circuits called transmons. Each transmon can be thought of as a site that photons can occupy. If two photons occupy the same site, they interact with each other at a substantial energy cost.

The authors implemented two different schemes to produce a Mott insulator, a simplified picture of which is a state that has exactly one photon per site. Here, I will describe only the simpler scheme (although the second one was observed to yield a higher-quality final state). To understand this scheme, consider a single site, and how this site might be driven to be occupied by a single photon. It is easy to add a photon to an empty site, without dissipation, by applying a microwave-frequency electric field. However, such a process is equally likely to remove a photon from an already occupied site.

What is needed is an irreversible process that adds a photon to an empty site. Such a process can be engineered by combining non-dissipative processes with a 'reservoir' that rapidly loses photons. In the authors' scheme, an applied microwave field causes photons to be added in pairs to a site (or subtracted in pairs, in the unavoidable reverse process). When the site is occupied by a pair of photons, it has the same energy as the reservoir and one photon can move to the reservoir and be lost, resulting in the site being left with a single photon (Fig. 1a). A single photon on the site is not energetically matched with the reservoir, and therefore remains on the site (Fig. 1b).

This idea extends to more than one site. In Ma and colleagues' scheme, the chain of sites in which the Mott insulator is to be prepared is attached at one end to a reservoir (Fig. 1c). If any site in the chain is doubly occupied, one of the photons from this site will wander through the chain until it reaches the end site. This photon will then move to the reservoir and be lost, ultimately resulting in a Mott-insulator state (Fig. 1d).

Although this simple picture makes it look as if the sites could be prepared independently to have exactly one photon, the actual Mott-insulator state is more complicated, and has quantum fluctuations that excite the system to include empty and doubly occupied sites. The authors' scheme prepares the system to include just the right excitations to be in the true Mott-insulator state. This state is an example of a strongly correlated phase of matter, which has been studied for decades in condensed-matter and ultracold-matter physics owing to its importance in quantum materials.

The strongly correlated state prepared in the current experiment is relatively simple, but the superconducting-circuit platform is flexible, and could be used to realize systems that have different geometries and different couplings between sites. Ma and colleagues' scheme is predicted to be able to prepare any gapped phase of matter — defined as having a non-zero energy cost to add or remove a particle — that occurs in any of these systems. One type of gapped phase that will surely be the target of future work is 'topological' matter. Fundamental open questions about the behaviour of topological matter can be explored in superconducting-circuit systems using dissipative preparation schemes[9].

At least two further advances are needed if researchers are to use the authors' scheme to prepare complex quantum states. First, the technique needs to be extended to larger quantum systems. Second, the quality of state preparation needs to be increased. Currently, there is a relatively small (roughly 10%) density of defects — sites that have either zero or two photons. Nevertheless, this density is at least ten times larger than that of comparable experiments that use, for example, ultracold atoms[10]. Reducing the defect density is challenging, but it seems to be an engineering issue rather than a fundamental one.

The ability to engineer quantum states promises to revolutionize areas ranging from materials science to information processing. Because quantum states are often as fragile as they are useful, robust state preparation will be essential to realizing their potential. Ma and colleagues' technique engineers dissipation to drive the system to the desired state and is therefore intrinsically robust to perturbations and noise. The robustness and generality of this scheme will ensure that, as it is refined, it will find a home in the quantum mechanic's toolbox. ■

Kaden R. A. Hazzard *is in the Department of Physics and Astronomy and the Rice Center for Quantum Materials, Rice University, Houston, Texas 77005, USA.*
e-mail: kaden.hazzard@gmail.com

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AGEING

An evolving picture of cell senescence

DNA sequences called retrotransposons can copy themselves and reintegrate at new sites in the genome, causing damage. It now seems that inhibiting this process can prevent age-related health decline in mice. SEE ARTICLE P.73

BENNETT CHILDS & JAN VAN DEURSEN

Old[1] and diseased[2] tissues often contain cells that have entered a state called senescence, in which they stop dividing and become resistant to death-inducing pathways. These cells secrete a collection of factors, collectively known as the senescence-associated secretory phenotype (SASP), that have inflammatory, protein-degrading and other biologically active properties, and can impair tissue function. There is therefore interest in targeting the SASP to combat age-related diseases. The composition of the SASP varies, and might change over the lifetime of the senescent cell[3]. However, the molecular drivers involved in this evolution are incompletely understood. On page 73, De Cecco *et al.*[4] identify a key contributor to the 'late' SASP: the reactivation of dormant DNA sequences called retrotransposons.

Retrotransposons are often called 'jumping genes', because the messenger RNA transcribed from them can undergo a process called reverse transcription to produce an identical DNA sequence that then reinserts into the genome at a different site. Although retrotransposons comprise about 42% of the human genome, most carry mutations that render them functionally inactive[5]. Transcription of those that remain functional must be prevented by protein- or RNA-based regulatory mechanisms to prevent the jumping of retrotransposons, which can cause either genetic mutations or genomic instability and might lead to cancer[6]. However, retrotransposons can be reactivated during ageing[7].

De Cecco *et al.* found that one type of retrotransposon, LINE-1, was highly activated in senescent human cells within 16 weeks after they had stopped dividing — a stage the authors term late senescence. The group showed that high levels of the transcriptional repressor protein RB1 and low levels of the transcriptional activator protein FOXA1 normally keep LINE-1 in check. These proteins are abnormally expressed in late-senescent cells, enabling LINE-1 reactivation (Fig. 1).

At this late stage, the SASP is known to include two related inflammatory proteins called interferon-α and interferon-β. This signalling protein is part of an ancient antiviral mechanism called the cGAS–STING pathway, which is activated by the presence

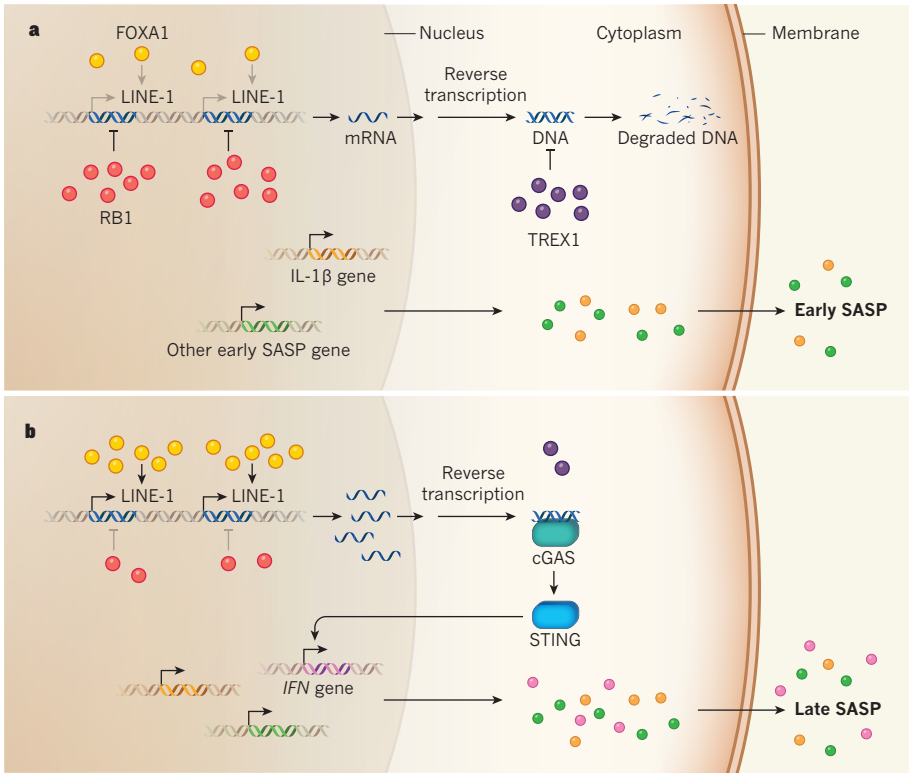

Figure 1 | From early to late senescence. Senescent cells have stopped dividing and secrete inflammatory proteins, collectively known as the senescence-associated secretory phenotype (SASP). De Cecco *et al.*[4] report changes in the SASP over time. **a**, During early senescence, the expression of DNA sequences called retrotransposons (such as LINE-1) is repressed by low levels of the transcriptional-activator protein FOXA1 and high levels of the transcriptional repressor RB1. The low levels of messenger RNA produced enter the cytoplasm and undergo a process called reverse transcription to produce DNA. This DNA is degraded by the protein TREX1 — as a result, retrotransposons have no effect on the early SASP, which involves the expression and secretion of proteins that include IL-1β. **b**, In late senescence, RB1 and TREX1 levels decline and FOXA1 levels rise, leading to increased cytoplasmic LINE-1 DNA. The DNA is sensed by a pathway involving the proteins cGAS and STING, leading to transcription of *IFN* genes that encode the proteins interferon-α and interferon-β. These interferon proteins contribute to the late SASP, and support the expression of early SASP factors.

of DNA in the cell cytoplasm. When viral DNA is present in the cellular cytoplasm, the cGAS–STING system triggers the production of interferon proteins and related proteins that together drive an infected cell down a cell-death pathway called apoptosis, preventing the spread of infection. The cGAS–STING pathway has previously been linked to senescence[8,9] — cytoplasmic DNA accumulates in senescent cells because they produce abnormally low levels of the DNA-digesting enzyme TREX1 (ref. 10). However, the source of the DNA that accumulates in the cytoplasm of senescent cells has not been completely clear.

Because retrotransposons were originally derived from ancient viruses, they can activate cGAS–STING (ref. 11). De Cecco *et al.* showed that the cytoplasmic DNA in senescent cells is produced, at least in part, by reactivated LINE-1 elements. The authors confirmed that abnormally low levels of TREX1 permit LINE-1-derived DNA to accumulate in the cytoplasm in late senescence. If they blocked LINE-1 transcription using inhibitory RNA molecules, or blocked reverse transcription using the drug lamivudine, the interferon response was not triggered in late senescence. Such LINE-1 inhibition had no effect on the 'early' SASP protein IL-1β, or on the cell-cycle arrest associated with senescence, but did cause loss of other SASP factors (including the proteins CCL2, IL-6 and MMP3) late in senescent-cell life. This suggests that the late interferon response is required to sustain the SASP in the long term, but that it is dispensable for the early SASP.

Next, De Cecco *et al.* showed that retrotransposon transcription promotes the late SASP *in vivo* in ageing mice. Moreover, by using lamivudine to block the reverse transcription of retrotransposons in mice from 20 to 26 months of age, the authors could prevent the animals from developing several age-related conditions, including degeneration of the blood-filtration system in the kidneys, atrophy of skeletal muscle fibres and hallmarks of chronic inflammation.

In a final set of experiments, the researchers demonstrated that ORF1, a protein encoded by LINE-1 elements, is expressed specifically in senescent cells in aged human skin, but that not all senescent cells express ORF1. Combined with *in vivo* experiments showing that the expression of LINE-1 peaks later than the expression of other senescence markers in mice, and *in vitro* data demonstrating that mouse cells can still enter senescence in the presence of lamivudine, these data suggest that LINE-1 reactivation is a consequence, rather than a cause, of senescence.

The implications of this study for human biology are speculative but encouraging. For instance, the importance of the interferon response for killing virus-infected cells raises the possibility that it has a central role in the body's natural ability to clear senescent cells. However, a more thorough examination of aged or diseased human tissue will be required to determine whether the late-SASP mechanism generally applies to humans.

Senescent cells are rare, even in advanced age[2,3]. Nonetheless, eliminating these cells and their SASP prevents age-related declines in health[1]. As a result, strategies for killing or modifying senescent cells (referred to as senolytic and senomorphic approaches, respectively) have received much attention. The first senolytic compounds, which inhibit the anti-apoptosis protein Bcl, are generally accepted as effective[12]. De Cecco and colleagues' work demonstrates that lamivudine can act as a senomorphic compound.

Because a senomorphic compound would have to be continuously present to suppress the SASP, it might require more-frequent administration than a senolytic compound, which removes senescent cells outright, so that no further treatment is needed until more accumulate. Encouragingly, lamivudine has been used in humans as a long-term antiretroviral therapy without major side effects — unlike other senomorphic compounds such as rapamycin, which blunts the SASP[13] but is a potent immunosuppressant. However, there are as yet no reports that lamivudine improves the healthy human lifespan or any indications that it represses retrotransposons in humans.

One potential risk of senomorphic compounds is the development of cancer, because, in preventing the proliferation of diseased or damaged cells, senescence can have a beneficial, tumour-suppressive role. De Cecco and co-workers' cell-culture experiments suggest that lamivudine does not disrupt cell-cycle arrest, which is key to this beneficial effect of senescence. However, they monitored lamivudine-treated animals for just six months. Longer-term *in vivo* follow-up is required to prove that this therapy would not increase the risk of cancer. If this can be confirmed, the current study could open the door to the use of reverse-transcription inhibitors and, perhaps, inhibitors of the cGAS-STING pathway, as a way of combating diseases such as osteoarthritis and atherosclerosis, which have been linked to the accumulation of senescent cells. ■

Bennett Childs *and* **Jan van Deursen**
are in the Department of Pediatric and

Adolescent Medicine, Mayo Clinic, Rochester, Minnesota 55905, USA.
e-mails: childs.bennett@mayo.edu; vandeursen.jan@mayo.edu

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CLIMATE SCIENCE

Fate and future role of polar ice sheets

Mass loss from the Greenland and Antarctic ice sheets is accelerating as a result of rising global temperatures. Two studies explore how this mass loss will affect sea level and other aspects of the climate in the future. SEE ARTICLES P.58 & P.65

HÉLÈNE SEROUSSI

Rising sea level is one of the greatest threats posed by climate change. The Greenland and Antarctic ice sheets have been losing mass at an increasing rate during the past few decades, and are the largest source of uncertainty in projections of future sea level[1,2]. How much these ice sheets will change over the coming decades to centuries, and how they will affect Earth's climate, remain largely unknown. Two studies now provide some answers to these questions. On page 58, Edwards *et al.*[3] revisit estimates of the contribution of the Antarctic Ice Sheet to sea-level rise over the next few centuries. And on page 65, Golledge *et al.*[4] investigate how polar ice sheets affect other components of the climate system, demonstrating the ice sheets' crucial role in shaping ocean currents.

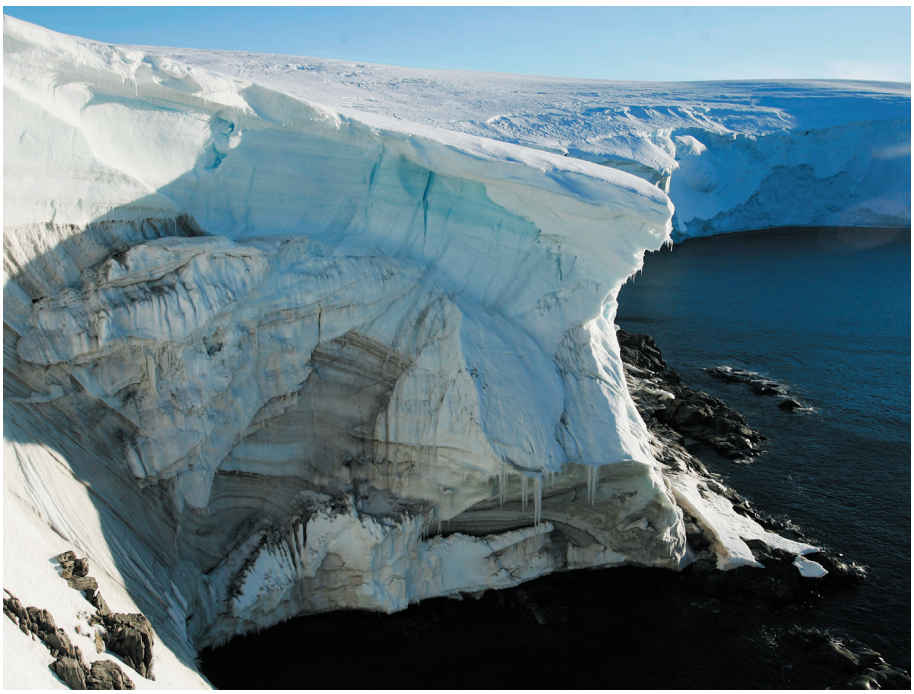
In the first study, Edwards and colleagues determine the future contribution of Antarctic ice to sea-level rise by examining a theoretical mechanism known as marine ice-cliff instability, which was proposed[5] in 2011 and revisited[6] in 2016. The idea is that, when a floating extension of a glacier collapses, a tall ice cliff is exposed at the glacier terminus (Fig. 1). This cliff is too tall to sustain its own weight and starts to collapse rapidly, leading to further glacier retreat and mass loss.

By taking this process into account, a numerical model predicted[6] that Antarctica alone could contribute as much as one metre to sea-level rise by 2100 in a 'business as usual' scenario of carbon emissions — which assumes that little, if anything, is done to abate emissions. For comparison, other models that do not include this process estimated[7] that Antarctica could contribute less than 40 cm. Marine ice-cliff instability was first used to reconcile models of ice-sheet flow in the Antarctic with sea-level estimates in warm periods of Earth's history[6]. However, the mechanism has been questioned by some glaciologists, partly because it has not been directly observed and is therefore difficult to model.

Edwards *et al.* use emulators of complex ice-sheet models to run large ensembles of simulations and explore the full spectrum of model parameters. They show that, for many sets of parameters, marine ice-cliff instability is not needed to reproduce the estimated Antarctic ice loss during three past warm periods: the mid-Pliocene (about 3 million years ago), the most recent interglacial (roughly 130,000–115,000 years ago) and 1992–2017. They also find that, without this mechanism, the projected contribution of Antarctic ice to sea-level rise by 2100 agrees well with the results of previous work[7–10]: a 5% chance of more than 30–40 cm under high-emissions scenarios and a 5% chance of more than 10–20 cm under low-emissions scenarios.

In the second study, Golledge and colleagues analyse the impact of the changing Greenland and Antarctic ice sheets on Earth's climate. Climate models typically include a dynamic atmosphere, ocean and sea ice, but do not consider changes in ice-sheet size and volume. Because ice sheets evolve on much longer timescales than those that govern the atmosphere or oceans, their evolution is assumed to have no effect on the other components of the climate system for simulations that cover a few centuries. As a result, ice-sheet simulations are carried out independently — with the influence of the atmosphere and oceans specified — and the impact of the ice sheets on these other components is therefore neglected.

Golledge *et al.* investigate the validity of this approach by including changes in the release of melted ice into the oceans in a climate model. They show that the increased discharge of fresh water from the ice sheets has important consequences for ocean circulation on much shorter timescales than expected. For example, in the Northern Hemisphere, the increased amount of fresh water released by the Greenland Ice Sheet gradually slows the Atlantic Meridional Overturning Circulation — a large system of



PAULINE ASKIN/REUTERS

Figure 1 | An ice cliff at Landsend, Cape Denison, Antarctica. Edwards *et al.*[3] and Golledge *et al.*[4] investigate how mass loss from polar ice sheets will affect Earth's climate. Shown here is an ice cliff that was exposed at the terminus of a glacier when a floating extension of the glacier collapsed.