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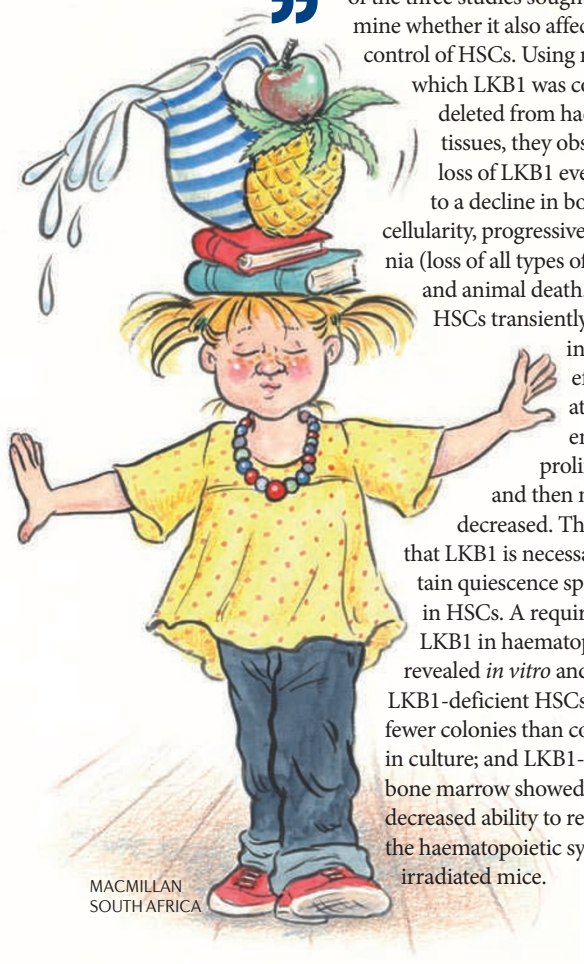
STEM CELLS

LKB1 maintains the balance

> LKB1 balances proliferation and quiescence in HSCs



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The Ser/Thr kinase LKB1 (also known as STK11) is essential for the maintenance of haematopoietic stem cell (HSC) homeostasis, according to three studies published in *Nature*.

LKB1 regulates the metabolism of many adult cell types, so the authors of the three studies sought to determine whether it also affects metabolic control of HSCs. Using mice in which LKB1 was conditionally deleted from haematopoietic tissues, they observed that loss of LKB1 eventually led to a decline in bone marrow cellularity, progressive pancytopenia (loss of all types of blood cells) and animal death. Moreover, HSCs transiently increased in number, an effect associated with enhanced proliferation, and then markedly decreased. This suggests that LKB1 is necessary to maintain quiescence specifically in HSCs. A requirement for LKB1 in haematopoiesis was revealed *in vitro* and *in vivo*: LKB1-deficient HSCs formed fewer colonies than controls in culture; and LKB1-deficient bone marrow showed a markedly decreased ability to repopulate the haematopoietic system of irradiated mice.

The decrease in HSC numbers could be caused by cell death; indeed, all three groups observed increased levels of apoptosis in LKB1-deficient HSCs. Furthermore, Gurumurthy *et al.* observed increased autophagy in haematopoietic tissues of LKB1-deficient mice, as well as an enhanced expression of phosphorylated histone H2AX, a marker of DNA damage. These findings, together with the observation by Nakada *et al.* that many LKB1-deficient HSCs are aneuploid, suggest that increased apoptosis could be caused by metabolic or genotoxic stress.

The cell cycle and apoptosis are known to be influenced by metabolism, and LKB1 deficiency in other tissues leads to metabolic defects. Indeed, Gan *et al.* observed that LKB1-deficient HSCs have reduced levels of PPARγ co-activator 1 (PGC1), a transcriptional co-activator with known roles in metabolism and mitochondrial biogenesis. Consistent with this, all three studies show that loss of LKB1 leads to reduced ATP levels and decreased mitochondrial potential.

LKB1 is known to limit cell growth in the absence of nutrients by phosphorylating AMP-activated protein kinase (AMPK), thereby inhibiting mammalian target of rapamycin complex 1 (mTORC1) signalling. However, the three studies find that the downstream effects of LKB1 are mTORC1 independent, as treatment with the mTORC1 inhibitor rapamycin did not did not rescue the effects of LKB1 deficiency, including HSC depletion. Furthermore, Gurumurthy *et al.* and Gan *et al.* observed that treatment with an AMPK activator did not restore the depleted cells in the bone marrow and thymus, and Nakada *et al.* found that AMPK-deficient HSCs were neither rapidly depleted nor unable to reconstitute irradiated mice, in contrast to LKB1-deficient HSCs. Thus, most of the effects of LKB1 on HSC homeostasis are independent of AMPK and mTORC1.

So, it seems that LKB1 balances proliferation and quiescence in HSCs by regulating cell survival, cell cycle progression and mitochondrial function. Candidate downstream effectors of LKB1 signalling include AMPK-related kinases, and further studies are needed to determine whether they are involved in this LKB1-mediated function.

Rachel David

ORIGINAL RESEARCH PAPERS Nakada, D., Saunders, T. L. & Morrison, S. J. Lkb1 regulates cell cycle and energy metabolism in haematopoietic stem cells. *Nature* **468**, 653–658 (2010) | Gurumurthy, S. *et al.* The Lkb1 metabolic sensor maintains haematopoietic stem cell survival. *Nature* **468**, 659–663 (2010) | Gan, B. *et al.* Lkb1 regulates quiescence and metabolic homeostasis of haematopoietic stem cells. *Nature* **468**, 701–704 (2010)