

### Stem Cell Factor Serum Levels May Not Be Clinically Relevant

To the Editor:

Erythropoietin is a classic hormone. It is synthesized by the kidney, in response to perceived hypoxia, and transported through the circulation to its site of activity, the erythroid marrow. Because this physiology is clear, the measurement of serum erythropoietin levels is of clinical importance. Serum thrombopoietin levels may have a similar clinical significance, although it is not known whether regulation occurs predominately at the level of production or with metabolism and/or use. A recent article by Lyman et al,<sup>1</sup> shows that the serum level of *flt3* ligand may increase 30-100 fold with pancytopenia and raises the possibility that this reflects a physiologic response to the depletion of hematopoietic stem and/or progenitor cells. The serum level of other growth factors relevant to hematopoiesis (eg, G-CSF, granulocyte macrophage-colony stimulating factor [GM-CSF], interleukin-3 [IL-3]) may change in certain clinical circumstances, (as reviewed in reference 2); however, their measurements are of unclear clinical utility. Fluctuations are small and/or transient.

Stem Cell Factor ([SCF], also termed *kit* ligand or Steel factor) is structurally similar to *flt3* ligand, is produced by fibroblasts and endothelial cells (including those within the marrow microenvironment), and likely functions as a paracrine and not an endocrine hormone. As mice lacking SCF or its receptor *c-kit*, are severely anemic, the major effect of SCF could relate to red cell differentiation. Others have reported statistically lower levels of SCF in patients with aplastic anemia, myelodysplastic syndrome (with anemia), and after transplantation, and have suggested that abnormalities of cells

within the microenvironment could result in less SCF production.<sup>3-5</sup> SCF, like *flt3* ligand, functions synergistically with late acting factors, including IL-3 and erythropoietin, so that small changes in SCF concentrations could exert a more major effect on erythroid development.

To determine relevance of SCF serum levels to erythropoiesis, we have studied sera from 34 patients with acquired pure red cell aplasia (PRCA) (hematocrits = 11 to 24, <2% of nucleated marrow cells contained hemoglobin). Their mean serum SCF value was  $3.05 \pm 1.67$  ng/mL (SD), which is equivalent to the mean value as seen in normal individuals ( $3.31 \pm 1.09$  ng/mL,  $n = 257$ ) ( $P > .1$ , Student's *t*-test). Erythropoietin levels were measured in samples from 11 of these patients and were uniformly high, as expected as a response to anemia (mean = 1,715 mU/mL, range 358 to 3840 mU/mL; normal range 6 to 20 mU/mL). There was no correlation between SCF and erythropoietin levels. Also, the coexistence of myelodysplasia and/or the presence of another associated condition (eg, human parvovirus B19, LGL leukemia, thymoma, recent drug exposure) failed to correlate with SCF levels ( $P$  values  $> .01$ , Student *t*-tests). Age and sex failed to correlate with SCF level, as also reported in studies in normal persons.<sup>6</sup> Similarly, mean serum SCF levels were normal in 15 patients with the congenital PRCA (Diamond-Blackfan anemia) ( $3.40 \pm 3.46$  ng/mL). Soluble *c-kit* receptor levels were measured in 9 of these patients and were also normal (mean =  $249 \pm 79$  ng/mL; normal mean value =  $324 \pm 105$  ng/mL<sup>7</sup>).

A single patient was noted to have an extremely high serum SCF

Table 1. Testosterone Study

	Patient Status	Testosterone (ng/mL)	Hct (%)	SCF (ng/mL)	Soluble <i>c-kit</i> (ng/mL)	Epo (U/mL)
Mean value $\pm$ SEM	Before rx	4.7 $\pm$ 0.4	45.0 $\pm$ 0.9	4.49 $\pm$ 0.29	408 $\pm$ 28	11.0 $\pm$ 0.9
	After rx	15.7 $\pm$ 2.7	48.6 $\pm$ 1.2	3.48 $\pm$ 0.43	356 $\pm$ 26	13.4 $\pm$ 2.5
<i>P</i> values		.003	.0009	.009	.19	.33

Statistical analyses were performed using two tail Student's *t*-tests.

level (14.6 ng/mL). She had remitted spontaneously at puberty while her daughter, age 3, (SCF level 2.66 ng/mL) was transfusion dependent.<sup>8</sup> Spontaneous remission at puberty has been described in both male and female patients with Diamond-Blackfan anemia. This clinical observation lead us to a study serum levels of SCF in a patient with moderate aplastic anemia and variable compliance with oxymetholone therapy. The intent was to determine if SCF levels increased with androgen therapy resulting in the increased erythropoiesis and amelioration of anemia.

To our surprise, the mean serum SCF levels from samples obtained when this patient was taking oxymetholone (3.12  $\pm$  0.30 ng/mL) were lower than SCF levels from samples obtained before oxymetholone therapy or when the patient was off oxymetholone therapy for over 2 weeks (5.72  $\pm$  0.99 ng/mL) ( $n = 7$  total samples). Similar results were obtained in 2 additional patients in which SCF levels were assessed before and during oxymetholone treatment. Table 1 shows results of studies of serum from 10 normal men participating in a study of male contraceptives that confirm these observations. Values of SCF, measured after 12 to 17 weeks of testosterone were significantly lower than at baseline ( $P = .009$ , Student's *t*-test). The hematocrits increased, as expected, whereas soluble *c-kit* levels and erythropoietin levels were unchanged.

We conclude that SCF levels in serum from patients with red cell aplasia (acquired or congenital) are normal. Thus this level does not increase as a physiologic response to a low hematocrit.

Our androgen data are more difficult to interpret. Although no information regarding the effect of androgens on SCF production is available, increased erythropoiesis (and not anemia) results from this therapy. Therefore, it is unlikely that androgens directly impair SCF production, and more probable that the lower serum levels are an indirect consequence of androgen activity or an effect on SCF metabolism and/or use. The interesting possibility that androgens increase *c-kit* receptor expression or the avidity of the *c-kit* receptor for its ligand, could be tested with direct experimentation. Consistent with this, androgens have been reported to increase the sensitivity of erythroid progenitor cells to erythropoietin.<sup>9</sup> As *c-kit* is expressed on the surface of many nonhematopoietic cells, modulation in these subtypes as well could affect the serum level.

Taken together, our data suggest that determination of serum SCF levels is not of clinical significance. Levels can be low (eg, with androgen administration) despite improved erythropoiesis, and are normal with severe anemia (eg, PRCA, Diamond-Blackfan anemia).

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