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Differential regulation of myeloid leukemias by the bone marrow microenvironment and its therapeutic targeting

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Normal hematopoiesis is influenced by constituents of the bone marrow microenvironment (BMM) and is also regulated by parathyroid hormone (PTH), which increases the activity of osteoblasts and osteoclasts and increases bone remodeling. The role of the niche in the biology of leukemic stem cells (LSC), frequently not eliminated by current therapies, however, is unclear. Targeting of the LSC niche is a novel concept aimed at eradication of LSC, the origin of relapse and progression of myeloid leukemias.

Using genetic and pharmacological murine models of BCR-ABL1+ chronic myelogenous leukemia (CML) and MLL-AF9+ acute myeloid leukemia (AML), we show that PTH treatment increased bioactive transforming growth factor β1 (TGFβ1) in the BMM and attenuated CML-like myeloproliferative neoplasia (MPN), while leukemic cell-specific knockdown of the receptor for TGFβ1 (TGFβRI) exacerbated the disease. In contrast, AML was accelerated by the PTH-modified BMM, which was reversed by overexpressing TGFbetaRI on leukemic cells. PTH treatment significantly reduced CML LSC frequency and cycling and, combined with the tyrosine kinase inhibitor (TKI) imatinib, led to prolonged survival of some mice with CML-like MPN compared to imatinib alone. PTH-treatment also reduced BCR-ABL1 transcript levels in a xenotransplantation model of human CML compared to saline-treated controls.

In summary, our results suggest that LSC niches in acute and chronic myeloid neoplasms are distinct and differentially modulated by PTH via TGFβ1. Combinations of TKIs with BMM-modulating agents may be a therapeutic strategy for LSC reduction necessary for the cure of CML.

Biography

Daniela S. Krause received her MD degree from the Free University Berlin, Germany, and received postgraduate training in leukemia research at Harvard University. She is a board certified clinical pathologist and blood banker with a special emphasis on coagulation and transfusion medicine. Her research focuses on the role of the bone marrow microenvironment and strategies to improve autologous and hematopoietic stem cell transplantation.

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