Identification and Characterization of a Soluble c-kit Receptor Produced by Human Hematopoietic Cell Lines

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Stem cell factor (SCF) triggers cell growth by binding to cell surface c-kit receptors. Soluble forms of several cytokine receptors have been described and may play a role in the modulation of cytokine activity in vivo. For these reasons, we investigated whether human hematopoietic cells produce soluble c-kit receptors. The human leukemia cell lines OCIM1 and M07e display ~80,000 and ~35,000 high-affinity cell surface c-kit receptors, respectively. Soluble c-kit receptors were detected by enzyme immunoassay in OCIM1 and M07e culture supernatants. We determined the molecular weight and binding affinity of soluble c-kit receptor produced by OCIM1 cells, soluble c-kit receptor purified from human serum, and recombinant soluble c-kit receptor expressed in CHO cells. The three soluble c-kit receptors each have a molecular weight of 98 kD. Quantitative binding experiments with 125I-SCF indicate that the soluble c-kit receptors obtained from human serum or OCIM1 cells have binding affinities for SCF of ~200 to 300 pmol/L, in contrast to the recombinant form, which has a binding affinity of ~1.5 nmol/L. All three forms of the soluble c-kit receptor were able to compete with c-kit receptors on OCIM1 cells for 125I-SCF binding. Thus human hematopoietic cells can produce a soluble form of the c-kit receptor that retains high-affinity SCF binding activity. We speculate that the soluble c-kit receptor may bind SCF and function as a receptor antagonist in vivo.

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STEM CELL FACTOR (SCF) and its receptor c-kit play an important role in hematopoiesis, spermatogenesis, melanogenesis, and mast cell development.12 The c-kit receptor has endogenous tyrosine kinase activity and is similar in structure to the PDGF receptor, the CSF-1 receptor, and the fkl/flk-2 receptor.3,4 Soluble forms of receptors, consisting of the extracellular ligand binding domain, have been identified for many cytokines.6 Soluble receptors may play a role in regulation of cytokine bioactivity, cytokine transport, and modulation of receptor signaling.6 In addition, recombinant soluble receptors that function as receptor antagonists have been developed as tools for the study of receptor/ligand interaction and mechanisms of receptor activation.9,10 We report here the identification of a soluble form of the c-kit receptor produced by two human leukemia cell lines, OCIM1 and M07e, that express large numbers of c-kit receptors on the cell surface. Biosynthetic labeling experiments suggest that the native soluble c-kit receptor is produced by proteolytic cleavage of the extracellular domain of the cell surface c-kit receptor. Recently, soluble c-kit receptors have been identified in human serum.11 We have characterized the OCIM1, serum, and recombinant soluble c-kit receptors in terms of molecular weight and binding affinity. The SCF binding affinity of the OCIM1 soluble c-kit receptor is ~200 pmol/L, similar to the binding affinity of the cell surface c-kit receptor.12 All three forms of the soluble c-kit receptor can block SCF binding to cell surface c-kit receptors. These results suggest that the soluble c-kit receptor may play a role in regulating c-kit activation in vivo.

MATERIALS AND METHODS

Cytokines. Purified recombinant human SCF expressed in Escherichia coli was provided by Amgen (Thousand Oaks, CA). Recombinant human granulocytemacrophage colony-stimulating factor (GM-CSF) was expressed in BHK cells and was provided by Dr. Kenneth Kaushansky (University of Washington, Seattle, WA). Recombinant human interleukin-3 (IL-3) was obtained from Genetics Institute (Cambridge, MA). Recombinant human erythropoietin (Epo) was expressed in BHK cells.13 Recombinant soluble c-kit receptor. Recombinant soluble c-kit receptor was produced by Chinese hamster ovary (CHO) cells transfected with plasmid pDSRaz-HuSk11 encoding the A+ isoform of c-kit that contains the 12-bp sequence (encoding Gly Asn Asn...Val) upstream of c-kit receptor.

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c-kit receptor was greater than 98%, as judged by staining with Coomassie Blue R-250.

In subsequent experiments, purified recombinant human SCF was coupled to Actigel ALD Superflow (Sterogene Bioseparations, Inc., St Arcadia, CA) at a ratio of 10 mg SCF to 5 mL Actigel, according to manufacturer’s directions. After coupling, the gel was washed extensively with PBS and conditioned media containing soluble c-kit produced by the OCIM1 cells or by transfected CHO cells were concentrated 25-fold in an Amicon stirred cell ultrafiltration unit over a YM-10 membrane. The concentrate was added to the SCF-Actigel and the slurry was rocked overnight at 4°C to 8°C. The concentrate was drained and the gel bed was washed with PBS until the OD 280 nm absorbance of the wash was less than 0.01 absorbance units. The c-kit bound to the SCF-Actigel was then eluted with ActiSep Elution Medium. The eluate was dialyzed extensively with PBS and concentrated by ultrafiltration over an Amicon YM-10 membrane. The concentrate was sterile filtered and aliquots were quantitatively assayed for SCF and for c-kit by enzyme immunoassay (EIA) as described below.

**Cell lines.** The factor-independent human erythroleukemia cell line, OCIM1, was maintained in Iscove’s modified Dulbecco’s medium (IMDM; Gibco) supplemented with 10% calf serum (CS; HyClone, Logan, UT). The SCF-responsive human megakaryoblastic cell line M07e was maintained in IMDM supplemented with 10% fetal calf serum (FCS; HyClone) and GM-CSF (3 ng/mL). The Daudi cell line was grown in RPMI 1640 (M.A. Bioproducts, Walkersville, MD) supplemented with 10% FCS. The HEL cell line was maintained in IMDM supplemented with 10% FCS.

**Binding affinity and quantitation of c-kit receptors on OCIM1, M07e, and HEL cells.** SCF was iodinated using the chloramine T method. The radiologic specific activity of 125I-SCF was determined by self-displacement analysis and was approximately 2,000 Ci/mmol.IODination of SCF did not alter its biologic activity.

The binding affinity and the number of c-kit receptors expressed on the surface of OCIM1, M07e, and HEL cells were determined by Scatchard analyses of equilibrium binding experiments. The cells were incubated with varying amounts of 125I-SCF (10 pmol/L to 5 nmol/L) with or without a 100-fold excess of unlabeled SCF in binding buffer for 4 hours in a 15°C shaking water bath. At the conclusion of the incubation, the cells were separated from the media containing free 125I-SCF by sedimentation through phthalate oil (di-butyl phthalate:dinonyl phthalate 3.5:2.0). Cell-associated and free 125I were quantitated using a Packard 5330 gamma counter (Packard Instrument Co, Downers Grove, IL). All measurements were performed in triplicate, and the data were analyzed using the ligand program.

**Soluble c-kit receptor binding studies.** The binding affinity of the serum-derivered, OCIM1, and recombinant soluble c-kit receptor was determined by incubating purified soluble c-kit receptor (2 nmol/L) with increasing concentrations of 125I-SCF (50 pmol/L to 7 nmol/L) with or without a 100-fold excess of unlabeled SCF in binding buffer. After an overnight incubation at 4°C, 125I-SCF—c-kit receptor complexes were immunoprecipitated by the addition of 2 µL of polyclonal anti-c-kit antibody no. 1855 and 10 µL of protein A-Sepharose beads (Pharmacia LKB, Uppsala, Sweden) for 2 hours at 4°C. Antibody no. 1855 was raised by immunizing rabbits with the synthetic peptide SAYFNFAFKGNNKEQIHPHT, a sequence found at the C-terminus of the extracellular domain of the A+ isoform of c-kit. Binding studies were performed in parallel in which the 125I-SCF—c-kit receptor complexes were immunoprecipitated with polyclonal antibody no. 951-960 was obtained by immunizing rabbits with the A+ isoform of the human recombinant soluble c-kit receptor. The immunoprecipitates were washed twice with TNTG (20 nmol/L Tris [pH 7.5], 150 mmol/L NaCl, 0.1% Triton X-100, 10% glycerol). 125I-SCF bound to the soluble c-kit receptor was measured in the immunoprecipitates; free 125I-SCF was quantitated in the supernatant. Measurements were performed in duplicate, and the data were analyzed using the ligand program.

The ability of the native and the recombinant soluble c-kit receptor to block binding of 125I-SCF to cells was also evaluated. OCIM1 cells (10^4) were incubated with 125I-SCF (40 pmol/L) and increasing concentrations of affinity-purified OCIM1, serum-derived, or recombinant soluble c-kit receptor (50 pmol/L to 50 mmol/L) for 6 hours at 15°C. OCIM1 cells incubated with 125I-SCF in the absence of soluble c-kit receptor or with a 100-fold excess of unlabeled SCF served as a control.

**Affinity cross-linking.** To determine the molecular weight of the M07e and OCIM1 cell surface c-kit receptor, we performed 125I-SCF cross-linking as previously described. Briefly, the cells (5 × 10^5) were incubated with 1 nmol/L 125I-SCF for 4 hours at 15°C to saturate cell surface c-kit receptors. Cross-linking was performed by adding 1 nmol/L bis-sulfosuccinimidyl suberate (BS3; Pierce, Rockford, IL) and incubating for 30 minutes at 22°C. The reaction was terminated with 20 mmol/L Tris HCl (pH 7.6). The cells were washed and then lysed in buffer, as previously described. The cell lysates were spun at high speed to remove cellular debris. The receptor-ligand complexes were immunoprecipitated using polyclonal antihuman SCF antibodies (antibody no. 1334; Amgen) followed by incubation with protein A-Sepharose beads (Pharmacia LKB) for 3 hours at 4°C. The immunoprecipitates were washed once in TNTG, then resuspended in 2× sample buffer (0.125 mmol/L Tris HCl [pH 6.8], 4% SDS, 0.008% bromophenol blue, 20% glycerol), and subjected to electrophoresis on a 5% polyacrylamide gel (SDS-PAGE).

The molecular weight of the OCIM1, M07e, and recombinant soluble c-kit receptor was determined by 125I-SCF cross-linking as described above, except that 50 nmol/L of soluble receptor was incubated with 5 mmol/L 125I-SCF overnight at 4°C. The receptor-ligand complexes were crosslinked, immunoprecipitated, and analyzed by SDS-PAGE as described above.

**EIA for soluble c-kit receptor.** OCIM1, M07e, and HEL cells were washed twice in IMDM and resuspended in culture media at 7.5 × 10^4 cells/mL to test for the production of soluble c-kit receptors. Culture media conditioned by the three cell lines were collected at various intervals and tested for the presence of soluble c-kit receptor by EIA. The fraction of viable cells was greater than 95% for all samples. The EIA for soluble c-kit receptor was modified from a technique previously described. Media alone with 10% FCS ± 3 ng/mL GM-CSF as well as media conditioned by a cell line without detectable cell surface c-kit receptors (Daudi) were tested in parallel. The samples were concentrated fivefold using a Centricon 10 microconcentrator (Amicon, Beverly, MA) before performing the EIA. The EIA was performed using microtiter wells coated with an affinity-purified rabbit polyclonal anti-c-kit antibody no. 951-960. Purified recombinant soluble c-kit (amino acids 1-519) produced in CHO cells was used to generate a standard curve. Recombinant human soluble c-kit or conditioned media (100 µL) were added to the wells and incubated for overnight at 22°C. For signal detection, the SR-1 anti-c-kit receptor monoclonal antibody covalently coupled to horseradish peroxidase was added and the incubation was continued for 2 hours at 22°C. The wells were washed four times with 0.01% Tween 20 in 50 mmol/L Tris (pH 7.4), 150 mmol/L NaCl, 10 mmol/L EDTA, and 100 µL of TMB Microwell Peroxidase substrate solution (Kirkegaard and Perry Laboratories, Gaithersburg, MD) was added as previously described. The absorbance was read at 450 nmol/L using a Molecular Devices Vmax Kinetic Microplate Reader (Molecular Device Corp, Menlo Park, CA). All samples were run
RESULTS

Characterization of c-kit receptors on the OCIM1 MO7e and HEL cell surface. Equilibrium binding experiments showed that the OCIM1 cells express a single class of high-affinity c-kit receptors (kd $210 \pm 52$ pmol/L; mean $\pm$ SEM of 5 experiments) with approximately 80,000 receptors per cell (Fig 1). Scatchard analysis of MO7e binding data also showed a single class of c-kit receptors. There are approximately 35,000 c-kit receptors per MO7e cell, with a kd of $150 \pm 42$ pmol/L (mean $\pm$ SEM of 3 experiments). Scatchard analysis of HEL binding data showed a single class of high-affinity receptors with a kd of 240 pmol/L and $\sim 80,000$ receptors per HEL cell (average of 2 experiments; Table 1).

To determine the molecular weight of the c-kit receptor, $^{125}$I-SCF was cross-linked to its receptor on the MO7e cell surface using BS$_3$. The $^{125}$I-SCF/c-kit receptor complexes were precipitated with an anti-SCF polyclonal antibody and analyzed by SDS-PAGE. Two major bands, at 170 kD and 340 kD, were apparent (data not shown). After accounting for the contribution of the E coli-expressed recombinant SCF (18 kD), the molecular weight of the c-kit receptor in MO7e cells is estimated to be 152 kD, which is consistent with a previous report. The 340-kD species likely represents the dimerized form of the c-kit receptor. Both the 170-kD and the 340-kD complexes were absent when the MO7e cells were cross-linked with $^{125}$I-SCF in the presence of a 200-fold excess of unlabeled SCF. Affinity cross-linking experiments with OCIM1 cells showed radiolabeled bands at approximately 155 kD and 310 kD, indicating that the molecular weight of the c-kit receptor on OCIM1 cells is slightly lower than that of MO7e cells (data not shown).

Detection of soluble c-kit receptors produced by OCIM1 and MO7e cells. To determine whether human hematopoietic cells can produce soluble c-kit receptors, we used two cell lines (OCIM1 and MO7e) that display large numbers of high-affinity c-kit receptors on the cell surface. Media conditioned by the Daudi cell line, which does not express c-kit receptors on the cell surface, was used as a control. The cells were washed twice and resuspended in fresh culture media. Conditioned media were collected after 24 to 96 hours of incubation and were tested for soluble c-kit receptors by EIA (Table 2). Neither the media incubated in the absence of cells nor the Daudi conditioned media contained detectable soluble c-kit receptors. Soluble c-kit receptor was detected in MO7e conditioned media as early as after 24 hours of incubation and increased over time (Table 2).

SCF binding affinity and molecular weight of the OCIM1, recombinant, and human serum-derived soluble c-kit receptors. The binding affinity of the soluble c-kit receptor was determined by equilibrium binding analysis. The OCIM1 soluble c-kit receptor displayed high-affinity SCF binding (kd of $\sim 200$ pmol/L), similar to the binding affinity of the transmembrane c-kit receptor (Fig 2). Purified recombinant soluble c-kit receptor displayed a lower SCF binding affinity of 1 to 2 nmol/L (Table 1). The kd was similar when immu-

| Table 1. Binding Affinity of c-kit Receptors for $^{125}$I-SCF |
|-----------------|-----------------|-----------------|
| Cell line       | kd*             | c-kit Receptors/Cell |
| OCIM1           | 210 $\pm$ 52 pmol/L | $\sim$80,000 |
| MO7e            | 150 $\pm$ 42 pmol/L | $\sim$35,000 |
| HEL             | 240 pmol/L       | $\sim$38,000 |
| Soluble c-kit receptor |
| OCIM1 derived   | 213 $\pm$ 74 pmol/L |
| Human serum derived | 320 $\pm$ 88 pmol/L |
| Recombinant      | 1.50 $\pm$ 0.17 nmol/L |

* $^{125}$I-SCF binding affinity of leukemia cell lines and soluble c-kit receptors. Cells were incubated with increasing concentrations of $^{125}$I-SCF $\times$ cold SCF. kd is presented as mean $\pm$ SEM. The kd for the HEL cell line is the average of two experiments.
Table 2. Production of Soluble c-kit Receptor by Human Hematopoietic Cell Lines

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>No. of Cells/mL</th>
<th>Soluble c-kit Receptors (ng/mL)</th>
<th>Soluble c-kit Receptors Produced/Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control media</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>M07e (24 h)</td>
<td>$1.4 \times 10^6$</td>
<td>2.9</td>
<td>5,600</td>
</tr>
<tr>
<td>M07e (96 h)</td>
<td>$3.2 \times 10^6$</td>
<td>34.1</td>
<td>66,000</td>
</tr>
<tr>
<td>OCIM1 (96 h)</td>
<td>$0.7 \times 10^6$</td>
<td>12.7</td>
<td>110,000</td>
</tr>
<tr>
<td>HEL (96 h)</td>
<td>$1.6 \times 10^6$</td>
<td>12.3</td>
<td>47,000</td>
</tr>
<tr>
<td>Daudi† (72 h)</td>
<td>$1.6 \times 10^6$</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Soluble c-kit receptors were quantitated by EIA. The conditioned media were concentrated fivefold before performing the EIA. The data are presented as the quantity of soluble c-kit receptor present in the original unconcentrated media and represent the average of duplicate determinations.

†Daudi is a B-cell line that lacks cell surface c-kit receptors.

Table 3. Production of Soluble c-kit Receptor by Human Hematopoietic Cell Lines

Fig 3. Dimerization of the recombinant soluble c-kit receptor in the presence of 125I-SCF. Recombinant soluble c-kit receptor was cross-linked to 125I-SCF and immunoprecipitated with polyclonal anti-SCF antibody.

Fig 2. Scatchard analysis of 125I-SCF binding to the OCIM1 soluble c-kit receptor. Soluble c-kit receptor (2 nmol/L) was incubated with 125I-SCF (50 pmol/L to 7 nmol/L) and immunoprecipitated as described. The SCF binding affinity in this figure is 360 pmol/L.

Biosynthesis of the c-kit receptor. The time course of production of c-kit receptor protein was determined by biosynthetic labeling and immunoprecipitation with the SR-1 antibody (Fig 4). Two c-kit receptor proteins of molecular weight ~120 kD and ~130 kD are detected in the OCIM1 cell lysates after 1 hour of biosynthetic labeling (time 0; Fig 4A). Two hours after biosynthetic labeling, the 120-kD c-kit protein was no longer detectable. The 130-kD c-kit protein, consistent with the size of the transmembrane c-kit receptor in OCIM1 cells, increased in quantity until the 5-hour time-point and then gradually declined. A smaller c-kit receptor protein (98 kD) consistent with the size of the soluble c-kit receptor was first detected in the cell conditioned media 5
hours after biosynthetic labeling (Fig 4B). The quantity of the soluble c-kit receptor protein increased over the next 25 hours. The 98-kD band was not present when the immunoprecipitation was performed with the control antibody (Fig 4B, lane 6).

**Biologic activity of the recombinant soluble c-kit receptor.** The OCIM1, human serum-derived, and recombinant soluble c-kit receptors were tested for the ability to block binding of $^{125}$I-SCF to OCIM1 cells (Table 3). Incubation with the OCIM1 soluble c-kit receptor and with the serum-derived soluble c-kit receptor (50 nmol/L) blocked $^{125}$I-SCF binding to OCIM1 cells as effectively as a 100-fold excess of unlabeled SCF. Recombinant soluble c-kit receptor blocked $^{125}$I-SCF binding to OCIM1 less effectively, consistent with its lower binding affinity for SCF.

**DISCUSSION**

We have identified a soluble form of the c-kit receptor produced by two human hematopoietic cell lines and have characterized the native form and a recombinant form of the soluble c-kit receptor in terms of molecular weight, SCF binding affinity, and ability to compete with transmembrane c-kit receptors on OCIM1 cells. Our results show that soluble c-kit receptors are produced in high quantity by the OCIM1, M07e, and HEL cell lines. Soluble c-kit receptor was detected in media conditioned by the cell lines as early as 96 hours: by 96 hours, the quantity of soluble c-kit receptors produced per cell was equivalent to the total quantity of SCF, thereby leaving less ligand available for binding to cell surface. Another possible mechanism for inhibition is binding of the soluble c-kit receptor monomer to the transmembrane form of the c-kit receptor.

**Table 3. Effect of Soluble c-kit Receptors on $^{125}$I-SCF Binding to OCIM1 Cells**

<table>
<thead>
<tr>
<th>Concentration of Soluble Receptor</th>
<th>OCIM1 Soluble Receptor</th>
<th>Human Serum Soluble Receptor</th>
<th>Recombinant Soluble Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2,945 (100%)</td>
<td>2,945 (100%)</td>
<td>2,945 (100%)</td>
</tr>
<tr>
<td>50 pmol/L</td>
<td>2,945 (100%)</td>
<td>2,945 (100%)</td>
<td>2,945 (100%)</td>
</tr>
<tr>
<td>500 pmol/L</td>
<td>2,566 (87%)</td>
<td>2,827 (96%)</td>
<td>2,749 (93%)</td>
</tr>
<tr>
<td>5 nmol/L</td>
<td>798 (27%)</td>
<td>1,975 (64%)</td>
<td>2,605 (88%)</td>
</tr>
<tr>
<td>50 nmol/L</td>
<td>53 (2%)</td>
<td>304 (10%)</td>
<td>1,469 (50%)</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not determined.

* OCIM1 cells were incubated with $^{125}$I-SCF with or without soluble receptor at the concentrations indicated.
membrane c-kit receptor in the presence of SCF, leading to the formation of a nonfunctional heterodimer. However, multiple experiments in which OCIM1 or MO7e cells were cross-linked to 125I-SCF in the presence of soluble c-kit receptor failed to show the formation of receptor heterodimers (A. Turner, unpublished data). Recombinant soluble c-kit receptor can block the ability of SCF to induce c-kit receptor autophosphorylation\(^{30}\) and can bind to the transmembrane form of SCF displayed on the surface of fibroblasts.\(^{31}\) Thus soluble c-kit receptors may be able to block the activity of both the soluble and the cell surface forms of SCF, which both play an important role in the narrow microenvironment.\(^{32}\)

Soluble forms of cell surface receptors are generally produced either by alternative splicing of mRNA or by proteolytic cleavage of the transmembrane receptor at the junction of the extracellular domain and the transmembrane domain.\(^{53}\) As stated above, two normal isoforms of the c-kit receptor have been reported\(^{15,25}\); these differ only by a 4 amino acid insertion within the extracellular domain, and both isoforms are expressed in erythroleukemia cell lines.\(^{15,25}\) Yee et al\(^{26}\) reported the release of a 100-kD protein from murine mast cells that they suggest is the extracellular domain of the c-kit receptor formed by proteolytic cleavage of the transmembrane c-kit receptor. Our \(^{35}\)S-methionine and \(^{35}\)S-cysteine pulse-chase experiments support the hypothesis that the soluble c-kit receptor is produced by posttranslational processing of the full-length transmembrane c-kit receptor. Although two cell-associated c-kit receptor proteins of molecular weight 120 kD and 130 kD are initially seen after 1 hour of biosynthetic labeling of OCIM1 cells, the 120-kD protein is converted into the 130-kD species over the next 2 hours, consistent with a prior report.\(^{35}\) After 2 hours, all the labeled c-kit protein is represented in the 130-kD band. The 98-kD soluble c-kit receptor is not present in the cell lysates, does not appear in the cell supernatant until 5 hours after pulse labeling, and continues to increase in quantity up to 30 hours. These data suggest that the soluble receptor is generated by cleavage of the 130-kD transmembrane c-kit receptor. As noted above, amino acid sequence analysis of the carboxy terminus of the native soluble c-kit receptor may be required to identify the proteolytic cleavage site.

The biologic significance of naturally occurring soluble c-kit receptors is presently unknown. Possible roles for the soluble c-kit receptor include altering the half life of circulating SCF and modification of SCF-induced receptor activation. The ratio of soluble c-kit receptor to SCF may locally affect the bioactivity of SCF in vivo. The quantity of soluble c-kit receptor in human serum (320 ng/mL)\(^{11}\) exceeds the quantity of soluble SCF (3 ng/mL)\(^{27}\) by a 30-fold molar excess, suggesting that sufficient amounts of soluble c-kit receptor are present in vivo to modulate SCF bioactivity. Soluble cytokine receptors may have clinical applications. The soluble IL-2 receptor can be used to monitor graft rejection in solid organ transplants\(^{36}\) or to monitor disease progression from asymptomatic human immunodeficiency virus to acquired immunodeficiency syndrome.\(^{37}\) Phase II trials investigating the use of soluble IL-1 receptors for the treatment of systemic inflammatory response syndrome are presently underway.\(^{38}\) Because of their small size and lack of antigenic potential, soluble receptors may have a clinical advantage as receptor antagonists over antiligand or antireceptor monoclonal antibodies.\(^{8}\) Our data suggest that the soluble c-kit receptor can act as a receptor antagonist and therefore may play an important role in SCF/c-kit interactions.

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