Brief Communication

Stem Cell Factor (SCF), a Novel Hematopoietic Growth Factor and Ligand for c-kit Tyrosine Kinase Receptor, Maps on Human Chromosome 12 between 12q14.3 and 12qter

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Abstract—Recently a novel hematopoietic growth factor, stem cell factor (SCF), was cloned and demonstrated to be the ligand for the c-kit tyrosine kinase receptor. In the mouse, SCF is encoded by Sl (steel), a gene critical to the development of several distinct cell lineages during embryonic life and which has important effects on hematopoiesis in the adult animal. The Sl/SCF locus maps to the distal region of mouse chromosome 10, in the vicinity of genes that have been mapped to human chromosome 12. Here we report the use of somatic cell hybrid lines to localize SCF to the long arm of human chromosome 12, between 12q14.3 and 12qter. In addition to localizing the Sl homolog in man, these data provide further evidence for the conservation of synteny between the long arm of human chromosome 12 and the distal end of mouse chromosome 10.

INTRODUCTION

When combined with other hematopoietic growth factors such as G-CSF, GM-CSF, IL-3, or EPO, recombinant human SCF (rhSCF) exhibits potent synergistic effects in promoting the proliferation in vitro of both myeloid and lymphoid progenitors (1, 2). Recombinant rat SCF is also a growth factor for mouse mast cell lines in vitro as well as for connective tissue-type cutaneous mast cells in vivo (1–3). Mutations that influence the expression of SCF and c-kit in the mouse have established the importance of the c-kit signaling pathway in the development of several cell types including both hematopoietic and nonhematopoietic lineages. Murine c-kit is encoded at the W (dominant white-spotting) locus (3), while the c-kit ligand, SCF, is the product of the Sl (steel) gene (4–9). Mice carrying two severe mutations at W or Sl lack pigment in their coat hairs, are severely anemic, sterile, and profoundly mast cell-deficient (for reviews see references 10–13).

Despite their similar phenotypes, the developmental defect in W mutant mice is intrinsic to the stem cells of the affected lineages, whereas the Sl mutant animals express defects in the microenvironments necessary for the normal development of the affected cell types (10–13). c-kit expression has been demonstrated in the cells influenced by W mutations, i.e., hematopoietic cells of the erythroid lineage, primordial germ cells, mast cells, and melanoblasts, as
well as in tissues that are not obviously affected by \( W \) mutations, i.e., the germ cells of the adult mouse, the embryonic and adult brain, and the gestational uterus and placenta (3, 14–21). Although the tissue distribution of SCF expression in intact mice has yet to be reported, SCF activity is expressed by bone marrow stromal cell lines in vitro (4) and in vivo analyses indicate that direct cell–cell contact between SCF-positive stromal cells and c-kit-positive target cells is required for many of the biological responses regulated by \( W \) and \( Sl \) loci (12, 22). Therefore, SCF is likely to be produced by stromal cells within tissues that contain cell lineages expressing c-kit.

SCF maps at the \( Sl \) locus on mouse chromosome 10 (4, 6), distal to peptidase-2 (Pep-2) and proximal to phenylalanine hydroxylase (Pah), \( Hsd \), a gene controlling the rate of histidase synthesis and is closely linked (10 cM) with gamma interferon (Ifg) (6, 23) (ENG, data not shown). In man, peptidase B, \( Ifg \) and \( Pah \) map on the distal end of the long arm of chromosome 12 (24). \( Hsd \) and citrate synthase (Cs), another marker on mouse chromosome 10, also map to human chromosome 12, but these genes have not yet been localized precisely in both species (23–26). Thus, the \( Sl/SCF \) locus seems to be part of a conserved linkage group that maps on the long arm of human chromosome 12 (Figure 2B below). However, mouse chromosome 10 also contains linkage groups that map to three other human chromosomes (20, 21). Therefore, the location of SCF in the human genome could not be unequivocally determined without direct investigation. Here we report that SCF maps on human chromosome 12, between 12q14.3 and 12qter.

**MATERIALS AND METHODS**

SCF was mapped in the human genome using a panel of somatic cell hybrid lines derived from fusions between human cells and either hamster or mouse cells. Two hybrids, GM7301 and GM6317, were purchased from the NIGMS Human Mutant Cell Repository in Camden, New Jersey, and are described in their catalog (27). The other hybrids were described previously (28–44). Each of the hybrid lines retains a defined complement of human chromosomes with most human chromosomes represented several times in the hybrid series. Hybrids were scored by Southern analysis for the presence or absence of human SCF-specific hybridizing fragments.

High-molecular-weight DNA was prepared from somatic cell hybrids, human and hamster cell lines, or mouse liver (3). Ten micrograms of genomic DNAs were digested overnight at 65°C with Taq 1 and subjected to Southern hybridization analysis as previously described (3). As probe for human SCF sequences we employed a Klenow-labeled SaeI/HindIII fragment of the human cDNA clone pGemSCF9, which includes nucleotide base-pairs (bp) 363–818 of the published hSCF cDNA sequence (1).

**RESULTS**

The results of the somatic cell hybrid mapping analysis are shown in Figs. 1 and 2 and Table 1. Under the conditions employed in these studies, the human SCF cDNA probe hybridized to two Taq 1 fragments in human DNA (approximately 3.5 kb and 0.7 kb) (the smaller fragment is shown in Fig. 2A), which were distinct from the fragments detected in hamster (4.4 kb) or mouse (8.5 kb and 4 kb) DNAs. The two SCF-hybridizing human fragments cosegregated together in four of the original 31 hybrids tested, indicating that the DNA fragments represent a single SCF structural gene. There was no evidence for the presence of SCF pseudogenes or other highly homologous sequences in the human genome. Comparison of the pattern of segregation of SCF sequences with the human chromosomes retained by the