# Sinister Symbiosis: Pathological Hematopoietic-Stromal Interactions in CML

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**The impact of myeloid malignancies on the nonhematopoietic components of the bone marrow remains poorly understood. In this issue of *Cell Stem Cell*, Schepers et al. (2013) describe how malignant myeloid cells alter the endosteal hematopoietic stem cell (HSC) niche, resulting in the expansion of osteoblastic lineage cells that preferentially support malignant HSCs.**

Normal and leukemic stem cells receive a complex array of cues from the bone marrow niche that regulate their survival and biological behavior. In this issue of *Cell Stem Cell*, Schepers et al. (2013) examine the reverse flow of information, signals that emanate from neoplastic hematopoietic cells that alter the biology of the cells comprising the niche. These pathologic interactions remodel multiple cellular components of the bone marrow, establishing a pathologic environment that preferentially supports the neoplastic cells, suppresses normal hematopoietic stem cells (HSCs), and ultimately leads to bone marrow fibrosis (Schepers et al., 2013). A particularly compelling aspect of this study is its use of a clinically relevant in vivo murine model of myeloproliferative neoplasms (MPNs) to determine the changes that occur in the HSC niche in the setting of malignancy and to investigate how a corrupted, remodeled endosteal niche contributes to disease progression.

Many of the requisite cellular components of the HSC bone marrow niche have now been defined (reviewed in Frenette et al., 2013). The endosteal (also called "osteoblastic") niche is defined anatomically by close proximity to trabecular or cortical bone. Osteoblastic lineage cells (OBCs) are derived from multipotent stromal cells (MSCs) and play a key role in HSC maintenance (Park et al., 2012). To examine the functional impact of malignant myeloid cells on the endosteal niche and the consequent effects of the remodeled microenvironment on normal and malignant hematopoiesis, Scheppers et al. employ an inducible *BCR-ABL* transgenic model of chronic myelogenous leukemia (CML) (Koschmieder et al., 2005; Reynaud et al., 2011), which is a subtype of MPN.

Examining bone marrow cell populations enriched for endosteal MSCs ($Lin^-$, $CD45^-$, $CD31^-$, $CD51^+$, $Sca\text{-}1^+$) and their OBC derivatives ($Lin^-$, $CD45^-$, $CD31^-$, $CD51^+$, $Sca\text{-}1^-$) (Winkler et al., 2010), Schepers et al. make the striking observation that the number of OBCs is increased in primary mice expressing *BCR-ABL*. This expansion in OBCs is associated with myelofibrotic changes in the bone marrow, as indicated by increased trichrome-positive staining for collagen. OBC expansion is also observed in wild-type recipient mice transplanted with HSCs purified from diseased mice expressing *BCR-ABL*. Moreover, the authors demonstrate that OBC expansion is reversible upon re-exposure of diseased BCR-ABL mice to doxycycline, thereby removing *BCR-ABL* expression and eliminating the CML. In aggregate, the results demonstrate that MPN development is necessary and sufficient for OBC expansion in the model.

Using an in vitro coculture assay, Schepers et al. showed that OBC expansion is driven by $Mac\text{-}1^+$ myeloid MPN cells acting on MSCs and that direct cell-cell interaction or close-proximity signaling is required to promote this effect. They evaluated candidate cytokines as soluble mediators of the changes induced in endosteal BM stromal cells in CML. The authors demonstrated that both thrombopoietin (TPO) and CCL3 (MIP1a) expand MSCs and that this effect is potentiated in the presence of wild-type bone marrow cells. They then go on to characterize, using gene expression profiling, the molecular changes that occur in OBCs derived from diseased BCR-ABL-expressing mice. OBCs from mice with CML had elevated expression of genes involved in extracellular matrix organization, regulation of cell adhesion, and inflammatory responses.

Finally, the authors demonstrated that MPN-expanded OBCs are functionally altered. MPN-expanded OBCs are impaired in their ability to support normal HSC activity but do not have diminished capacity to support *BCR-ABL*-expressing neoplastic HSCs. On the basis of the results of gene expression analyses, the authors propose that the compromised HSC-supportive activity of OBCs from diseased CML mice relates to the reduced expression of HSC retention factors, such as Cxcl12, Scf, and Lepr, and increased expression of molecules such as Tgfb2, which promote myeloid differentiation. Collectively, these results indicate that the endosteal HSC niche is remodeled in the presence of MPN, and the resulting microenvironment preferentially supports malignant stem cells.

While the alterations in the bone marrow in response to a myeloid malignancy are clearly complex, the authors performed a meticulous and systematic interrogation of the alterations in endosteal bone marrow stromal cells in MPN and elucidated the functional consequences of these changes on normal and malignant HSCs (Figure 1). Their detailed dissection of the pathological interactions that occur between malignant myeloid cells and the endosteal HSC niche in CML advances the understanding of the pathogenesis of myelofibrosis and of the cell nonautonomous mechanisms of clonal dominance in MPN. Characterization of the early

molecular changes that occur in the endosteal niche in myelofibrosis raises the possibility that biomarkers that predict the development of myelofibrotic transformation in MPN could be identified. Interestingly, despite a large body of evidence implicating megakaryocytes in the pathogenesis of myelofibrosis (Mullally et al., 2012), Schepers et al. did not observe any defects in megakaryopoiesis in mice expressing *BCR-ABL*, indicating that other myeloid cell populations are sufficient to drive fibrotic transformation in MPN. Future studies will be needed to more fully characterize the immunophenotype of Mac-1$^+$ myeloid MPNs that act on MSCs to promote OBC expansion, particularly in view of the recently described role of monocytes and macrophages as regulators of the HSC niche (Winkler et al., 2010; Chow et al., 2011).

While myelofibrosis can occur in CML, the major clinical challenge currently is the treatment of primary myelofibrosis or myelofibrosis that occurs as a secondary complication of polycythemia vera (PV) or essential thrombocythemia (ET). The majority of these *BCR-ABL*-negative MPNs are driven by the *JAK2V617F* oncogenic kinase. Although JAK2 kinase inhibitors have been disappointing in their ability to preferentially target *JAK2V617F* mutant malignant cells (Harrison et al., 2012), unlike the efficacy of imatinib in CML, recent preliminary reports suggest that JAK1/2 kinase inhibition over years may have the potential to stabilize or improve myelofibrosis (Kvasnicka et al., 2013, J. Clin. Oncol., abstract). While these results require validation, it is plausible that suppressing the inflammatory cytokine milieu through JAK1 and/or JAK2 kinase inhibition could contribute to these effects. Ultimately, the findings of Schepers et al. provide further hope that therapeutic targeting of the malignant hematopoietic clone could reverse the pathologically remodeled bone marrow, regenerating a normal microenvironment with resolved myelofibrosis that supports normal hematopoiesis.

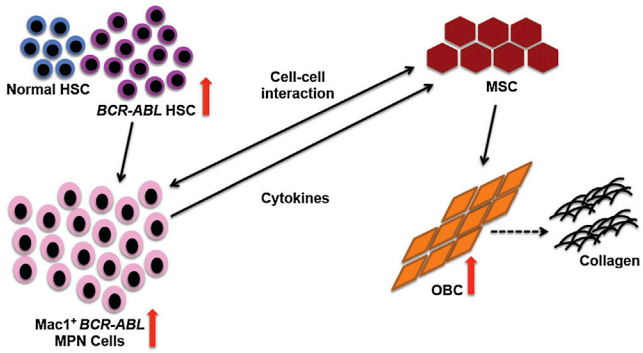


**Figure 1. Hematopoietic-Stromal Interactions in Chronic Myelogenous Leukemia**

Osteoblastic lineage cells (OBCs) obtained from mice expressing BCR-ABL in the hematopoietic compartment are impaired in their ability to support normal hematopoietic stem cells (HSCs) but are supportive of BCR-ABL-expressing HSCs. Mac-1$^+$ myeloproliferative neoplasm (MPN) cells are markedly expanded and act on multipotent stromal cells (MSCs) to promote OBC expansion. OBCs are increased in number, and this expansion is associated with collagen deposition in the bone marrow. OBCs have an altered molecular signature including reduced expression of HSC retention factors such as Cxcl12, Scf, and Lepr. Aberrantly secreted cytokines contribute to paracrine feedback loops. HSC, hematopoietic stem cell; MPN, myeloproliferative neoplasm; MSC, multipotent stromal cell; OBC, osteoblastic lineage cell.

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