50 Years Ago

The mathematician of to-day is a much more powerful figure in research than his predecessor of fifty years ago. Indeed, it is fair to say that the mathematician is gradually taking over much of applied physics. This need not worry the physicist, who is moving into chemistry with growing momentum. Nor the chemist, who, with the physicist, is now a key figure in biological research: and what of the biologist? Does he need to worry? The answer is surely no, for he will become more and more a leader in the sociological fields, ergonomics being a case in point.

From *Nature* 23 February 1963

100 Years Ago

Nutrition Physiology. By Prof. P. G. Stiles — It is not possible to regard the book as a mere addition to the already numerous primers of physiology; it is something beyond this, although it makes no pretensions to being anything profound. It can be read with profit by the junior student, and still more by the senior student, and even the professed physiologist. Old truths are often put in new ways, and so fresh light is shed upon familiar problems … The book contains the inevitable chapter on alcohol; this is written in a moderate strain, and may, perhaps be viewed with disfavour by the extreme teetotaller because it is not intemperate. As one reads it, one almost feels that its author was writing it because he had to, but was protesting all the time inwardly against the American law which excludes all physiological books from scholastic institutions which do not obey the tyrannical behests of the party in power.

From *Nature* 20 February 1913

of autophagy in adult stem-cell function.

Warr *et al.* explore this question in both young mouse haematopoietic stem cells (HSCs) and in more-differentiated HSC progeny, including progenitor cells of the immune cells granulocytes and macrophages. The authors find that little or no autophagy occurs in freshly isolated young HSCs, but that this process can be rapidly induced when the cells are exposed to metabolic stress both *in vitro* and *in vivo*. Moreover, when autophagy is inhibited during such metabolic stress, young HSCs rapidly die through apoptosis, indicating that autophagy is crucial for their survival. By contrast, granulocyte–macrophage progenitor cells show higher baseline levels of autophagy, but no shift under starvation conditions.

Autophagy can be stimulated in several ways[2], including through inhibition of the signalling molecule mTOR and activation of stress-induced transcription factors such as FoxO3 and p53. Warr and colleagues find that the primary driver in HSCs is FoxO3, with little contribution from mTOR or p53.

FoxO3 is a member of the FoxO family of transcription factors, which are involved in diverse processes, including stress resistance, apoptosis and metabolism. Loss of a single type of FoxO protein has been found to have little effect on HSCs, but simultaneous loss of three of them (FoxO1, FoxO3 and FoxO4) leads to dramatic changes in HSC proliferation and in levels of reactive oxygen species[3]. Warr *et al.* propose that a similar redundancy may explain the incomplete loss of autophagy seen when only FoxO3 is missing. It is also possible that sirtuin proteins act upstream of FoxO3, as they are known to promote autophagy and increase longevity — in part by activating FoxO transcription factors — and to affect the proliferation of aged HSCs and their response to metabolic stress[2,4,5].

The implication of autophagy in ageing necessitates a better understanding of whether old stem cells use autophagy for similar purposes to their younger counterparts. Such knowledge should provide insight into the mechanisms underlying ageing and disease, and lead to improved strategies for enhancing health and longevity. Warr and co-authors show that, unlike young HSCs, freshly isolated old HSCs show some autophagy. Also, old cells could mount a similar response to their younger counterparts under starvation conditions. These findings contradict the currently held belief that autophagy diminishes with age.

Nonetheless, abrogated autophagy had different effects on the function of old and young HSCs. The authors report that blocking autophagy diminished the colony-forming potential of old HSCs to a much greater extent than in young cells. Colony formation is an *in vitro* metric used to determine the capacity of blood cells to form differentiated cell types. So although old and young cells show the same levels of autophagy, old cells seem to be more dependent on autophagy for their functioning. Confirmation of this would be to show that loss of autophagy more severely affects the capacity of old than young HSCs to repopulate the blood system of an individual whose immune system has been destroyed by radiation — the gold standard for assessing the function of HSCs.

The differences in autophagy between old and young HSCs did not seem to be due to changes in the activities of FoxO3, p53 or mTOR, and the transcriptional program triggered by FoxO3 was still active in old cells. Surprisingly, however, the old cells showed defects in the uptake of glucose, and so were in a state of metabolic stress even under normal conditions (Fig. 1). Feeding old cells a nutrient source that bypassed the need for glucose uptake restored the cells' colony-forming ability even when autophagy was blocked.

A study in mice recently indicated[6] that deregulation of cytokine proteins might be one explanation for the altered nutrient uptake in aged HSCs, as cytokines help to promote glucose uptake from the cellular environment. If such metabolic stress also occurs in humans, correcting it could help to improve stem-cell function in elderly people. Alternatively, experiencing prolonged autophagy may affect metabolism in old HSCs, as autophagy mediates the clearance of damaged mitochondria (organelles that act as cellular powerhouses), potentially resulting in lower energy output and slowing with age of essential cellular processes.

An intriguing question is whether the age-associated increase in autophagy is specific to HSCs or also occurs in stem cells of other tissues. So far, most of the other tissues studied for traits associated with age-related autophagy, such as the brain and heart, are those with a slow turnover of cells[2]. It could be that stem cells in highly proliferative tissues such as the blood have a different dependence on autophagy. For a definitive answer to this, researchers should examine stem cells in other tissues with a high cell turnover, such as the skin and gut. ■

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1. Warr, M. R. *et al. Nature* **494,** 323–327 (2013).
2. Rubinsztein, D. C., Mariño, G. & Kroemer, G. *Cell* **146,** 682–695 (2011).
3. Tothova, Z. *et al. Cell* **128,** 325–339 (2007).
4. Kroemer, G., Mariño, G. & Levine, B. *Mol. Cell* **40,** 280–293 (2010).
5. Ou, X. *et al. Blood* **117,** 440–450 (2011).
6. Ergen, A. V., Boles, N. C. & Goodell, M. A. *Blood* **119,** 2500–2509 (2012).

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