MICROENVIRONMENT

A disturbed background

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URLs

RB1

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView&TermToSearch=59256&ordinalpos=1&itool=EntrezSystem2.PEntrez.Gene_Gene_ResultsPanel.Gene_RVDocSum

Rarg

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView&TermToSearch=194116&ordinalpos=1&itool=EntrezSystem2.PEntrez.Gene_Gene_ResultsPanel.Gene_RVDocSum

TNF α

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView&TermToSearch=71246&ordinalpos=5&itool=EntrezSystem2.PEntrez.Gene_Gene_ResultsPanel.Gene_RVDocSum

Remember the last time you moved house? Disorder in your 'niche' is certainly disruptive, and two papers published recently in *Cell* show that this is also true for haematopoiesis — single genetic changes in the bone marrow microenvironment can induce myeloproliferative-like disease.

Haematopoiesis relies on the ordered self-renewal or differentiation of haematopoietic stem cells (HSCs), and this involves intrinsic and extrinsic cues. The bone marrow microenvironment is known to be important for this, but it has not been clear exactly how it contributes. Given that changes in cell-cycle regulation can alter the fate of stem cells, Stuart Orkin and colleagues investigated the function of the retinoblastoma protein (RB) — a negative regulator of the cell cycle — in haematopoiesis. *Rb* was deleted specifically from haematopoietic cells, including HSCs, using Cre-Lox technology in adult mice. 12 weeks after *Rb* ablation, the mice developed a highly cellular bone marrow and a myeloproliferative-like disease, with extramedullary haematopoiesis evident in the spleen and liver. Further investigation showed that the HSCs

in these mice were more likely to differentiate than self-renew, and more HSCs were redistributed to extramedullary sites; so is there an intrinsic defect in the HSCs? A set of elegant transplantation experiments showed that the loss of RB in HSCs did not alter the function of these cells, but that the loss of RB in the bone marrow niche prevented the retention of HSCs and extrinsically affected their behaviour. In addition, the intrinsic loss of RB from more differentiated cells of the myeloid lineage, in combination with the extrinsic loss of RB in the bone marrow niche, disrupted cell–cell interactions and enabled the development of a myeloproliferative-like disease.

Many genes other than *RB* have been implicated in the development of haematopoietic disease, including the retinoic acid receptor (RAR) family of nuclear hormone receptors. *Rarg*-null mice have reduced numbers of HSCs and an increased number of immature progenitor cells in the bone marrow. Louise Purton and colleagues investigated whether the production of mature cells was affected in these mice. In the bone marrow, increased numbers of immature and mature granulocytes

were evident, but in contrast to the mice discussed above, HSC number was not increased in extramedullary sites, indicating that the retention of these cells in the bone marrow was not an issue. Having ruled out functional impairment as a reason for the increased production of granulocyte-macrophage progenitor cells, the authors investigated the fate of these cells in the small number of *Rarg*-null mice that survived to 12 months of age. These mice developed a myeloproliferative-like disease, but did not develop leukaemia or lymphoma. Transplantation of *Rarg*-null haematopoietic cells into wild-type mice did not result in disease, but transplantation of wild-type haematopoietic cells into congenic mice with *Rarg*-null bone marrow resulted in an increased number of granulocytes. So what changes in the bone marrow microenvironment does the loss of RAR γ induce? Levels of tumour necrosis factor- α (TNF α) are significantly increased in *Rarg*-null mice, and transplantation of these mice with *Tnf α* -null haematopoietic cells reduced the severity of the myeloproliferative disease, but did not prevent it. The authors also confirmed that *Rarg*-null bone marrow is required to maintain the myeloproliferative-like disease phenotype.

These results indicate that myeloproliferative diseases are not purely the result of cell intrinsic defects, but are heavily influenced by, and can be caused by, mutations in cells that contribute to the bone marrow microenvironment.

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ORIGINAL RESEARCH PAPERS Walkley, C. R., Shea, J. M., Sims, N. A., Purton, L. E. & Orkin, S. H. *Rb* regulates interactions between hematopoietic stem cells and their bone marrow microenvironment. *Cell* **129**, 1081–1095 (2007) | Walkley, C. R. *et al.* A microenvironment-induced myeloproliferative syndrome caused by retinoic acid receptor- γ deficiency. *Cell* **129**, 1097–1110 (2007).