The vascular bone marrow niche influences outcome in chronic myeloid leukemia

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ABSTRACT

The endosteal bone marrow niche is known to protect leukemic stem cells (LSC) from chemotherapy, but the role of the vascular niche in the bone marrow microenvironment in leukemia is largely unknown. E-selectin, which is expressed on and imatinib, considered standard of care in CML. This increased the survival of mice leading to improved eradication of LSC in case of treatment with the tyrosine kinase inhibitor imatinib. Hypothesizing that E-selectin influences the cell cycle of leukemic stem cells (LSC) in CML, leading to improved treatment with the tyrosine kinase inhibitor imatinib, we treated murine recipients of CML-initiating cells in the reconstitution/transplantation model with the E-selectin inhibitor GM1-1271 and imatinib, considered standard of care in CML. This increased the survival of mice compared to animals treated with imatinib alone and decreased the engraftment of CML-initiating cells in this model, as well as in the majority of mice in a xenotransplantation model of NOG SCID IL2 receptor-knockout (NSG) mice injected with human CML cells and treated with GM1-1271. GM1-1271 also decreased the contact time of injected human CML cells with the bone marrow endothelium. As shown in vivo and in vitro experiments treatment with GM1-1271 and non-adhesion to E-selectin increased the cycling of BCR-ABL1+ LSC with a concomitant increase in expression of the transcriptional regulator and CD44 phosphorylation target of BCR-ABL1 and a negative transcriptional regulator of CD44 expression. In confirmation of our findings in mice, we also showed a negative correlation between SCL/TAL1 and CD44 expression in leukocytes of healthy patients with CML and that increased CD44 expression is associated with increased probability of relapse and increased relapse-free survival in human CML patients after allogeneic hematopoietic stem cell transplantation.

In summary, inhibition of E-selectin in murine CML may lead to ‘non-adherence’ of LSC to the vascular niche and improved eradication by imatinib. This is likely due to an increase in cell cycle and an increase of SCL/TAL1 expression, which is shown to be regulated by BCR-ABL1. These data connect the adhesion of LSC in CML to the vascular niche via CD44 with the regulation of CD44 expression by SCL/TAL1 and BCR-ABL1, offering a potential new avenue for treatment.

Inhibition of adhesion to E-selectin increases the cycling of leukemia-initiating cells

Figure 1: A) Representative 2-photon microscopy image of the bone marrow niche in vivo of a Rag-2–/-, CD47-/- IL-2 receptor knockout (NSG) mouse injected with human CML patient cells. B) Time course analysis of cell cycle progression in the majority of mice in a xenotransplantation model of NOG SCID IL2 receptor-knockout (NSG) mice injected with human CML cells and treated with vehicle (black), GM1-1271 (red), vehicle plus imatinib (blue), or GM1-1271 plus imatinib (white). C) Increase in Scl/Tal1 binding to the CD44 regulatory element, which was increased in vivo and in vitro experiments treatment with GM1-1271.

Figure 2: Kaplan-Meier curve of survival of mice treated with vehicle (black), GM1-1271 (red), and imatinib (gray) and the combination of both treatments and GM1-1271 (purple). The difference in survival between imatinib and double-treatment was statistically significant (P = 0.03). Figure 3: A) Relative expression of CD44 in HSK2 cells after infection with an empty vector (white) or an anti-CD44 siRNA (gray). B) CD44 expression (mean ± SEM) of CD45+ HSK2 cells transduced with an empty vector control (black) or in a plasmid expressing CD44-encoding cDNA (green). C) CD44 expression in HSK2 cells transduced with an anti-CD44 siRNA (gray) or in a vector expressing CD44-encoding cDNA (green). D) CD44 expression in HSK2 cells transduced with an empty vector control (black) or in a plasmid expressing CD44-encoding cDNA (green). E) The combination treatment of GM1-1271 plus imatinib leads to prolongation of survival compared to imatinib alone.

Inhibition of adhesion to E-selectin leads to the upregulation of Scl/Tal1

Figure 4: A) Relative expression of Scl/Tal1 in NOG SCID IL2 receptor-knockout (NSG) mice injected with human CML patient cells. B) Time course analysis of cell cycle progression in the majority of mice in a xenotransplantation model of NOG SCID IL2 receptor-knockout (NSG) mice injected with human CML cells and treated with vehicle (black), GM1-1271 (red), vehicle plus imatinib (blue), or GM1-1271 plus imatinib (white). C) Increase in Scl/Tal1 binding to the CD44 regulatory element, which was increased in vivo and in vitro experiments treatment with GM1-1271.

Figure 5: Schematic representation of the BCR-ABL1 expression in the endosteal niche via CD44 with the regulation of CD44 expression by SCL/TAL1 and BCR-ABL1, offering a potential new avenue for treatment.