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Distinguishing CML LSCs from HSCs using CD26

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In this issue of Blood, Herrmann et al elegantly demonstrate that CD26 is a new, specific chronic myeloid leukemia (CML) stem cell biomarker that phenotypically distinguishes leukemic stem cells (LSCs) from normal hematopoietic stem cells (HSCs), and that it is a potential therapeutic target in CML.1

CML is a clonal, multilineage myeloproliferative disorder defined by the presence of a BCR–ABL fusion gene originating in a hematopoietic stem cell. The BCR–ABL fusion gene encodes a chimeric oncoprotein (p210BCR–ABL) that displays constitutively activated tyrosine kinase activity and drives CML pathogenesis. The treatment of chronic-phase CML has been significantly improved by imatinib mesylate (IM) and other tyrosine kinase inhibitor (TKI) therapies.2–4 However, TKI monotherapies are not curative, and early relapse and primary and acquired TKI resistance remain issues.5,6 Despite the effectiveness of TKI monotherapy, most patients harbor residual LSCs, and disease typically recurs if therapy is discontinued.7 LSCs are known to be genetically unstable and less responsive to TKI treatments and are of critical importance in mediating TKI resistance.5,6,8,9 These observations emphasize the need to identify new LSC biomarkers to predict patient response to TKI therapies and to develop new therapeutic agents and combination strategies to target TKI-resistant LSC subclones.

LSCs from CML patients have been difficult to study because of their rarity and phenotypic similarity to normal HSCs, with selective methods for their prospective isolation yet to be established. Therefore, it has been a great challenge to define the unique properties of LSCs and identify biologically and clinically relevant biomarkers of BCR–ABL+ stem cells that explain their unusual biology and that may help in the development of prognostic markers and design of improved treatment of CML patients.

The study by Herrmann and colleagues demonstrated for the first time that the surface enzyme CD26 is a specific biomarker of CD34+CD38– CML LSCs in chronic-phase patient samples using microarray and flow cytometry analysis.1 The authors convincingly demonstrated that BCR–ABL+ cells are only detected in CD34+CD38–CD26+ CML LSCs with significantly high purity and leukemia-initiating potential, but not in CD34+CD38+CD26– cells, and that CD26 is also not detectable in normal HSCs. This finding enables phenotypic distinction of CML LSCs from normal HSCs and characterization of their unique properties both in vitro and in vivo. At the translational level, the authors demonstrated that the percentage of CD26+ LSCs is significantly reduced to low or undetectable levels in CML patients who respond to IM therapy; however, the percentage of CD26+ LSCs remains at high levels in IM-nonresponder patients and in patients who have relapsed after IM therapy, indicating that CD26 could be a useful predictive biomarker for monitoring TKI treatment in CML patients.

Interestingly, aberrant expression of CD26 in CML LSCs disrupts the SDF-1–CXCR4 pathway by cleaving SDF-1, a chemokine protein that binds to G-protein–coupled CXCR4 and plays an important role in the regulation of LSC niche interactions in the bone marrow (BM) microenvironment. Targeting the activity of CD26 with sitaglaptin and vildagliptin reduces the growth of BCR–ABL+ LSCs from CML patients. These findings are of particular interest in light of growing evidence that protection within the BM microenvironment by stromal cells that surround CML LSCs is a critical mechanism of disease persistence on TKI therapy.6,10 Therefore, it is important to identify complementary therapies that target key molecular events active in both CML LSCs and their associated BM niche, to prevent acquisition of resistance. Because the authors demonstrated that aberrant expression of CD26 in CML LSCs is independent of BCR–ABL activity and is potentially regulated by disrupting the SDF-1–CXCR4 pathway in the BM microenvironment, CD26 thus emerges as an attractive, druggable target for complementary therapies to target both CML LSCs and their BM niche. It would be interesting to further determine whether combination treatment of TKIs with CD26-targeting drugs is more effective in eliminating TKI-insensitive LSCs from TKI-nonresponder patients in vitro and in vivo, and to understand the molecular mechanisms underlying the regulation of CD26 expression/activity and its effects on the properties of LSCs and their BM niche interactions. Indeed, this new study has identified CD26 as a novel and unique biomarker for phenotypic purification and functional characterization of the properties of CML LSCs and as a potential prognostic marker and therapeutic target for the development of more effective treatment options to ultimately eradicate CML LSCs.

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REFERENCES


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