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STEM CELLS

Self-consumption will keep your blood young

> “autophagy prevents metabolic activation of HSCs”

Mammalian haematopoietic stem cells (HSCs) are rare adult stem cells that reside in the bone marrow and produce all blood cell types. To ensure their life-long maintenance, HSCs are quiescent, but the mechanisms responsible for this prolonged state of dormancy are elusive. Passegué and colleagues demonstrate that autophagy — a process of cellular self-consumption — promotes HSC quiescence and prevents degeneration of old HSCs.

Autophagy declines with age in many tissues, and a loss of autophagy in skeletal muscles leads to a reduced regeneration potential. The regeneration capacity of HSCs also declines with age. Concomitantly, the blood undergoes age-related changes that include a loss of the balance between its two main lineages — myeloid and lymphoid — with myeloid cells being overproduced with age. Interestingly, the authors reproduced this myeloid cell bias in mice by suppressing autophagy in adult HSCs. Autophagy-deficient HSCs also had impaired regeneration capacity when transplanted into irradiated mice, indicating that a loss of autophagy recapitulates functional defects that are associated with ageing.

Autophagy-deficient HSCs are larger and various membranous compartments, including metabolically active mitochondria, are expanded, suggesting that a loss of autophagy is linked to the exit of HSCs from quiescence and their activation. Indeed, forcing HSC activation with cytokine-rich medium resulted in reduced autophagy, as well as increased mitochondrial mass and high metabolic activity, accompanied by a switch from glycolytic to oxidative metabolism. Similar metabolic changes were observed in autophagy-deficient HSCs, and this metabolic activation was also associated with increased cell cycle activity and enhanced *in vitro* differentiation that favoured the myeloid lineage. Collectively, these data indicate that the loss of HSC quiescence upon their activation results in enhanced metabolic activity and increased, pro-myeloid cell differentiation, and that autophagy directly counteracts these effects.

The gene expression profiles of cytokine-activated and autophagy-deficient HSCs resembled the profiles of more differentiated haematopoietic progenitor cells rather than those of control HSCs. These changes in gene expression were accompanied by DNA hypomethylation. Promoting demethylation in activated HSCs further enhanced their differentiation, whereas stimulating methylation supported their stemness. Thus, HSC activation is associated with epigenetic changes that direct HSC fate, driving them out of quiescence and inducing cell differentiation programmes.

Similarly to autophagy-deficient and cytokine-activated HSCs, old HSCs also demonstrated characteristics of metabolic activation. Analysis of autophagy in old HSCs revealed the presence of two subpopulations: old HSCs with high autophagy, which resembled young HSCs, and old HSCs with low autophagy, which were morphologically and metabolically similar to autophagy-deficient HSCs. These differences translated into differences in *in vivo* functionality: following transplantation into irradiated mice, old HSCs with high autophagy supported long-term regeneration of the blood system and the HSC pool, whereas old HSCs with low autophagy were progressively lost and failed to establish long-term engraftment.

In summary, this study reveals that autophagy prevents metabolic activation of HSCs and the subsequent induction of genetic programmes that lead to HSC differentiation, thereby contributing to the maintenance of HSC quiescence and to lasting, healthy haematopoiesis. As autophagy can be pharmacologically modulated, it will be interesting to explore whether it could be harnessed for therapeutic approaches such as blood rejuvenation or improving the efficiency of HSC transplantation.

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ORIGINAL ARTICLE Ho, T. T. *et al.* Autophagy maintains the metabolism and function of young and old stem cells. *Nature* http://dx.doi.org/10.1038/nature21388 (2017)
FURTHER READING Ito, K. & Tsuda, T. Metabolic requirements for the maintenance of self-renewing stem cells. *Nat. Rev. Mol. Cell Biol.* **15**, 243–256 (2014)