elongation provides an additional boost to fructose uptake, which might decrease fructose spillover into the colon and the liver as a consequence of persistent fructose consumption[5]. In such a scenario, even though villus elongation promotes fat absorption, it might also partly mitigate the harmful effects of fructose itself on the liver. It will be interesting to determine how the complex balance between the intestine's absorptive and metabolic capacities for fructose, lipids and other nutrients, and the intersection of these processes with the activity of microorganisms in the colon together contribute to obesity-related conditions.

Considering the therapeutic potential of this work, the authors' experiments strongly suggest that PKM2 supports the survival of the intestinal cells in which it is expressed. However, PKM2 is also expressed in many other types of cell, such as immune cells, which mediate the functions necessary to maintain the health of both the intestine and the liver.

Curiously, despite its ability to prevent villus elongation mediated by HFCS, TEPP-46 did not improve liver steatosis in the authors' experiments. This finding contrasts with the decrease in fructose-induced steatosis that the authors observed with the *Pkm* deletion that prevents PKM2 expression. This discrepancy between genetic and pharmacological approaches to PKM2 modulation raises the possibility that the combined action of PKM2 activators on multiple cell types might ultimately determine their ability to modulate specific tissue functions in disease. Despite early hopes, PKM2 activators have yet to reach the clinic as cancer therapies. Taylor and colleagues' work highlights the fact that gaining an in-depth understanding of tissue and disease contexts could allow researchers to suggest new therapeutic areas in which PKM2 activation might prove useful. Regardless, avoiding sugary drinks altogether might be a good start to curbing obesity.

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Physiology

A stem-cell basis for skeletal ageing

Matthew B. Greenblatt & Shawon Debnath

How ageing contributes to bone loss is unclear. In ageing mice, skeletal stem cells lose their ability to generate bone-forming cells called osteoblasts, and instead promote the generation of bone-resorbing cells called osteoclasts. **See p.256**

Ageing is a key driver of bone-mass reductions and skeletal fragility. The bone loss that occurs with ageing reflects the confluence of many molecular and cellular processes, and it has therefore been more difficult to understand than the mechanistically distinct form of bone loss associated with the decline of oestrogen in women after menopause[1–3]. However, insights into the identity of skeletal stem cells (SSCs) and other related progenitor cell populations that produce bone-forming cells called osteoblasts[4,5] have facilitated investigation into how ageing affects skeletal cells. On page 256, Ambrosi *et al.*[6] now determine how, with ageing, the function of SSCs changes, contributing to bone loss and impaired skeletal regeneration.

To distinguish the effects of intrinsic ageing-driven changes in these stem cells from environmentally driven changes, Ambrosi *et al.* isolated SSCs from the bones of young (2-month-old) and aged (24-month-old) mice and transplanted them into young recipient mice, in which the transplants formed small masses of bone tissue. This approach revealed two key differences between young and aged SSCs (Fig. 1a, b). First, the bone mass produced by aged SSCs was much smaller than that produced by young SSCs. Second, aged SSCs exhibited an increased ability to promote the formation of osteoclasts, the blood-derived cell type responsible for bone resorption. Thus, ageing hobbles the ability of SSCs to maintain a healthy balance between driving bone formation and bone destruction.

Next, the degree to which the aged environment affects SSCs was examined. The authors surgically joined old and young mice, thereby placing old and young SSCs in a shared blood circulation. In line with aged SSCs retaining functional deficits after transplantation, this approach did relatively little overall to normalize bone formation in the aged mice. Therefore, the ageing-driven reprogramming of SSCs seems to be a function of the direct effects of ageing on SSCs, rather than being

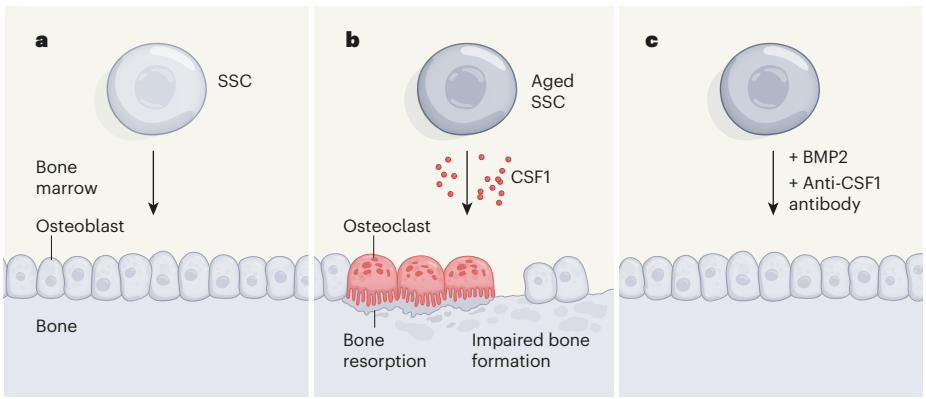

Figure 1 | The effects of ageing on skeletal stem cells (SSCs). a, SSCs serve as the cellular source of bone-forming cells called osteoblasts. The ability of these cells to generate osteoblasts is one of the determinants of overall bone formation and the resistance of the skeleton to fracture. **b**, Ambrosi *et al.*[6] show in mice that, with ageing, SSCs become less able to generate osteoblasts. Aged SSCs also secrete increased levels of CSF1, a soluble protein that contributes to the generation of bone-resorbing osteoclast cells. Together, these effects disrupt the normal balance between bone formation and resorption and therefore contribute to ageing-associated bone loss. **c**, A therapeutic strategy emerging from this model focuses on the administration of antibodies that block CSF1, together with BMP2 protein to promote SSC function. The authors show that this strategy improves fracture healing in aged mice.

driven by ageing-associated factors circulating in the blood.

Given that a young circulatory environment did not seem to reverse SSC ageing, efforts to counteract SSC ageing might be best targeted towards the effects of ageing on the downstream functions of SSCs. By measuring gene expression in aged SSCs, the authors found that colony stimulating factor 1 (CSF1), a soluble protein that promotes osteoclast maturation, is secreted at increased levels by aged SSCs compared with young SSCs.

Accordingly, the authors tested a therapeutic strategy to address SSC ageing. They mixed antibody molecules that specifically bind and block the function of CSF1 together with BMP2 — a protein with complex effects that can include the promotion of bone formation[7] — into a gel, which they placed around bone fractures in young and aged mice. Remarkably, the combination of BMP2 and anti-CSF1 antibody treatment reversed the deficits in fracture healing observed in aged mice (Fig. 1c).

Overall, this report clearly establishes that ageing directly affects SSCs and that ageing-associated deficits in SSCs contribute to skeletal deterioration over time. However, it remains unclear to what degree these ageing-driven deficits specifically reflect changes in the stem-cell functions of these SSCs, such as self-renewal, as opposed to changes in how these cells differentiate or in the function of the mature osteoblasts they produce.

As one of the first studies that defines the basis of skeletal ageing in terms of specific and well-characterized stem-cell populations, this report serves as a powerful starting point for future mechanistic studies, including those clarifying how specific skeletal cell types participate in ageing-associated bone loss. In particular, parallel studies in mice have demonstrated that a population of bone-marrow-resident skeletal cells expressing the proteins CXCL12, EBF3 and LEPR account for a progressively increasing fraction of bone-forming cells with ageing[8–10]. How this population relates to the stem cells in Ambrosi and colleagues' study remains unclear. Clarifying this point will be crucial to piecing together the broader cellular basis of skeletal ageing.

Skeletal ageing also encompasses a broader range of changes beyond the effects explained here, including the accumulation of senescent cells, increases in marrow fat content and changes in articular cartilage and bone architecture that include an overall widening of bones[11]. Future work will need to evaluate which of this broader set of ageing-associated changes are specifically due to intrinsic changes in SSCs, and which reflect the impact of other mechanisms of ageing.

Furthermore, definitions of the cell types that make up bone, including SSCs, are rapidly becoming more precise, and it is likely that an iterative process of refining these definitions will continue over the next few years. Indeed, a study published in February indicated that certain combinations of protein markers used by some researchers to define SSCs can also be expressed by mature bone-forming cells[12]. This suggests that extra markers will be needed to define SSCs as a pure population of stem cells. Our understanding of SSC-based mechanisms of ageing will need to keep pace as the definitions of skeletal cell types continue to evolve.

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Cell biology

Ubiquitin protein helps cells to de-stress

Titus Franzmann & Simon Alberti

In stressed cells, proteins and RNA molecules cluster together to form stress granules. It emerges that the small protein modifier ubiquitin is needed to disassemble stress granules in recovering cells.

The biggest threat to a cell during exposure to environmental stress factors, such as high temperature, is the unfolding of its proteins. Two strategies prevent the accumulation of damaged proteins: refolding, which is assisted by chaperone proteins, and protein degradation. In one degradation pathway, ubiquitin molecules are attached to target proteins to signal that they are to be degraded by a protein complex called the proteasome. Early work showed that heat stress induces the ubiquitination and proteasomal degradation of cellular proteins[1]. Now, writing in *Science*, Maxwell *et al.*[2] and Gwon *et al.*[3] report that ubiquitination of a large set of proteins is required to recover normal cellular function when stress subsides.

Maxwell *et al.* analysed ubiquitinated proteins from cultured cells that had been exposed to five different stressors, including heat stress (42 °C). Each type of stress led to the ubiquitination of a distinct set of proteins, suggesting that different proteins are susceptible to different stressors. The authors found that 381 proteins were ubiquitinated under heat stress. These proteins include those involved in protein synthesis at ribosomes (the cell's translational apparatus) and in the transport of RNA and proteins from the cell nucleus to the cytoplasm. They also include proteins that bind to RNA molecules in the cytoplasm of stressed cells to form large RNA–protein structures called stress granules.

Maxwell *et al.* and Gwon *et al.* next showed that ubiquitination is required for the recovery of normal transport between the nucleus and the cytoplasm, and for the dissolution of stress granules during recovery from heat stress (Fig. 1). However, the authors did not examine the molecular underpinnings of recovery. The proteins are exposed to a large amount of energy during heat stress, so it is likely that their 3D structure is disrupted and that the proteins are then ubiquitinated and destroyed by the proteasome.

Previous research has shown that most heat-stress-induced ubiquitination can be blocked by treatment with cycloheximide[4,5], a compound that blocks protein synthesis by ribosomes. Thus, many of the proteins that are ubiquitinated during heat stress could be defective ribosomal products (DRiPs): newly synthesized proteins that misfold at the ribosome. One possible scenario is that, in stressed cells, proteins involved in translation (including RNA-binding proteins) misfold because of their interaction with DRiPs, and these misfolded proteins must be degraded before cells can restart crucial processes after the stress subsides.

Stress granules assemble when protein synthesis by ribosomes stops. G3BP1 is a scaffold protein needed for the assembly of stress granules[6–8], and Maxwell *et al.* found