Expression of Stem Cell Factor and c-kit in Human Neuroblastoma

By Pamela S. Cohen, Jane P. Chan, Margarita Lipkunskaya, June L. Biedler, Robert C. Seeger, and The Children's Cancer Group

During development, mice with mutations of stem cell factor (SCF) or its receptor c-kit exhibit defects in melanogenesis, as well as hematopoiesis and gonadogenesis. Because melanocytes derive from neural crest cells, the role of SCF and c-kit was investigated in the neural crest-derived childhood tumor neuroblastoma. Using reverse transcription-polymerase chain reaction analysis, simultaneous expression of steady-state mRNA for the SCF ligand and its receptor c-kit was found in 14 of 14 (100%) human neuroblastoma cell lines and clones and in 8 of 18 (45%) human neuroblastoma tumor samples. Functional blockade of c-kit receptors in the cell lines SK-N-BE(2) and SH-SY5Y using the mouse monoclonal anti-c-kit antibody SR-1 resulted in a significant decrease in cellular growth rate when measured by either \( {\text{H}} \)-thymidine incorporation or clonogenicity. In addition, higher levels of c-kit mRNA expression were associated with parental neuroblastoma cell lines and subclones with a neuronal (N) differentiation phenotype, whereas lower levels of c-kit mRNA were associated with neuroblastoma cell line subclones having a schwannian/glial/melanocytic pattern of differentiation. However, the differentiation phenotype of neuroblastoma cell lines was not directly altered when c-kit expression was blocked using the SR-1 antibody. In summary, these data indicate that c-kit receptor expression may play a significant role in the growth regulation of the two neuroblastoma cell lines examined and suggest that c-kit may also play a similar role in neuroblastoma growth regulation in vivo. Simultaneous expression of SCF and c-kit mRNA in both neuroblastoma cell lines and tumors implies that c-kit may act as part of an autocrine growth loop in conjunction with endogenous production of SCF in this disease.

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Reverse transcriptase–polymerase chain reaction (RT-PCR). Total RNA preparations from various cell lines were subjected to RT-PCR. Primers used for analyses of SCF, c-kit, and β2-microglobulin (β2-m) mRNA expression were based on published sequence information for each gene and were selected to skip at least one intron to specifically detect mRNA. The sequences used are shown in Table 1. RT-PCR using the c-kit primers described resulted in two bands representing known alternatively spliced transcripts that differ by 12 bp in size. Reverse transcription of 0.5 μg of total RNA was performed for 30 minutes at 42°C using 2.5 U/pL Moloney murine leukemia virus (M-MLV) RT in 1× RT-PCR buffer (10 mmol/L Tris-HCl, pH 8.3, 50 mmol/L KCl, 5 mmol/L MgCl2, and 1 mmol/L each of dATP, dGTP, dCTP, and dUTP) containing 1 U/μL RNasin (Promega, Madison, WI) and 0.15 μmol/L of random primers. Samples for PCR contained 10 μL cDNA: 1.25 U AmpliTaq DNA polymerase; 10 mmol/L Tris-HCl, pH 8.3; 50 mmol/L KCl; 2 mmol/L MgCl2; 1 U/μL RNasin (Promega); 1 mmol/L each of dATP, dGTP, dCTP, and dUTP; and 0.15 μmol/L upstream and downstream primers for the gene of interest. The reaction mixture final volume was 50 μL and was overlaid with 25 μL mineral oil. Samples were amplified for 1 cycle at 94°C for 5 minutes and 60°C for 2 minutes and then amplified for 38 sequential cycles at 94°C for 1 minute and 60°C for 2 minutes. The final extension cycle was 94°C for 1 minute and 60°C for 10 minutes. One-tenth (5 μL) of each completed RT-PCR reaction was then electrophoresed on a 1% agarose/2% NuSieve GTG gel and stained with ethidium bromide.

To enhance detection of SCF and c-kit mRNA expression by RT-PCR, the electrophoresed RT-PCR products were transferred to Nytran membranes (Schleicher and Schuell, Keene, NH) and then placed in a hybridization solution containing 0.5 mol/L NaPO4, 1 mmol/L EDTA, 1% BSA, 7% sodium dodecyl sulfate (SDS), 100 μg/mL salmon sperm DNA, and 102 cpml/μL of 32P-labeled probe. These blotts were hybridized for 16 hours at 65°C and washed twice with 2× SSC, 0.1% SDS, and twice with 0.1× SSC, 1% SDS for 15 minutes at 65°C. Autoradiography was performed on Kodak X-Omat AR film (Eastman Kodak, Rochester, NY). Probes were prepared by performing RT-PCR using the SCF or c-kit primers described above on mRNA from a cell line known to express SCF or c-kit [HepG2 or HL60(k), respectively] and electrophoresis of RT-PCR products on a 1% agarose gel and by cutting out the desired DNA fragment from the gel and labeling it with random 32P-dCTP–labeled oligonucleotide primers.

Clonogenic assay. A total of 5 x 103 cells/well were plated in triplicate in RPMI 1640 plus penicillin, streptomycin, and L-glutamine with 10% heat-inactivated FCS, 0.3% agar, and 1 μg/mL of SR-1 or MOPC 21 irrelevant, nonisotype controlled antibody (Cap-}

Table 1. Oligonucleotide Primers Used for RT-PCR

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sequence</th>
<th>Sequence Base Pairs</th>
<th>Fragment Size (bp)</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCF</td>
<td>5' End: ACTTGAATCCTGAGATTT</td>
<td>bp 199-221</td>
<td>505</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>3' End: CCTTCTCAGGATTAATGTGAAG</td>
<td>bp 690-704</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-kit</td>
<td>5' End: GCCCACAATGATGGTATTT</td>
<td>bp 1326-1347</td>
<td>550</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>3' End: AGGCATCTTTAAGCAGGACGT</td>
<td>bp 1975-1986</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β2-m</td>
<td>5' End: ACCCCACAGAAAAAGATGA</td>
<td>bp 1544-1563</td>
<td>126</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>3' End: CAATGCAATGAGCAGTT</td>
<td>bp 3513-3532</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RESULTS

Detection of SCF and c-kit mRNA in neuroblastoma cells.

To initially determine whether SCF and c-kit play a role in neuroblastoma, SCF and c-kit mRNA expression in neuroblastoma cell lines was analyzed using the technique of RT-PCR. Figure 1A indicates that all of the neuroblastoma tumor cell lines examined express some level of SCF mRNA. The results of RT-PCR analysis of these same cell lines for c-kit mRNA expression are shown in Fig 1B and D. Upon short x-ray film exposure time, all cell lines show c-kit mRNA, except for BE(2)-C and SH-EP1 (Fig 1B). On longer film exposure, expression of c-kit mRNA could also be detected in these two cell lines, although at lower levels (Fig 1D). Two alternative c-kit transcript sizes, varying by 12 bp, were seen when visualizing the RT-PCR result after ethidium bromide staining in Fig 1B (data not shown), but only one band is seen clearly after Southern blotting in this figure, due to bluriness of the x-ray film image. The extra band seen in lane 2 of Fig 1D may be a PCR artifact or an aberrant c-kit product, because the sizes vary by much more than 12 bp. Thus, all neuroblastoma cell lines and clones and the one neuroepitheliolemma cell line examined appear to coexpress mRNA for SCF and c-kit. RT-PCR of mRNA from these cell lines for β2-m mRNA expression was also performed to control for mRNA integrity (Fig 1C).

In Fig 1B and D, c-kit mRNA levels appeared to vary depending on the type of differentiation phenotype of the neuroblastoma cell line examined. Most human neuroblastoma cell lines can be cloned into lines with features of neuroblastic (N) and schwannian/glial/melanocytic (S) differentiation. Intermediate (I) clones are felt to be “stem cells” that maintain features of both N- and S-type cells and can differentiate to either N- or S-type cells under appropriate conditions. Table 2 outlines the relative levels of SCF and c-kit mRNA expression in three parental neuroblastoma cell lines and their respective N, I, or S clones, as shown previously in Fig 1B and D. c-kit mRNA is easily detectable and is thus expressed at higher levels in the parent cell lines SK-N- BE(2), SK-N-SH, and LA-N-1, as well as in the N-clones BE(2)-M17, and SH-SY5Y. c-kit mRNA levels are lower in the I-clone BE(2)-I and the S-clones SH-EP1 and...
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Fig 1. Expression of SCF and c-kit mRNA in tumor cell lines. RT-PCR was performed as described using primers for (A) SCF, (B) c-kit, and (C) β2-m. Either the ethidium-stained gel (A and C) or a Southern blot of the gel hybridized with a PCR-generated radiolabeled c-kit probe (B and D) is shown. The results of RT-PCR on cell lines known to express (+) or not express (−) the gene of interest are shown in the first two lanes. Cell lines used as positive controls for SCF, c-kit, and β2-m are HepG2, HL60k, and HepG2, respectively. The cell line used as a negative control (−) for both SCF and c-kit is CCRF-CEM. RT-PCR was also performed using CCRF-CEM in the (−) lane using β2-m RT-PCR primers. The fourth lane is the respective positive control RNA sample without RT added. Lanes numbered 1 through 15 represent different human neuroblastoma and neuroepithelioma tumor cell lines and clones: (1) SK-N-BE(2); (2) BE(2)-M17; (3) BE(2)-C; (4) SK-N-SH; (5) SH-SYSY; (6) SH-EP1; (7) IMR-32; (8) CHP-134B; (9) CHP-234; (10) CHP-404; (11) SMS-KAN; (12) LA-N-1; (13) LA-N-1-5S; (14) LA-N-2; and (15) TC-71. A longer exposure of a Southern blot of c-kit-specific RT-PCR products from BE(2)-C (lane 1) and SH-EP1 (lane 2) is shown in (D). These experiments were performed three times and representative examples are shown.

LA-N-1-5S. Thus, parental cell lines and their N-clones express markedly greater amounts of c-kit mRNA than their respective I- or S-clones.

Neuroblastoma tumors were then examined for c-kit and SCF mRNA expression by RT-PCR to see whether the coexpression of c-kit and SCF mRNA found in neuroblastoma cell lines was also a feature of neuroblastoma tumors. Total RNA from 18 neuroblastoma tumors was subjected to RT-PCR analysis of SCF and c-kit mRNA expression. In addition, RT-PCR analysis of β2-m was performed on each sample to show the integrity of tumor mRNA samples in which c-kit and SCF expression could not be detected. Eight of 18 (45%) of tumor samples analyzed express both SCF and c-kit mRNA, and none of these tumors express SCF or c-kit alone (Fig 2). The double band seen in Fig 2B represents alternative c-kit mRNA transcripts that vary by 12 bp because of an alternative splice site between exons 9 and 10. The multiple bands seen in lane 7 of Fig 2A appeared on multiple RT-PCR attempts and are unexplained, but may represent mutation of the SCF gene in this tumor sample or RT-PCR artifact. The lack of SCF and c-kit mRNA expression by ethidium staining in negative samples was confirmed by hybridization of these gels with radiolabeled SCF or c-kit probes (data not shown). Thus, SCF and c-kit are simultaneously expressed in a large subset of neuroblastoma tumors, similar to our findings in the cell lines. The tumors that were analyzed represent a spectrum of Evans’ stage, age at diagnosis, and MYCN DNA amplification, all data obtained previously (Table 3). However, no statistical significance can be derived regarding the relationship between SCF/c-kit expression and other neuroblastoma prognostic factors, given the small sample size.

Effect of anti–c-kit antibody on neuroblastoma cell growth. Because simultaneous expression of SCF and c-kit mRNA was a consistent finding in neuroblastoma cell lines and a frequent finding in neuroblastoma tumors, these data suggested the existence of an autocrine loop involving SCF and c-kit in neuroblastoma. To test whether c-kit expression contributes to neuroblastoma cell growth, the neuroblastoma cell line SK-N-BE(2) and its I-clone BE(2)-C were initially treated in culture with varying concentrations of SCF for up to 10 days and assayed for changes in growth using a [3H]-thymidine uptake assay. As a positive control, the human erythroleukemia cell line TF-1, which expresses
Table 2. Comparison of c-kit mRNA Expression in Cloned Neuroblastoma Cell Lines

<table>
<thead>
<tr>
<th>Cell Line and Subclones</th>
<th>Parent or Subclone Type (N/S/I)</th>
<th>Relative c-kit mRNA Expression*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SK-N-SH</td>
<td>Parent</td>
<td>++++</td>
</tr>
<tr>
<td>SK-SY5Y</td>
<td>N</td>
<td>++++</td>
</tr>
<tr>
<td>SH-EP1</td>
<td>S</td>
<td>+</td>
</tr>
<tr>
<td>SK-N-BE(2)</td>
<td>Parent</td>
<td>++++</td>
</tr>
<tr>
<td>SK-N-BE(2)-M17</td>
<td>N</td>
<td>++++</td>
</tr>
<tr>
<td>SK-N-BE(2)C</td>
<td>I</td>
<td>+</td>
</tr>
<tr>
<td>LA-N-1</td>
<td>Parent</td>
<td>++++</td>
</tr>
<tr>
<td>LA-N-1-55</td>
<td>S</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: N, neuroblastic; S, substrate-adherent ("Schwann/glial/melanocytic"); I, intermediate.

* Relative amounts of c-kit mRNA expression (based on intensity of signal in RT-PCR analysis in Fig 1B): +, faintly positive with overexposure of blot; ++, ++++, and ++++, various degrees of signal positivity.

A functional c-kit receptor but not its ligand SCF, was also tested for proliferative response to SCF in a similar manner. No significant proliferative response to SCF was detected with either neuroblastoma cell line tested, whereas the TF-I cell line proliferated in an expected dose-dependent manner in response to SCF, as has been described (data not shown).

Because both neuroblastoma cell lines coexpress SCF and c-kit mRNA, a proliferative response to exogenous SCF may not have been observed because of already maximal stimulation of an autocrine loop, which could not be further stimulated by additional, exogenous SCF. To test this possibility, we used a blocking monoclonal antibody to the human c-kit receptor, SK-1, to determine whether an exogenous blockade of c-kit receptors in the face of endogenous SCF expression might affect neuroblastoma cell growth. Two cell lines, SK-N-BE(2) and SH-SY5Y, were chosen for this experiment because they make relatively larger amounts of c-kit transcripts, as shown by RT-PCR (Fig 1).

Alterations in the growth of the SK-N-BE(2) and SH-SY5Y cell lines after treatment with SR-1 antibody were first measured by the \(^3\)H-thymidine uptake assay. A significant decrease is observed in \(^3\)H-thymidine incorporation in both SH-SY5Y and SK-N-BE(2) cells treated with anti-c-kit antibody when compared with controls (Fig 3). In SH-SY5Y cells, there is approximately a 50% decrease in \(^3\)H-thymidine uptake by day 6, which persists through day 8. SK-N-BE(2) cells show a more marked growth inhibition, reaching 75% by day 7. This effect was entirely reversible with removal of antibody in both cell lines (data not shown).

The addition of anti-c-kit antibody also has a significant effect on the clonogenicity of neuroblastoma cell lines grown in soft agar (Fig 4). Both the total number (Fig 4A) and the size of neuroblastoma colonies (Fig 4B) decreases when grown in agar-containing SR-1 antibody for 14 days when compared with the number of colonies resulting from culture with either no additional antibody (control) or with irrelevant MOPC 21 antibody. For the cell line SK-N-BE(2), there is a 25% decrease in total colony count and a significant 64% decrease in the growth of colonies greater than 100 μm in diameter when treated with SR-1 antibody compared with control treated cells. In these experiments, SK-N-BE(2) cells treated with MOPC 21 also showed a 21% decrease in growth of colonies greater than 100 μm compared with control, but this decrease is significantly less than that seen after SR-1 treatment. In the SH-SY5Y line, there is a 39% decrease in total colony count and a 60% decrease in growth of colonies of greater than 100 μm in diameter when treated with SR-1 antibody compared with control or MOPC 21 antibody-treated cells.

Lack of direct effect of anti-c-kit antibody on neuroblastoma differentiation. Because there was a difference in the level of c-kit mRNA expression that correlated with the differentiation phenotype of neuroblastoma subclones...
Table 3. Demographics of Patients With Neuroblastoma Analyzed for SCF and c-kit mRNA Expression by RT-PCR

<table>
<thead>
<tr>
<th>Tumor RT-PCR Result</th>
<th>SCF/c-kit(-)</th>
<th>SCF/c-kit(+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (mo)</td>
<td>25.2</td>
<td>14.4</td>
</tr>
<tr>
<td>No. of MYCN amplified</td>
<td>1/10</td>
<td>1/8</td>
</tr>
<tr>
<td>Evans stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>IVS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

(N, S, or I; Fig 1 and Table 2), we tested the possibility that c-kit blockade of neuroblastoma cells could directly differentiate neuroblastoma cells along a schwannian/glial/melanocytic pathway. Neuroblastoma cells were treated with SR-1 or control antibody and evaluated by Northern blot for changes in mRNA expression of various genes (neurofilament, L-NGFR, and tyrosinase) that are known markers for neuronal, schwannian, and/or melanocytic differentiation.25,26 No change was observed in the pattern of expression of neurofilament, L-NGFR, or tyrosinase mRNA expression in either SK-N-BE(2) or SH-SY5Y cells treated with SR-1 antibody or control antibody for various periods of time up to 10 days (data not shown). Thus, it is unlikely that c-kit mRNA expression directly regulates differentiation phenotype of neuroblastoma cells, at least as is measured by molecular markers of neuroblast maturation.

**DISCUSSION**

This report shows that the c-kit receptor may play a significant role in human neuroblastoma growth regulation and is the first report of functional evidence of an autocrine SCF/c-kit growth regulatory loop in a human neoplastic tumor. Coexpression of steady-state mRNA for the SCF ligand and its receptor c-kit was detected in 14 of 14 human neuroblastoma cell lines and clones (Fig 1) and in 8 of 18 human neuroblastoma tumor samples (Fig 2). Blockade of c-kit function in the cell lines SK-N-BE(2) and SH-SY5Y using the SR-1 antibody results in a significant decrease in neuroblastoma growth rate when measured by either the 3H-thymidine uptake assay (Fig 3) or clonogenic assay (Fig 4). Thus, these data indicate that growth is significantly regulated by c-kit receptor expression in the two neuroblastoma cell lines examined, possibly as part of an autocrine growth loop in conjunction with autocrine secretion of SCF.

The concept that SCF may play a trophic role in cells derived from neural crest has been substantiated by recent studies in human and animal systems. Nuclear protein immunologically related to c-kit exists in the medullary cells of normal human adrenal gland as well as in the corresponding tumor, pheochromocytoma.27 In situ hybridization studies have shown that SCF and the c-kit receptor are expressed at high levels by some neurons in both mice and rats.28,29 Synaptic connections have also been shown between c-kit-positive and SCF-positive neurons.30 A functional role for SCF and c-kit expression has also been defined in dorsal root ganglion cells (DRGs) of normal embryonic mice.31 In this study, the addition of recombinant murine SCF induced outgrowth of c-kit-positive neurites and had a trophic effect on c-kit-positive neurons from normal mouse embryo DRGs. Furthermore, most c-kit-positive neurons responded to NGF as well, with the SCF-responsive subpopulation representing about 10% of NGF-responsive neurons.32 Thus, in the murine system, SCF and c-kit play an important trophic role during development of the peripheral nervous system.

It is less clear what role c-kit plays if any in neuronal differentiation of neuroblastoma. In the cell lines examined, parental and N-clones express significantly higher levels of steady-state c-kit mRNA than I- or S-clones (Table 1). However, blockade of c-kit receptor expression of N-type subcloned neuroblastoma lines does not change the differentiation phenotype of cells that are known to be characteristic of S-subclones. In particular, no decrease is observed in...
neurofilament and L-NGFR mRNA, concomitant with an increase in tyrosinase mRNA expression, which is the pattern to be expected if cells switched from N- to S-type after SR-1 treatment. Thus, although higher c-kit mRNA expression may be consistent with a neuronal, or N-type pattern of differentiation, c-kit does not appear to directly regulate neuroblastoma differentiation along the neuronal pathway. Instead, higher c-kit expression may be an epiphenomenon of the neuronal differentiation program of neuroblasts, as is the case with other genes such as bc12, which is expressed in N primordial germ cells. In melanocytes, SCF has no activity on its own, but is a mitogen in the presence of 12-o-tetradecanoylphorbol-13-acetate (TPA), which may mimic the action of some as yet uncharacterized melanocytic growth factor.

Given this paradigm of synergistic growth in other target tissues, it will be of interest to see whether other known neuroblastoma growth factors, such as IGF-II, FGF, NGF, and BNDF, may synergize with SCF to enhance neuroblastoma growth.

Whether c-kit and SCF plays a significant role in the growth of neuroblastoma tumor cells in vivo remains to be determined. It is possible that the SCF and c-kit mRNA transcripts detected in mRNA extracted from tumor samples derive not from the tumor cells themselves, but from contaminating hematopoietic cells within the sample. However, the other evidence presented here strongly argues for a functional role of SCF and c-kit coexpression in the cell lines examined, making it likely that SCF and c-kit coexpression play a similar role in at least a subset of neuroblastoma tumors in vivo. These data also suggest that the c-kit receptor may be a target for therapeutic intervention in neuroblastoma patients.

In patients receiving autologous bone marrow transplantation for neuroblastoma, hematopoietic growth factors may be used either to harvest peripheral stem cells or to speed recovery during the period of posttransplant bone marrow aplasia. Because c-kit is involved in neuroblastoma growth regulation, these findings raise concern regarding the potential proliferative effect of exogenous SCF on residual neuroblastoma cells left in harvested marrow or other sites. However, it is possible that c-kit receptors are maximally stimulated by endogenously produced SCF, so that additional exogenous SCF may not further enhance neuroblastoma growth, similar to what is seen in vitro. Thus, it remains to be seen whether treatment of patients with SCF, in the context of bone marrow transplant for example, will adversely affect outcome, but use of SCF in patients with neuroblastoma should be approached with caution.

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**Fig 4.** Clonogenic assays of neuroblastoma cell lines. SK-N-BE(2) (BE2) and SK-SYSY (SYSY) cells were grown in 0.3% soft agar (as described in Materials and Methods) with the addition of either diluent (control), irrelevant antibody (MOPC), or anti-c-kit antibody (SR1) for 14 days. Both total colonies (left) and colonies greater than 0.1 mm in diameter (right) were counted. The mean of three wells is shown (±SD shown in error bars). This experiment was repeated twice with similar results.
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