

is now blossoming. Besides the examples discussed<sup>1–3</sup>, experiments continue on trapping excitons in coupled quantum wells<sup>17</sup>, on excitons in bulk semiconductors<sup>18</sup>, and on tripletons in magnetic insulators<sup>19</sup>. The appeal of quasiparticles in solids as systems to observe condensation is, in part, their light mass. The smaller the mass, the higher the critical temperature at which condensation occurs, and there is no reason why condensation of one of these quasiparticles cannot occur at room temperature. In fact, Demokritov and colleagues' experiments with magnons<sup>2</sup> supply evidence that this might already have been observed. Some of these schemes of quasiparticle condensation also, intriguingly, imply superconductivity<sup>20</sup>.

We now have several examples of systems with evidence of spontaneous coherence caused by a thermodynamic phase transition. Some people may not want to call certain cases Bose–Einstein condensation, but these systems collectively represent a new frontier in coherent phenomena. ■

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## AGEING

# Balancing regeneration and cancer

Christian M. Beausejour and Judith Campisi

**The proliferation of cells must balance the longevity assured by tissue renewal against the risk of developing cancer. The tumour-suppressor protein p16<sup>INK4a</sup> seems to act at the pivot of this delicate equilibrium.**

Tissue repair and regeneration are essential for longevity in complex animals, and often depend on the proliferation of unspecialized cells known as stem or progenitor cells. In many tissues, the regenerative capacity of such cells declines with age, and it is thought that this decline drives many age-related symptoms<sup>1</sup>. But stem/progenitor-cell proliferation is a double-edged sword. Although it ensures tissue repair and regeneration, it also puts tissues at risk of hyperproliferative diseases, the most deadly of which is cancer. This risk is mitigated by tumour-suppressor mechanisms, which either eliminate potential cancer cells by programmed cell death (apoptosis) or prevent their proliferation, often by permanently halting the cell division cycle (senescence). Therefore, the benefits to longevity afforded by stem/progenitor-cell proliferation might be compromised by mechanisms that prevent life-threatening cancer<sup>2</sup>. Three papers\* in this issue now find that this is indeed the case<sup>3–5</sup>.

In mammals, the p16<sup>INK4a</sup> protein inhibits cell-cycle progression and induces cellular senescence<sup>6</sup>, and its expression rises with age in many tissues, as does the accumulation of dysfunctional senescent cells<sup>7,8</sup>. Janzen *et al.*<sup>3</sup>

(page 421) find that p16<sup>INK4a</sup> levels increase with age in mouse 'haematopoietic' stem cells (HSCs) derived from the bone marrow. Other bone-marrow cells did not express p16<sup>INK4a</sup> in an age-dependent manner, so p16<sup>INK4a</sup> is a biomarker of ageing HSCs in the bone marrow.

But is this rise in p16<sup>INK4a</sup> expression biologically important? HSCs give rise to mature white blood cells. They can reconstitute these immune cells after being transplanted into mice that have been irradiated, and so have no HSCs. This reconstitution ability declines with age. Janzen *et al.*<sup>3</sup> report that young mice (2–3 months old) that lack the p16<sup>INK4a</sup> protein (p16<sup>INK4a</sup>−/− mice) have similar numbers of HSCs to normal, 'wild-type' mice of the same age. Moreover, the wild-type and p16<sup>INK4a</sup>−/− HSCs are equally able to reconstitute an immune system after transplantation.

Later in life (14–20 months), however, the p16<sup>INK4a</sup>−/− mice had significantly more HSCs than wild-type mice. The older p16<sup>INK4a</sup>−/− HSC populations also had more dividing cells and were better able to reconstitute an immune system than were wild-type HSCs from mice of the same age. So lack of p16<sup>INK4a</sup> slows the age-associated decline in HSC function. Unexpectedly, however, the young p16<sup>INK4a</sup>−/− HSCs were less effective at reconstituting an immune

system than were wild-type HSCs of either age. These findings suggest that, in young animals, p16<sup>INK4a</sup> prevents premature HSC exhaustion under the intense proliferative demand following transplantation. But in older animals, p16<sup>INK4a</sup> restricts HSC proliferation both under normal steady-state conditions and after transplantation.

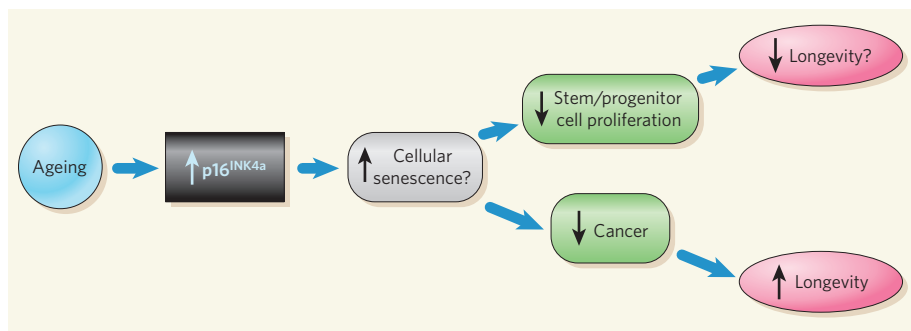
Krishnamurthy *et al.*<sup>4</sup> (page 453) studied a very different tissue in mice — the pancreas, which also shows an age-associated decline in function (here measured by insulin production) and in regenerative capacity. Expression of p16<sup>INK4a</sup> also increased in the pancreas during ageing (3–4 months compared with 16–20 months). This rise was confined mainly to the pancreatic islets, the cell clusters that contain insulin-producing β-cells and their progenitors.

The authors report two lines of evidence that p16<sup>INK4a</sup> limits islet-cell proliferation during ageing. First, mice genetically engineered to overexpress p16<sup>INK4a</sup> at young ages — to levels found in older wild-type animals — showed reduced islet-cell proliferation at all ages. Second, in mice deficient in p16<sup>INK4a</sup>, the age-associated decline in islet-cell proliferation was markedly diminished. When older wild-type mice were given a toxin that selectively kills β-cells, they developed diabetes that was eventually fatal. But, importantly, older mice deficient in p16<sup>INK4a</sup> developed only mild diabetes when exposed to the toxin. Recovery from the toxin requires β-cell proliferation and the regeneration of functional islets. After toxin treatment, the p16<sup>INK4a</sup>−/− mice had better islet-cell regeneration, greater insulin production and reduced blood-glucose levels than did wild-type mice. These differences occurred only between mice from the older age group, suggesting that the age-associated rise in p16<sup>INK4a</sup> impairs islet-cell regeneration and function, presumably by inhibiting the proliferation of β-cells and/or their progenitors.

In the third paper, Molofsky *et al.*<sup>5</sup> (page 448) link p16<sup>INK4a</sup> expression in mice to decreased formation of neurons originating in the forebrain 'subventricular zone' (SVZ). As with HSCs and the pancreas, p16<sup>INK4a</sup> expression increased in the SVZ with ageing (from 2 to 24 months). Moreover, SVZ cell proliferation declined *in vivo* with age, as did the number of stem/progenitor cells that form clusters that can proliferate and retain the ability to differentiate in culture. Deficiency of p16<sup>INK4a</sup> partially mitigated both of these traits in older animals, but there was no effect in young animals. Lack of p16<sup>INK4a</sup> also slowed the age-associated decline in the formation of neurons in the olfactory bulb. Olfactory neurons are known to originate in the SVZ. Notably, p16<sup>INK4a</sup> deficiency slowed the age-dependent loss of SVZ stem cells (which divide continually but slowly), rather than stimulating the rapid proliferation of progenitor cells (the progeny of stem cells).

These findings suggest that p16<sup>INK4a</sup> causes a substantial part of the age-associated decline in

\*This article and the papers concerned<sup>3–5</sup> were published online on 6 September 2006.



**Figure 1 | Dual activities of p16<sup>INK4a</sup> during ageing.** Ageing causes an increase in p16<sup>INK4a</sup>, a potent tumour suppressor that promotes longevity by suppressing the development of cancer. Three papers show that p16<sup>INK4a</sup> suppresses the proliferation of stem or progenitor cells in the bone marrow, pancreas and brain<sup>3–5</sup>. The mechanisms that induce p16<sup>INK4a</sup> during ageing are not known (black box). Once expressed, p16<sup>INK4a</sup> causes cellular senescence (grey box), a permanent growth-arrested state, which may be the mechanism by which this protein suppresses the proliferation of stem/progenitor cells. The decline in stem/progenitor-cell proliferation compromises tissue regeneration and repair, which is likely to reduce longevity.

the potential to form new SVZ neurons. However, p16<sup>INK4a</sup> deficiency did not prevent age-associated declines in cell proliferation in the dentate gyrus region of the brain or the enteric nerves in the gut, so different mechanisms may drive the ageing of stem/progenitor cells in other parts of the nervous system.

These three papers uncover a novel role for the p16<sup>INK4a</sup> tumour suppressor in promoting ageing (Fig. 1), a role shared by the p53 tumour suppressor<sup>9,10</sup>. But they also raise many questions. Does p16<sup>INK4a</sup> drive stem/progenitor-cell

ageing by inducing an irreversible senescence arrest, a reversible quiescent state or another mechanism? What causes the age-dependent rise in p16<sup>INK4a</sup> expression? Is it induced by hormones such as those that regulate the insulin/IGF pathway during ageing<sup>11</sup>? Or is it caused by stress or damage signals within the cells? Given that p16<sup>INK4a</sup> deficiency only partly mitigates most of the ageing effects studied, what other mechanisms cause stem/progenitor-cell ageing? Finally, how important is the ageing of cells, in this case stem/progenitor cells, for the longevity

of an organism? Does it depend on the type or level of stress that the organism experiences?

Answers to these questions might clarify whether drugs that blunt p16<sup>INK4a</sup> expression or activity will ameliorate certain age-related diseases. Whatever the answers, it is important to remember that p16<sup>INK4a</sup>-deficient mice frequently succumb to cancer in mid-life (1.5–2 years). We will therefore need to know much more about the regulators and effectors of p16<sup>INK4a</sup> before these remarkable findings can be harnessed to make effective longevity-promoting therapies.

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## CLIMATE CHANGE

# A nasty surprise in the greenhouse

Jos Lelieveld

**The Kyoto Protocol aims to reduce emissions of greenhouse gases such as methane. But it seems that the fall in human-induced methane emissions in the 1990s was only transitory, and atmospheric methane might rise again.**

Methane is a potent greenhouse gas — per molecule, more than 20 times as powerful as carbon dioxide<sup>1</sup>. Moreover, when methane emissions rise, so too does the concentration of the pollutant ozone in the troposphere, the lowest layer of Earth's atmosphere<sup>2</sup>. Methane also consumes hydroxyl radicals, whose oxidative effects are essential to atmospheric cleansing. On page 439 of this issue<sup>3</sup>, Bousquet *et al.* recount the results of an international effort to measure atmospheric methane concentrations and combine these data with a computer model of atmospheric chemistry and transport. The bad news is that the slowdown in global methane emissions in the past few decades was only temporary: reports of the emissions' control have been exaggerated.

At present, about two-thirds of global methane comes from anthropogenic sources, and most emissions occur in the Northern Hemisphere (Fig. 1, overleaf). Of naturally produced

methane, the largest proportion stems from bacteria in wetlands that produce the gas when decomposing organic material. The growth rate of atmospheric methane was more than 10% per decade before 1980, but by the 1990s it had dropped to nearly zero (Fig. 2, overleaf)<sup>4</sup>. Bousquet and colleagues<sup>3</sup> compute the global methane source distribution, especially its variability over recent decades. This is a rather controversial issue, as it is difficult to determine whether this variability should be attributed to fluctuations in the sources or in the sinks; the sink mechanisms are dominated by the good offices of the atmospheric hydroxyl radicals<sup>5</sup>.

The authors used a so-called inversion modelling technique, which starts from observed concentrations at Earth's surface and back-calculates using models of transport and loss processes to optimize source estimates. The measurements stem from a global network

of monitoring stations, and include isotope data (in particular, the relative proportion of carbon-13) that provide an additional clue as to what methane came from where. Methane from biomass burning, fossil-fuel-related sources and bacterial processes have distinct isotopic signatures; methane emissions from wetlands, for example, are substantially depleted in carbon-13.

The approach is novel because the model computations optimized both methane emissions and methane loss through hydroxyl oxidation. The crux of the findings is that fluctuations of natural emissions, in particular by wetlands in the tropics, are a dominant factor in the variability of methane from year to year. These emissions are in turn sensitive to meteorological parameters: during dry periods, methane flux from wetlands is depressed.

Thus, during the most recent part of the analysis period — from 1999 onward — extended droughts have reduced natural methane emissions. This has concealed the fact that anthropogenic emissions have resumed their increase, an increase perhaps associated with the accelerating use of fossil fuels by booming Asian economies. Continued monitoring of atmospheric methane, and especially its relation to wetland inundation and drying, will be needed to substantiate this prediction.

Bousquet and colleagues' study<sup>3</sup> is not incompatible with the recent suggestion that