TUMOUR MICROENVIRONMENT

Destroying leukaemia stem cell habitats

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Leukaemia stem cells (LSCs) in specific niches in the bone marrow microenvironment (BMM) might promote relapse following therapy. This argues that understanding how the BMM contributes to LSC survival could suggest ways in which these niches can be targeted for therapeutic benefit.

To follow up on a previous observation that parathyroid hormone (PTH) can activate osteoblastic cells in the bone marrow and alter normal haematopoiesis, Krause *et al.* examined the role of PTH in chronic myeloid leukaemia (CML) and acute myeloid leukaemia (AML). Expression of a constitutively active PTH1 receptor (caPTH1R) in mouse osteoblastic cells (collagen type I $\alpha 1$ promoter (COL1A1)-caPTH1R mice) improved the survival of mice transplanted with bone marrow expressing the BCR-ABL1 fusion protein (which induces CML-like disease in the mice), compared with transplantation of BCR-ABL1-expressing cells into wild-type recipients. Cells previously defined as LSCs in this system (lineage-negative, KIT⁺ and SCA1⁺) were able to engraft equally well in COL1A1-caPTH1R and wild-type mice, but the proliferation of LSCs was reduced in COL1A1-caPTH1R mice. Conversely, in a model of AML (in which transplanted cells expressed the MLL-AF9 fusion protein), transplantation into COL1A1-caPTH1R recipient mice led to increased engraftment of LSCs and reduced survival compared with wild-type mice. These data indicate that PTH

signalling in the BMM may have distinct effects on LSCs from different leukaemia subtypes.

One effect of PTH1R signalling is increased transforming growth factor $\beta 1$ (TGF $\beta 1$) expression, and indeed TGF $\beta 1$ protein levels were increased in the bones of COL1A1-caPTH1R mice. Furthermore, blockade of TGF $\beta 1$ signalling by short hairpin RNA-mediated knockdown of the TGF $\beta 1$ receptor (TGFBR1) in BCR-ABL1-expressing cells increased the incidence of CML in COL1A1-caPTH1R recipient mice. However, AML cells seemed to be insensitive to TGF $\beta 1$.

Wild-type donor mice with BCR-ABL1-expressing CML were treated with PTH; this reduced the frequency of LSCs and the ability of these CML cells to engraft into secondary wild-type recipients, leading to increased survival of the secondary recipient mice. In wild-type mice with established CML, treatment with the BCR-ABL1 inhibitor imatinib and PTH resulted in the greatest number of long-term disease-free survivors compared with either treatment alone. Similar results were observed with primary human CML cells: decreased engraftment of CML cells from untreated patients into immunodeficient mice occurred when the mice were pretreated with PTH, compared with saline treatment.

The data from Krause *et al.* indicate that, although the BMM may have different effects on LSCs of disparate origins, targeting the BMM to improve therapy of leukaemia seems feasible. Another paper has looked

more closely at how one might target LSCs in the BMM. Hartwell *et al.* carried out an *in vitro* screen of 14,718 compounds in a co-culture system using bone marrow stromal cell and primary LSC-enriched AML cells from mice expressing MLL-AF9. Specifically, they looked for compounds that had activity against LSCs but not against normal haematopoietic stem and progenitor cells, and also for compounds that affected LSCs through effects on the stromal cells (by treating stromal cells before adding LSCs). Two interesting hits emerged from this screen: BRD7116, which acted on stromal cells to inhibit LSCs, and lovastatin, a drug commonly used to treat hypercholesterolaemia, which showed cell-autonomous inhibition of LSCs in the co-culture system, but which did not inhibit cultures containing only established AML cell lines. Lovastatin pretreatment of LSC-stromal co-cultures also improved the survival of mice into which the cells were transplanted en masse.

Overall, these papers support the importance of understanding LSC niches in different leukaemia subtypes, and suggest several ways in which LSC and BMM interactions might be targeted to improve leukaemia therapy.

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ORIGINAL RESEARCH PAPERS Krause, D. S. *et al.* Differential regulation of myeloid leukemias by the bone marrow microenvironment. *Nature Med.* <http://dx.doi.org/10.1038/nm.3364> (2013)| Hartwell, K. A. *et al.* Niche-based screening identifies small-molecule inhibitors of leukemia stem cells. *Nature Chem. Biol.* <http://dx.doi.org/10.1038/nchembio.1367> (2013)