HAEMATOPOIESIS

Keeping HSCs under control

Although in certain situations haematopoietic stem cells (HSCs) can undergo extensive proliferation, they remain largely quiescent in normal adults. And whereas many nuclear factors that promote the proliferation of HSCs have been characterized, the factors that hold HSC proliferation in check have been difficult to identify. But now, two new reports indicate that the transcriptional repressor GFI1 (growth-factor independent 1) restricts HSC proliferation.

GFI1 has previously been shown to promote T-cell proliferation. So, because GFI1 is expressed by HSCs, both groups set out to investigate whether it also promotes proliferation of these cells. Surprisingly, Hock *et al.* observed that, compared with wild-type litter-mate controls, there were at least as many, if not more, phenotypic HSCs in the bone marrow of GFI1-deficient mice. By contrast, Zeng *et al.* observed that the number of phenotypic HSCs was decreased in the bone marrow of GFI1-deficient mice. However, both groups showed that HSC function was compromised; when lethally irradiated mice were transplanted with a mixture of GFI1-deficient bone marrow and wild-type bone marrow, GFI1-deficient HSCs were outcompeted as the mice aged, and haematopoietic cells derived from the GFI1-deficient bone marrow were undetectable. Together with the observation that bone marrow from recipients of GFI1-deficient bone marrow was unable to reconstitute a secondary lethally irradiated recipient

in a serial-transplantation assay, these results establish that GFI1 is crucial for HSC self-renewal and engraftment function.

Further analysis indicated that a larger proportion of GFI1-deficient bone-marrow HSCs were in the proliferative stages of the cell cycle, indicating that GFI1 functions to restrain HSC proliferation. Consistent with this proposed role for GFI1 in controlling proliferation and cell-cycle progression of HSCs, the level of mRNA encoding the G1 checkpoint regulator p21 (also known as CIP1 or WAF1), which is required to maintain HSCs in G0, was found to be decreased in GFI1-deficient HSCs.

These studies identify GFI1 as a negative regulator of HSC proliferation, and both groups suggest it is probable that the excessive proliferation of GFI1-deficient HSCs results in exhaustion and the observed loss of self-renewal function. This role as a factor restricting HSC proliferation is in contrast to the observation that GFI1 promotes T-cell proliferation, highlighting that transcription-factor function is context dependent and can be cell-type specific.

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References and links

ORIGINAL RESEARCH PAPERS Hock, H. *et al.* Gfi-1 restricts proliferation and preserves functional integrity of haematopoeitc stem cells. *Nature* **431**, 1002–1007 (2004) | Zeng, H., Yücel, R., Kosan, C., Klein-Hitpass, L. & Möröy, T. Transcription factor Gfi-1 regulates self-renewal and engraftment of haematopoietic stem cells. *EMBO J.* 23 September 2004 (doi:10.1038/sj.emboj.7600419).