LEUKAEMIA

Preparation is everything

Deregulation of haematopoietic stem cells (HSCs) is thought to be the driving force behind numerous haematological malignancies, but how changes to the HSC population are initiated remains unclear.

Loss of the tumour suppressor *Nf2* (encoding merlin) is associated with numerous malignancies and using conditional *Nf2* knockout mice Larsson and colleagues found that its loss causes reduced cellularity in the bone marrow, including the $Lin1^{-};Sca1^{+};Kit^{+}$ (LSK) fraction that is enriched for HSCs and progenitors. Levels of these cells increased in peripheral blood when *Nf2* was ablated but haematopoiesis was not exhausted, indicating that loss of *Nf2* has a biphasic effect whereby HSCs are mobilized and an increase in the size of the HSC population follows. Owing to the key role of merlin in cell–cell communication, the effect of *Nf2* loss might reflect cell-autonomous or non-cell autonomous activities. The HSC homing and retention defects, as well as increasing the HSC population at later times, also occurred when wild-type bone marrow cells were transplanted into *Nf2*-deficient mice to reconstitute haematopoiesis. Transplanting *Nf2*-deficient bone marrow cells into wild-type mice did not replicate these phenotypes, indicating that the tumour-suppressive role of *Nf2* might be to regulate the stem cell niche. Consistently, niche-associated non-haematopoietic stromal cells and vasculature increased, which was associated with increased vascular endothelial growth factor (VEGF) expression. VEGF did not affect proliferation or mobilization of HSCs and progenitors, indicating that these are indirect effects resulting from the changes to the microenvironment. Further, the niche increased in size, indicating that the increased HSC population reflects an increased capacity of the niche.

In a separate study, Goyama and colleagues investigated the effects on haematopoiesis of EVI1, whose activity is often increased in acute myeloid leukaemia and myeloid dysplastic syndromes. They found that the LSK compartment was reduced in $Evi1^{-/-}$ mouse embryos and that EVI1 was required for HSC activity *in vivo*, using haematopoiesis reconstitution experiments. Next, they showed that *Evi1* was required for the proliferation and maintenance of HSCs but was dispensable for the differentiation into myeloid, erythroid and lymphoid lineages. Interestingly, EVI1 had context-specific effects on proliferation and apoptosis in HSCs from the bone marrow or liver, respectively. So, do these activities affect leukaemogenesis? Loss of *Evi1* reduced the clonogenic ability of bone marrow progenitors transformed with leukaemia-associated translocations. Further, they looked at the role of EVI1 in the progression of tumour growth and found that loss of EVI1 prolonged survival of mice, indicating that EVI1 activity is important for leukaemogenesis and progression. Finally, they analysed gene expression data from HSCs and acute myeloid leukaemia samples and found that *GATA1*, *GATA2* and *ANGPT*, among others, are potential important EVI1 target genes.

Together, these studies provide insight into potentially tumorigenic effects on HSCs, which could be used to improve diagnosis and treatment of haematological malignancies.

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ORIGINAL RESEARCH PAPERS Larsson, J. *et al.* *Nf2*/Merlin regulates hematopoietic stem cell behavior by altering microenvironmental architecture. *Cell Stem Cell* **3**, 221–227 (2008) | Goyama, S. *et al.* Evi-1 is a critical regulator for hematopoietic stem cells and transformed leukemic cells. *Cell Stem Cell* **3**, 207–220 (2008)

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