Background and Objective. The receptor for stem cell factor (CD117) is the gene product of the c-kit proto-oncogene. Together with its ligand, the stem cell factor (SCF), it plays an important role in hematopoiesis. In this study, we review the cellular distribution of CD117 in normal hematopoiesis and in hematopoietic malignancies focusing on the differential expression in subtypes of acute leukemias.

Evidence and Information Sources. This review is based on a literature search in the Medline database, personal publications and results obtained as a reference laboratory of the German AML-BFM, AMLCG and ALL multi-center therapy studies.

State of the Art and Perspectives. Membrane expression of CD117 can be found on leukemic blasts from approximately 60% of adult and childhood AML patients, often associated with an immature immunophenotype (CD34+). Moreover, AML with t(8;21) are frequently CD117 positive. Despite earlier reports, most recent studies have not been able to demonstrate any significant prognostic impact of CD117 expression in either childhood or adult AML. A small proportion of T-lineage ALL (9%), mainly consisting of immature pre-T-ALL, is CD117 positive. CD117 expression is rare in B-cell-precursor-ALL and occurs in less than 3% of cases. CD117 in combination with other antigens might facilitate the immunologic characterization of acute leukemias, especially those of myeloid and early T-cell origin.

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Key words: CD117, c-kit, acute myeloid leukemia, acute lymphoblastic leukemia

The stem cell factor receptor (SCFR, CD117) is encoded by the c-kit proto-oncogene, which is the cellular counterpart of the v-kit oncogene of a transforming feline retrovirus (HZ4-feline sarcoma virus). It is a 145kD transmembrane glycoprotein which is homologous to several other growth factor receptors such as the receptors for macrophage colony stimulating factor (M-CSF, CSF-1, c-fms), platelet-derived growth factor α and β (PDGF-Rα, PDGF-Rβ), and the newly described growth factor receptor STK-1, which is the human homologue of the murine FLK2/FLT3 receptor.¹ These receptors are members of the class III receptor tyrosine kinase (RTK) family (reviewed in ref. #2), and are characterized by an extracellular ligand binding-region of five immunoglobulin-like domains, a hydrophobic transmembrane domain and a cytoplasmic domain with tyrosine kinase activity split by an insert.¹ The human gene for the c-kit receptor is in a region in the long arm of chromosome 4 (4q11-4q13).¹² Ligand binding induces formation of receptor homodimers, activation of tyrosine kinase and phosphorylation of several intracellular targets including autophosphorylation followed by activation of a signal transduction cascade. In addition to its expression in normal hematopoiesis, c-kit has been found on AML blasts, as well as myeloid, erythroid, megakaryocytic and lymphoid cell lines.¹³⁻¹⁵ Non-hematopoietic cells expressing c-kit include normal tissues such as epithelial cells of the breast, parotid and dermal sweat glands, melanocytes, central nervous system (particularly in the cerebellum, the hippocampus, and the dorsal horn of the spinal cord), placenta, interstitial cells of the testes and ovaries,¹⁶ as well as tissues from small cell lung cancer,¹⁷⁻¹⁸ breast cancer¹⁹⁻²¹ or melanoma,²² and cell lines derived from the respective tumors.¹⁶ The biology of c-kit and its ligand has been recently reviewed.²³⁻²⁵ In this study, we briefly sum-
marize c-kit expression in normal hematopoiesis and focus on the differential expression in hematologic malignancies, as well as its clinical and presumed prognostic implications in acute leukemias.

C-kit expression in hematopoietic cells

The cellular distribution of CD117 expression has been investigated at the mRNA and protein level with a variety of techniques, including polymerase chain reaction, Northern Blot, and flow cytometric analysis. The monoclonal antibodies (mAbs) YB5.B8,18-20 SR-1,21 17F11,22 and MTK123 have been applied to detect c-kit expression on the cell-surface membrane of various subpopulations of bone marrow cells. These mAbs recognize different epitopes of the c-kit receptor, and vary in their ability of inhibiting SCF action and intrinsic agonist activities.24 Using the mAb YB5.B8, expression of CD117 has been demonstrated in approximately 2-5% of normal bone marrow cells.22 Up to 60-70% of CD34+ bone-marrow progenitor cells co-express CD117,8,26,27 and the CD34+/CD117+ fraction contains the majority of clonogenic cells (CFU-GM [granulocyte/macrophage colony-forming unit], CFU-mix and BFU-E [burst-forming unit-erythroid]).27 Although in general, expression of CD117 during hematopoietic development is highest at the early stages and then continuously diminishes with maturation, the most primitive hematopoietic progenitors may express lesser amounts of c-kit than progenitors committed to the granulocyte/macrophage lineage.28 A considerable proportion of CD34+/CD117+ cells in normal bone marrow coexpress CD33, thus representing committed myeloid progenitors.29 Soluble SCF has a limited effect on several in vitro systems, but acts synergistically with GM-CSF, G-CSF, IL-3, IL-6 or erythropoietin in promoting proliferation and differentiation of hematopoietic stem cells and early myeloid progenitors.29-31 Membrane-bound SCF on stromal cells may be involved in adhesion mechanisms between hematopoietic progenitors and bone marrow stroma.32

Besides their effect on the myeloid lineage, c-kit and its ligand are also involved in early antigen-independent B-cell development, though c-kit might not be indispensable for B-cell ontogenesis.32-35 A small proportion of CD34+ immature bone marrow cells co-express c-kit and the B cell marker CD19.35,27 SCF synergizes with IL-7 in promoting proliferation of murine pre-B cells,37,38 and anti-c-kit antibody suppresses the growth of B-cell precursors in vitro.32 Thymic stromal cells contain mRNA for SCF, whereas both thymocytes and thymic stroma express c-kit, thus indicating that SCF/SCFR might also play a role in early T-cell development.32 A subset of triple negative thymocytes (CD3- CD4- CD8+) expresses the c-kit receptor that is functional in these cells.41

C-kit expression in hematopoietic malignancies

Reflecting its distribution in normal hematopoiesis, the highest frequency of CD117 expression is found in early myeloid neoplasias, i.e. acute myeloid leukemia (AML) and clonal stem cell disorders, such as myeloproliferative disorders (MPD) and myelodysplastic syndromes (MDS). In these malignancies, an increased CD117 expression has been found on peripheral blood mononuclear cells and bone marrow, as compared with normal controls. The highest percentages of CD117-positive cells were observed in the advanced stages of the disease, i.e. acceleration/myeloid blast crisis in MPS and RAEB/RAEB-t in MDS, respectively.42-43 Once regarded as a specific marker for AML,44 it was discovered that CD117 is also expressed in a small proportion of acute lymphoblastic leukemias (ALL) which is consistent with its putative role in early stages of B- and T-cell development. In malignant lymphomas, c-kit expression seems to be restricted to CD30+ anaplastic large cell lymphomas and Hodgkin’s disease.45 While Burkitt’s lymphomas,46 other high grade lymphomas or mature lymphoid neoplasias lack CD117 expression. Malignant cells from multiple myeloma seem to express the c-kit antigen, while normal plasma cells do not.47

C-kit expression in acute myeloid leukemia

The cell surface antigen encoded by the c-kit proto-oncogene was first identified in a subgroup of AML by using a mAb against AML blast cells.19 This finding was confirmed by many subsequent studies, indicating that c-kit expression can be found on the protein or at least on the mRNA level in the majority of AMLs. Depending on the method employed, CD117 surface expression could be demonstrated in blasts of approximately 50-70% (range from 29% to 89%) of all AML cases22,23,43,44,48-56 with the quantitative level of receptor expression in individual cases being highly variable, and generally similar to or less than that found in normal stem and progenitor cells.57

Expression of CD117 has been detected in all morphological subtypes of AML (see Table 1), while most of the studies published so far have not found a clear correlation with FAB-subtypes.21,44,48,58 Using antibody YB5.B8, the frequency of c-kit positivity seemed to be higher in the FAB M0/M1/M2 subtypes as compared with M5,50,60 although a higher incidence of c-kit expression was observed in M4 and M5 AML when a different antibody (SR-1) was applied.54 Interestingly, a significant proportion of promyelocytic leukemia expresses CD117.51

The role of CD117 expression in defining more immature leukemias is still a matter of controversy. Our own data, obtained in 429 adult and 173 childhood consecutive AML cases, did not disclose a significant correlation between CD117 expression
CD117 expression in acute leukemia

and immature M0/M1-subtypes, although an association of CD34 expression and CD117 positivity was found. The results, which represent the largest study in investigating CD117 expression by flow cytometry in blast cells from AML patients using monoclonal antibody YB5.88 with a direct immunofluorescence technique as previously described, are in accordance with other recent reports studying smaller groups of patients

Table 1. CD117 expression in 423 adult AML patients according to morphological subtype.

<table>
<thead>
<tr>
<th>FAB type</th>
<th>CD117 positive</th>
</tr>
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<tbody>
<tr>
<td>M0</td>
<td>33/47 (70.2)</td>
</tr>
<tr>
<td>M1</td>
<td>57/83 (68.7)</td>
</tr>
<tr>
<td>M2</td>
<td>105/124 (84.7)</td>
</tr>
<tr>
<td>M3</td>
<td>11/16 (86.7)</td>
</tr>
<tr>
<td>M4</td>
<td>50/102 (49.0)</td>
</tr>
<tr>
<td>M5</td>
<td>4/30 (11.7)</td>
</tr>
<tr>
<td>M6</td>
<td>14/16 (87.5)</td>
</tr>
<tr>
<td>M7</td>
<td>1/1 (–)</td>
</tr>
<tr>
<td>Total</td>
<td>275/423 (65.0)</td>
</tr>
</tbody>
</table>

Table 2. CD117 expression in 218 adult ALL patients.

<table>
<thead>
<tr>
<th>ALL subtype</th>
<th>CD117 positive</th>
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</thead>
<tbody>
<tr>
<td>B-cell precursor ALL</td>
<td>0/115 (0.0)</td>
</tr>
<tr>
<td>T-lineage-ALL</td>
<td>9/103 (8.7)</td>
</tr>
<tr>
<td>Pro T-ALL</td>
<td>5/21 (23.8)</td>
</tr>
<tr>
<td>T-ALL</td>
<td>4/82 (4.9)</td>
</tr>
<tr>
<td>myAg+ T-ALL</td>
<td>8/42 (19.0)</td>
</tr>
<tr>
<td>myAg- T-ALL</td>
<td>1/60 (1.6)</td>
</tr>
</tbody>
</table>

myAg: CD13, CD33, CD65.

CD7 is also often expressed in CD117-positive AML, on the other hand, CD14, CD15, CD64 and CD4 were rarely found (ref. #60 and unpublished results).

There is little data on cytogenetic features of c-kit-positive AML. In our series of 233 adult AML patients, chromosomal aberrations were more frequent in CD117 positive AML than in CD117 negative AML (41% vs. 60%, p < 0.05). In addition, we found CD117 expression in 10/10 AML cases with the t(8;21) aberration.

Previous studies regarding the prognostic significance of CD117 suggested an adverse influence of c-kit expression on treatment outcome in AML, but more recent studies and our own data revealed no prognostic impact of CD117 expression. In 92 adult AML patients treated according to the protocols of the German AMLCG multi-center therapy study (see Figure 1) and in 103 pediatric patients of the BFM-AML90 study (data not shown), there was no significant difference between CD117 positive and CD117 negative cases as to the response to induction chemotherapy and event-free survival.

In view of the heterogeneity of CD117-positive AML, which can include both poor and good prognostic subgroups [i.e. t(8;21)], this is not surprising.

Figure 1. Event-free survival of 92 adult patients treated according to the protocol of the AMLCG 1991 trial (64), CD117 positive vs. CD117 negative.
and T-ALL, could not detect c-kit expression in ALL,22,23,48,50,57,58,62 although few patients were investigated in each of these series. Based on these results, a specificity of CD117 for the myeloid lineage was postulated, which is reportedly useful for diagnostic purposes.49,55,56 In view of some recent reports and our own data, however, the specificity of CD117 for AML has to be reconsidered. A recent report described c-kit expression in 4 out of 12 CD7− ALL cases.63 Only two of these, however, had cytoplasmic (cy) CD3 and could be unequivocally classified as T-lineage-derived.

In another small series 4 out of 7 T-ALL samples expressed c-kit.68 Additional evidence that T-lymphoblasts might express a functional c-kit receptor is demonstrated by analysis of three T-cell lines derived from pediatric T-ALL. These cell lines were c-kit positive and in one of them SCF had a synergistic proliferative effect with IL-2.69

Of our group of 103 adult T-ALL, 9 (8.7%) cases were CD117-positive. All but one additionally expressed at least one myeloid antigen (CD13, CD33, CD65s).60 All of them were TdT positive and MPO-7 negative, and most of them (n = 5) disclosed a pro-T (CD7+/cyCD3+/CD2−/CD1a−/CD3−) immunophenotype. CD117 expression in B-lineage ALL is a rare event, but in a series of 753 consecutive cases of childhood B-precursor ALL (pro-B-ALL, n=53; c-ALL, n=561; pre-B-ALL, n=139) we found c-kit expression in 22 cases (2.9%). The majority of cases were classified as c-ALL (n = 18) and the 4 remaining cases were pre-B-ALL. Interestingly, we did not observe any CD117+ pro-B-ALL (unpublished observations).

Conclusions

Most recent studies, including both childhood and adult AML, were unable to demonstrate any significant differences in CR rate, survival rate, and event-free survival between CD117-positive and CD117-negative cases. Therefore, these studies do not confirm previous results suggesting that CD117 contributes to the identification of clinically-relevant AML subgroups.

A small proportion of T-lineage ALL (9%), mainly consisting of immature pro-T/pre-T-ALL often with co-expression of myeloid antigens, is CD117 positive. CD117 expression is rare in B-cell-precursor-ALL and occurs in less than 3% of cases.

Despite its lack of specificity and relatively low sensitivity for the myeloid lineage, expression of CD117 in combination with other antigens might facilitate the immunologic characterization of acute leukemias, especially of myeloid and early T cell origin.

References

22. Buhning HJ, Ullrich A, Schaudt K, Muller CA, Busch FW. The product of the proto-oncogene c-kit (P145c-kit) is a human bone marrow surface antigen of hemopoietic precursor cells which is expressed on a subset of acute non-lymphoblastic leukemias. Leukemia 1991; 5:854-60.
29. McNeice IK, Langley KE, Zsebo KM. Recombinant human stem cell


