KCa3.1-expressing glioma cells restores both periodic activity and proliferation. It therefore seems that these pacemaker cells and the associated network are self-organizing, and that a small number of such cells can restore network properties and glioma expansion.

These results raise the question of how the patterns of Ca^{2+} oscillation are converted into proliferative signals. Here, Hausmann *et al.* take advantage of research that links the activities of key intracellular signalling pathways to distinct Ca^{2+} oscillation frequencies[5,6]. Their analysis reveals that the frequency of the oscillations in pacemaker cells lies in the range that activates the MAPK and NF-κB cascades – two key pathways implicated in cancer-cell proliferation. When the researchers co-culture KCa3.1-deficient glioma cells with cells that have activated MAPK and NF-κB pathways, they find that the activated cells can restore network activity and proliferation.

Finally, the authors test directly whether inhibiting KCa3.1 affects tumour growth. They find that when transplanted into mouse brains, glioma cells with reduced expression of KCa3.1 form tumours at a much slower rate than do normal glioma cells. Extending these genetic studies towards prospective therapeutic approaches, they show that TRAM-34 and senicapoc also suppress glioma growth in mice. Together, these results indicate that KCa3.1 is essential for glioma formation, and suggest a potential therapeutic strategy rooted in targeting the glioma pacemaker cells.

Hausmann and colleagues' work expands on the group's previous observations of the glioma-cell microtube highway[4], demonstrating the use of Ca^{2+} to orchestrate the flow of information across the network. The activity of Ca^{2+} has a clearly defined role in neuronal signalling, but in glia it is used as a proxy for overall physiological activity, and its contributions to glial-cell function are enigmatic[7]. Extended to glioma, these observations raise questions about what else is being transported between cells, and how these signals are encoded in pacemaker cells and deciphered in adjoining network cells.

These pacemaker cells are rare and exhibit a degree of functional plasticity (characteristics that are reminiscent of tumour-initiating glioma stem cells[8]). This plasticity – in terms of the ability to interconvert between pacemaker and non-pacemaker oscillation states – could present a therapeutic challenge, because non-pacemaker cells can re-establish the network. The cells' properties should also stimulate research into how the pacemaker's periodic activity is acquired, the associated biology of KCa3.1 channels in gliomas, and the sources of Ca^{2+} that seem to drive the network.

Nonetheless, the demonstration that pharmacological inhibition of KCa3.1 activity can suppress glioma development is exciting, because it suggests that disrupting these glioma pacemakers has clinical potential. Given the dearth of therapeutic options for people with malignant glioma, these studies offer hope that strategies rooted in the tenets of cancer neuroscience might pave the way to improved treatment of this deadly disease.

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Ageing

Senescent cells damage the body throughout life

David J. Glass

Cells in a state of arrested growth, called senescence, have been characterized in skeletal muscle in mice. Senescent cells promote inflammation and block regeneration, and thus might induce harmful changes in aged muscle. **See p.169**

Ageing was long thought to be inevitable, but treatment to forestall it is increasingly argued to be feasible. Of particular interest for such treatments are the 'senescent' cells that accumulate with age – cells that have stopped dividing and instead become seemingly dormant, in a state of arrested growth[1]. But it has proved challenging to isolate senescent cells, preventing researchers from fully understanding their behaviour throughout life. On page 169, Moiseeva *et al.*[2] present an approach to isolate senescent cells from mice. Their subsequent analyses reveal that the cells cause inflammation, preventing skeletal-muscle regeneration even in young animals (a setting in which the cells were previously assumed to be beneficial). The work adds weight to the idea that removing senescent cells could help to combat ageing.

Senescent cells make up a small percentage of the body, even in older individuals, and yet they cause major damage by secreting signalling proteins through a process called the senescence-associated secretory phenotype (SASP)[3]. The SASP induces fibrosis – the thickening and scarring of tissue – and blocks the functions of healthy neighbouring cells. As such, senescent cells are thought to contribute to many diseases and unwanted side effects of ageing.

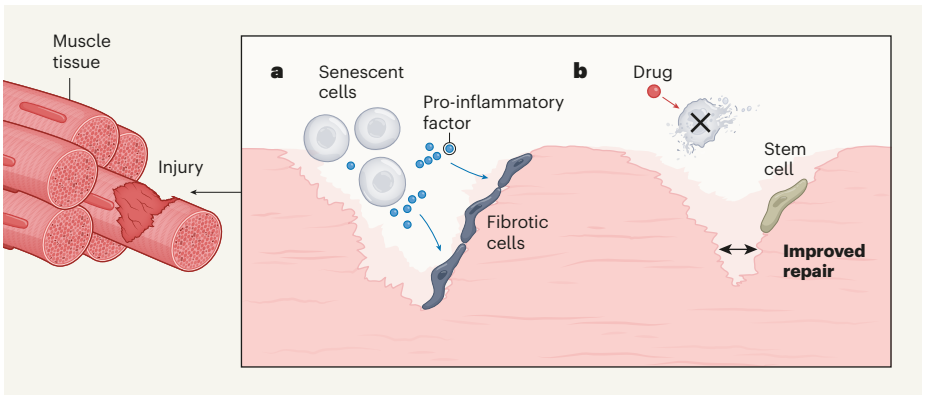

Figure 1 | Senescent cells inhibit recovery from injury. Moiseeva *et al.*[2] have analysed populations of senescent cells in injured muscle from mice of various ages. **a**, They found that, regardless of age, injury leads to an increase in the number of senescent cells (with the increase much more pronounced in older animals, not shown). The cells produce factors that trigger inflammation of the tissue and lead to the formation of fibrotic (scar) tissue, preventing muscle regeneration. **b**, When the authors gave the animals drugs that kill senescent cells, they found improved muscle repair by stem cells.

These side effects include sarcopenia — an age-associated decline in skeletal muscle mass and function that occurs as ageing skeletal muscle becomes replaced by fat and fibrotic tissue, pointing to an inability of the muscle to repair itself[4]. By contrast, healthy young skeletal muscle has a remarkable regenerative capacity, even after injury. Moiseeva *et al.* set out to investigate how the presence of senescent cells might underlie skeletal muscle's diminishing ability to regenerate with age in mice.

The first challenge was to selectively isolate senescent cells from muscle tissue. The enzyme senescence-associated β-galactosidase (SA-β-gal) is highly active in senescent cells. The authors collected muscle tissue that had previously been damaged, and treated it with a fluorogenic substrate that fluoresces when cleaved by SA-β-gal. This enabled them to separate fluorescent senescent cells from other cells using a well-established approach called fluorescence-activated cell sorting. The group observed many more senescent cells in ageing tissue than in young tissue after injury. They also used their cell-labelling strategy to identify and study the positions of the cells in the injured tissue *in vivo*.

Tissue regeneration requires both stem cells and surrounding 'niche' cells, which can influence the behaviour of the stem cells. Moiseeva and colleagues examined gene expression and chromatin (the DNA–protein complex in which genetic material is packaged in the nucleus) in the senescent cell populations from young and old animals. They found that senescent cells — even those from young animals — make up part of the niche and have inflammation-promoting characteristics, which are associated with age-related declines in health (Fig. 1). The authors showed that several different cell types give rise to senescent cells, including skeletal muscle stem cells, myeloid cells and fibro-adipogenic cells, the last of which can promote inflammation, fat deposition and fibrosis in ageing animals[5].

The group's discovery that senescent-cell numbers increased drastically after damage highlights a mechanism that might explain why some older people are more affected by ageing processes than others — if they have had an injury, more senescent cells might be present in their muscles. In line with this idea, geriatric mouse muscle that had been injured and so harboured senescent cells was less able to induce force than was uninjured geriatric tissue, even after the injury had repaired. However, the strength of the muscle was improved by giving the animals dasatinib and quercetin, drugs that can kill senescent cells. This shows that removal of senescent cells can improve muscle function.

Moiseeva *et al.* found that removal of senescent cells also improved muscle repair in younger animals. This finding was somewhat surprising, because senescence is not usually associated with younger animals (or people). The result therefore suggests that strategies to remove senescent cells might also help younger people to recover from muscle injury.

To explore the mechanism by which senescent cells block muscle regeneration, the group further profiled gene expression in the cells, and found a decrease in expression of genes related to the function of energy-producing organelles called mitochondria, and an increase in inflammatory genes, among other changes. In particular, interferon-stimulated genes (which are associated with inflammation) are upregulated in both ageing and senescence. Moreover, the authors found changes in collagen production, which have previously been linked to fibrosis[6]. Fibrosis interferes with regeneration by creating the equivalent of scar tissue, instead of competent normal tissue. In the case of skeletal muscle, fibrotic tissue forms instead of muscle fibres, thus impinging on muscle function.

Together, Moiseeva and colleagues' findings indicate that senescent cells trigger inflammation and block regeneration throughout the animal's life, and in particular seem to be responsible for many of the detrimental changes found in aged skeletal muscle. The changes in gene expression observed by the authors have also been shown to occur in the cells of aged tissue in general[6], indicating that age-induced changes might be driven by senescent cells. It was not previously known that senescence might be the main driver of age-related gene changes. The work therefore gives fresh rationale to the strategy of seeking treatments that selectively remove senescent cells to combat age-related muscle weakness.

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Epidemiology

Global estimates of excess deaths from COVID-19

Enrique Acosta

Estimating the number of deaths attributable to COVID-19 around the world is a complex task — as highlighted by one attempt to measure global excess mortality in 2020 and 2021. **See p.130**

Knowing how COVID-19 affects global mortality rates is crucial if we are to understand the factors that govern its spread and severity, and to be able to evaluate the effectiveness of government responses to the pandemic. In May, a team of researchers led by the World Health Organization (WHO) and the United Nations Department of Economic and Social Affairs published the first results from their attempt to estimate global, COVID-19-related death rates. On page 130, Msemburi *et al.*[1] present these estimates in more detail.

Many deaths from COVID-19 went undetected in official reports from 2020 and 2021, because of limited testing capacity and misclassification of causes of death. This lack of data makes it challenging to quantify the mortality toll of short-term events, such as wars and natural disasters, as well as pandemics. For this reason, excess mortality — defined as the difference between all observed and expected deaths in a given period — is considered the gold-standard approach for estimating the mortality toll of short-term events[2,3]. But it is hard to find a universally effective way to measure excess mortality[4,5], because there are substantial variations in underlying mortality trends and data availability across populations.

Msemburi and colleagues set out to estimate excess deaths from COVID-19 for every country in the world. The authors report that there were between 13.2 million and 16.6 million more deaths than expected in 2020 and 2021. This death toll was between 2.4 and 3.1 times higher than the officially reported number of COVID-19-related deaths. Four out of five excess deaths occurred in middle-income countries (Fig. 1), with some of the worst affected in Latin America. In both