into lineage-nonspecific early-acting cytokines and lineage-specific late-acting cytokines by biological activities and target cells (1). Cytokines such as SCF, IL-3, and GM-CSF belong to the former group and EPO, G-CSF, and TPO belong to the latter group. Several studies indicated that hematopoietic stem cells required both groups of these cytokines to differentiate and mature to the certain lineages in vitro. Early-acting cytokines can effectively interact with late-acting cytokines in the production of more mature cells (4). In both humans and mice, hematopoietic progenitors lose their responsiveness to IL-3 as they differentiate (4, 5). In erythropoiesis, erythroid progenitors lose their responsiveness to SCF and acquire responsiveness to EPO during differentiation (6, 7). The expression patterns of cytokine receptors throughout hematopoiesis are not abundantly documented. The down-regulation of early-acting cytokine receptors and up-regulation of lineage-specific late-acting cytokine receptors may possibly occur as hematopoietic stem/progenitor cells differentiate.

Attempts to clarify the mechanism of these processes are hindered as the numbers of hematopoietic stem/progenitor cells in various sources such as peripheral blood, bone marrow and cord blood are limited. Although several human cell lines had been established, one that requires both early-acting and lineage-specific late-acting cytokines and is suitable to elucidate these problems has apparently not been documented. Here, we demonstrate that the early-acting cytokine SCF induces the receptor gene of the lineage-specific cytokine EPO and consequent acquisition of responsiveness to EPO. We used a human hematopoietic stem cell-like line, HML/SE, established from childhood acute megakaryoblastic leukemia.

MATERIALS AND METHODS

Cytokines and Antibodies—Recombinant human (h) EPO, hGM-CSF, hIL-3, and hTPO were provided by Kirin Brewery (Tokyo, Japan), recombinant hSCF and hG-CSF were from Amgen Inc. (Thousand Oaks, CA), and recombinant hIL-6 was from Tosoh Co. (Kanagawa, Japan).

Mouse monoclonal antibodies (mAbs) for hCD2, hCD3, hCD4, hCD13, hCD14, hCD19, hCD33, hCD38, and hCD45RA mAbs conjugated with phycoerythrin and anti-hCD8 and hCD45RA mAbs conjugated with fluorescein isothiocyanate were from Becton Dickinson (San Jose, CA). Fluorescein isothiocyanate-conjugated anti-hCD41b and HLA-DR mAbs were from Nichirei, (Tokyo, Japan). Anti-hCD117 mAb conjugated with phycoerythrin was from Immunotech (Marseille, France). Purified mAbs for hCD130 and h-glycoprotein A were from PharMingen (San Diego, CA) and Immunotech, respectively. The preparation of anti-hCD123 mAb has been described elsewhere (8). Anti-h-hemoglobin a Ab for immunohistochemical staining was from Cosmo Bio (Tokyo, Japan).

Establishment and Culture of HML/SE—HML was originally established from mononuclear cells in peripheral blood obtained from a patient with childhood acute megakaryoblastic leukemia and 21-trisomy (9). HML/SE is one of the subclones of HML. The cells were cloned as follows; cells were cultured in semisolid culture containing 100 units/ml hIL-3, 10 ng/ml hGM-CSF, and 2 units/ml hEPO. On day 14, individual colonies were transferred to liquid cultures in the a-medium (Flow Laboratories, Rockville, MD) containing 10% fetal bovine serum (HyClone, Logun, UT), 1% bovine serum albumin (Sigma), with hIL-3,
hGM-CSF, and hEPO at the same concentration as semisolid cultures. After 1 month, the clones were expanded in the presence of 10 ng/ml hGM-CSF alone. Here, we used one of these subclones of HML, designated HML/SE, which was maintained stably in the presence of hGM-CSF for over 1 year.

HML/SE cells were maintained in suspension in α-medium supplemented with 10% fetal bovine serum, 1% bovine serum albumin, 0.05 mM 2-mercaptoethanol, and 10 ng/ml hGM-CSF. Passages were performed approximately every 3–4 days, diluting the cells four or five times. Every 10 days, dead cells were removed by Ficoll-Hypaque (Amersham Pharmacia Biotech, Uppsala, Sweden) centrifugation.

Cell Proliferation Assay—Cell proliferation was estimated by a colorimetric assay using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Sigma) as described (10, 11). For long term growth assay, the number of live cells were counted by trypan blue dye exclusion test.

Flow Cytometric Analysis and Immunohistochemical Staining—Flow cytometric analysis was done as described (11). Immunostaining with the alkaline phosphatase/anti-alkaline phosphatase method, using anti-h-hemoglobin α mAb was done as described (12, 13).

Northern Blotting Analysis—Messenger RNAs (mRNAs) were isolated from HML/SE cells cultured under various conditions using a QuickPrep Micro mRNA purification kit (Amersham Pharmacia Biotech). The same amount (1 μg) of each mRNA was electrophoresed on agarose formaldehyde gels and transferred to nylon membranes (Boehringer Mannheim). Hybridizations were done in Quick Hyb solution (Stratagene, La Jolla, CA) using cDNA fragment of h-β-globin, hEPO receptor (generous gift from Dr. H. Nakauchi, University of Tsukuba, Japan), hGATA-1 and -2 (generous gifts from Dr. M. Yamamoto, University of Tsukuba, Japan), or G3PDH (CLONTECH, Palo Alto, CA) as probes. The probe for h-β-globin was cloned by RT-PCR (31–471) from normal human erythroid cells, and the sequence was verified using an ABI PRISM 310 genetic analyzer (Perkin-Elmer, Foster City, CA). The membranes were visualized using a BAS2000 image analyzer (Fuji Film, Tokyo, Japan).

Construction of Plasmid for Luciferase Assay—Human EPO receptor (EPOR) 5' flanking sequence (−197 to −1) containing both GATA and Sp1 binding sites was cloned by PCR from human genomic DNA (14, 15). The PCR products were subcloned into pCR2.1 TA-cloning vector (Invitrogen, San Diego, CA), and the sequence was verified. The plasmid for the luciferase assay, pEPOR-W, was constructed using Xhol and Hind III restriction enzyme sites within both pCR2.1 and pGL3-Basic luciferase vector (Promega, Madison, WI). Mutants of pEPOR-W containing a mutation of the GATA site (pEPOR-mG), the Sp1 binding site (pEPOR-mS), or 100 ng/ml hIL-6 (●) in the absence of cytokines (□), 100 ng/ml hEPO (×), or 100 ng/ml hIL-6 (□), or in the absence of cytokines (□). Viable cells were assayed by trypan blue dye exclusion test every 24 h (A) or on days 4, 7, and 10 (B).

RESULTS

Expression of Cell Surface Antigens—We first examined by flow cytometric analysis the phenotype of HML/SE cells maintained in the presence of hGM-CSF (Table 1). Most HML/SE cells highly expressed myeloid markers such as CD13 and a megakaryocyte-specific antigen CD41b, often the basis of a diagnosis of acute megakaryoblastic leukemia. They also weakly expressed an erythroid-specific marker, glycophorin A, on their surface. These results are taken to mean that HML/SE is a multi-potent cell line that has the potential to differentiate toward three lineages: myeloid, erythroid, and megakaryocytic.

Effects of Cytokines on Proliferation of HML/SE Cells—We next analyzed proliferation of HML/SE cells in the presence of various cytokines. Cells maintained in the presence of hGM-CSF were washed three times with factor-free α-medium, and started to culture at a density of 1 × 10⁴/ml in the presence of 10 ng/ml hGM-CSF (●), 100 ng/ml hSCF (○), 2 units/ml hEPO (×), or 100 ng/ml hIL-6 (□), or in the absence of cytokines (□). Viable cells were assayed by trypan blue dye exclusion test every 24 h (A) or on days 4, 7, and 10 (B).
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Synergistic Action of Early-acting Cytokines and Lineage-specific Cytokines on Proliferation of HML/SE Cells—It is well documented that hematopoietic stem/progenitor cells require stimulation of the combination of two or more cytokines to proliferate and differentiate. We next investigated the synergistic action of early-acting cytokines SCF and GM-CSF, which can stimulate proliferation of this cell line alone, and lineage-specific cytokines EPO, G-CSF, and TPO on proliferation of HML/SE cells. The cells maintained in the presence of hGM-CSF were washed three times with factor-free α-medium, and the cultures were started at a density of 1 × 10^4/ml in the presence of 10 ng/ml hGM-CSF or 100 ng/ml hSCF, with or without 2 units/ml hEPO. The culture was continued to day 10, as described under “Materials and Methods.” In combination with hEPO and hGM-CSF, the cell number increased at almost the same rate as seen in the presence of hGM-CSF alone (Fig. 2A).

In contrast, in combination with hEPO and hSCF, the cell number increased more rapidly than in the presence of SCF alone (Fig. 2A). We further analyzed effects of various concentrations of hEPO on HML/SE cells, using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Addition of either hGM-CSF or hSCF alone stimulated proliferation of HML/SE, in a dose-dependent manner, but hEPO alone failed to do so, at any concentration used (Fig. 2B). When SCF was present in the medium, EPO stimulated proliferation of HML/SE cells, in a dose-dependent manner (Fig. 2C). We also examined the proliferation response of HML/SE cells in combination with hGM-CSF or hSCF and either one of hG-CSF or hTPO. No additional effect of hG-CSF and hTPO was observed in the presence of hGM-CSF or hSCF (data not shown).

Synergistic Action of SCF and EPO on Differentiation of HML/SE Cells—Because a synergistic action between SCF and EPO on proliferation of HML/SE cells occurred, we further examined synergistic actions of early-acting cytokines and lineage-specific cytokines on differentiation of HML/SE cells. In combination with hGM-CSF and hEPO, expression of an erythroid-specific surface antigen glycophorin A did not increase (Fig. 3A). In contrast, with 10 days of culture in combination with hSCF and hEPO, more than 50% of HML/SE cells markedly expressed glycophorin A on their surface (Fig. 3A), and β-globin mRNA markedly increased in comparison with hGM-CSF plus hEPO or hSCF alone (Fig. 3B). As induction of β-globin mRNA was detected in case of a combination of hSCF and hEPO, we examined the production of hemoglobin, at the protein level. Hemoglobin production was evident in cells cultured with hSCF plus hEPO, as determined immunohistochemically (Fig. 3C, d), but was not detectable in cells cultured with hGM-CSF (Fig. 3C, b), hGM-CSF plus hEPO, or hSCF alone (data not shown). In addition, the cells had erythroid features such as condensed nucleus and a basophilic cytoplasm (Fig. 3C, a) and the cell pellet was reddish (data not shown), suggesting that EPO signaling led to erythroid differentiation in the presence of SCF.

When HML/SE cells were maintained in the presence of hGM-CSF, almost all highly expressed CD13, a myeloid-specific surface antigen. We then asked if G-CSF would induce
HML/SE cells to a more mature stage of myeloid differentiation. However, more mature myeloids were not observed in the presence of hG-CSF, with either hGM-CSF or hSCF, as determined by histochemical staining (data not shown).

As most HML/SE cells also expressed CD41b, a megakaryocytic lineage-specific marker on their surface, it seemed important to determine if HML/SE cells would differentiate to more mature megakaryocytic cells by TPO. However, hTPO alone stimulated neither proliferation nor differentiation of HML/SE cells, as determined by histochemical staining (data not shown). In combination with hTPO and either hSCF or hGM-CSF, the intensity of expression of CD41b was almost the same as that in the presence of hSCF or hGM-CSF alone, and morphological changes were not observed with histochemical staining (data not shown), even in the presence of human...
platelet poor plasma instead of fetal bovine serum and/or low concentration of oxygen (5%).

**Induction of EPO Receptor mRNA by SCF**—In the presence of SCF, HML/SE cells seemed to acquire responsiveness to EPO; therefore, we investigated whether the expression of the EPOR had been changed by SCF. In general, it is difficult to detect EPOR protein due to the low expression of endogenous EPOR on the cell surface. We then examined changes of hEPOR mRNA expression. The mRNA expression of hEPOR was analyzed by Northern blotting using 1 μg of purified mRNAs extracted from HML/SE cells cultured for 10 days in the presence of hGM-CSF, hSCF, hSCF plus hEPO, and hGM-CSF plus hEPO, respectively. When HML/SE cells were maintained in the presence of hGM-CSF alone, the expression of hEPOR mRNA was hardly detectable (Fig. 4A). With addition of hEPO, the amount of hEPOR mRNA did not increase (Fig. 4A). In the presence of hSCF alone, the expression of hEPOR mRNA increased (Fig. 4A), and in combination with hEPO, the hEPOR mRNA level was dramatically increased (Fig. 4A). As it appeared that SCF transcriptionally activated the EPOR gene, we examined the time course of hEPOR mRNA changes; hEPOR mRNA in HML/SE cells increased time-dependently in the presence of hSCF (Fig. 4B).

**SCF Activated EPOR Promoter**—As described above, SCF induced EPOR mRNA. To clarify the mechanism of EPOR gene induction by SCF, we investigated whether SCF activated the EPOR promoter by transient system. We cloned hEPOR promoter region containing both GATA and Sp1 binding sites from human genomic DNA, and the cloned fragment was fused with luciferase coding region as described under “Materials and Methods.” HML/SE cells (3 × 10⁶) were transfected with 15 μg of either pGL3-Basic or pEPOR-W, divided into two aliquots and cultured with 10 ng/ml hGM-CSF or 100 ng/ml hSCF for 3 days, and then 1 μg of each mRNA was electrophoresed on agarose formaldehyde gels, transferred to nylon membranes, and hybridized to [α-32P]dCTP-labeled human cDNA fragment of EPOR or G3PDH. As expected, only background luciferase activity was observed with pEPOR-W mutants lacking the GATA and/or Sp1 binding site, luciferase activity was dramatically reduced. We also examined both GATA-1 and GATA-2 mRNA expressions of GATA-1, GATA-2, or G3PDH.

**DISCUSSION**

We obtained evidence of induction of the receptor gene of the lineage-specific cytokine EPO by the early-acting cytokine SCF and the consequent acquisition of responsiveness to EPO in HML/SE, a human leukemia cell line. Modulation of the process of hematopoietic differentiation by a series of early-acting hematopoietic cytokines, including SCF, IL-3, GM-CSF, and lineage-specific hematopoietic cytokines such as EPO, G-CSF, and TPO has been proposed (2). Multi-potent progenitor cells must interact with an appropriate combination of both groups...
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of these hematopoietic cytokines in order to proliferate and to progress to the next stage of differentiation. In erythropoiesis, both the early-acting cytokines and the lineage-specific cytokine EPO are required (19). The importance of SCF in erythroid cell development is demonstrated by the severe macrocytic anemia in SI/SI and W/W mice, which are mutated at the loci encoding SCF and its receptor c-Kit, respectively (20). Reduced levels of CFU-E in these mice (21) means that generation of CFU-E from pluri-potent stem cell is largely dependent on SCF. Studies on knock-out of EPO or EPOR showed that generation of committed erythroid BFU-E and CFU-E progenitors did not require EPO or EPOR (22). It was also reported that most purified BFU-E were insensitive to EPO and had a very low number of EPOR on their surface, but the number of EPOR did increase and acquired responsiveness to EPO when differentiated to CFU-E (6). EPO alone could stimulate neither proliferation nor differentiation to erythroid, and both SCF and EPO were indispensable for erythroid proliferation and differentiation of HML/SE cells. These results suggest that HML/SE cells consist of very early stage progenitors that have not acquired responsiveness to EPO as the number of EPOR is scanty. Other cell lines reported to proliferate and differentiate to erythroid in the presence of EPO alone such as F36, UT-7, MTAT, and TF-1, seem to have already expressed EPOR and consequently acquired responsiveness to EPO (23–26). Thus, HML/SE cells seem to have a unique feature corresponding to normal progenitors that are more immature than CFU-E. It may be that early-acting cytokines SCF up-regulate EPOR of BFU-E level progenitors and consequently give rise to CFU-E with acquired responsiveness to EPO. Lack of this mechanism may result in reduced levels of CFU-E in SI/SI and W/W mice. The physical interaction between c-Kit and EPOR has been reported (27). The binding of SCF to its receptor c-Kit may cause trans-phosphorylation of EPOR and result in transduction of differentiation signal. We propose another mechanism to explain the co-operation between SCF and EPO.

Because EPOR mRNA was much more increased by SCF plus EPO than by SCF alone, EPO signaling seems to lead to further erythroid differentiation by positive feedback regulation. It was reported that the EPOR gene was trans-activated by transcription factor GATA-1 (15, 17, 28), and that GATA-1 expression was stimulated by EPO (28–30). GATA-1 has been also reported to trans-activate other erythroid-specific genes such as globin and GATA-1 itself (31). In the presence of SCF and EPO, as well as EPO in normal erythroid, erythroid-specific genes such as globin and EPOR were induced in HML/SE cells. In contrast, in the presence of SCF alone, only induction of the EPOR gene was observed. We found that SCF activated the hEPOR promoter, determined using a luciferase vector inserted the hEPOR promoter containing the GATA binding site. However, activation of the hEPOR promoter by SCF was not affected by a GATA binding site mutation and SCF did not increase mRNA expression levels of either GATA-1 or GATA-2, which is assumed to be involved in the induction of EPOR mRNA (32). Taken together, these results suggest that neither GATA-1 nor GATA-2 participate in the induction of the hEPOR gene by SCF. Abrogation of hEPOR promoter activation by SCF through a mutation of the Sp1 binding site suggests a role for Sp1 in hEPOR promoter activation by SCF. Because other erythroid-related genes are reported to be regulated by GATA-1, it can be speculated that specific induction of the EPOR gene by SCF is achieved by Sp1.

Acknowledgments—We thank I. Suyama for technical support and M. Ohara for comments on the manuscript.

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J. Biol. Chem. 1998, 273:16921-16926.

doi: 10.1074/jbc.273.27.16921

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