bird and land-cover databases would surely yield quantitative evidence of the influence of habitat. Practically all ecologists agree that species have habitat requirements that limit where they can live — tropical trees cannot survive on the Arctic tundra. Graves and Rahbek are correct that neutral theory cannot predict the resulting influence of habitat on community composition because it ignores species differences entirely.

But does the importance of habitat disagree with the letter or the intent of neutral theory? In other words, does it contradict the overall principle of dispersal-assembly?

Not necessarily. The idea of dispersal-assembly is not that differences between species do not exist — they are the inevitable result of disparate evolutionary histories. Rather, the idea is that species similarities, not their differences, lead them to find the same region habitable and to coexist. Neutral theory applies only in that realm of intermingling, where species are similar.

Habitat influence on species' distributions at any scale does indicate a role for niche-assembly, which has implications for ecological dynamics. The species that differ in the habitat they do best in cannot out-compete each other. Their differences allow them to coexist stably in the landscape.

However, unless habitat and species change in lock-step, habitat effects do not rule out a simultaneous role for dispersal-assembly. As Graves and Rahbek acknowledge, their observations limit only the spatial scale and groups of species within which neutral theory's unstable ecological dynamics may apply. Furthermore, differences between species in habitat requirements can arise from sources that are consistent with dispersal-assembly in a heterogeneous landscape over evolutionary timescales, such as from local selection for capabilities on a par with those of competitors. Selection for the avoidance of competition (or niche-assembly) may not be the evolutionary origin of these differences.

More empirical work is needed to distinguish between niche-assembly and dispersal-assembly on both ecological and evolutionary timescales. We also need to understand the implications of this distinction, and more refined ones, for judging the robustness and resilience of communities in the face of anthropogenic change. ■

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CANCER

Crime and punishment

Norman E. Sharpless and Ronald A. DePinho

Cellular senescence stops the growth of cells. This process, first glimpsed in cell culture, is now confirmed by *in vivo* evidence as a vital mechanism that constrains the malignant progression of many tumours.

Societies have traditionally taken three approaches to handling recidivist criminals: exile, execution and lifetime imprisonment. It seems that human cells use similar strategies to prevent rogue cells harbouring dangerous mutations from turning into fully fledged cancers. Epithelial tissue, such as that lining the airways and intestines, continuously renews and sloughs off, thereby sentencing some precancerous cells to extra-corporeal exile. There is also a cellular version of the death penalty — apoptosis, a well-established anticancer mechanism. And in this issue, four groups[1–4] report striking *in vivo* evidence that the body can subject potential cancer cells to the equivalent of a life-sentence: cellular senescence.

Senescence is a specific form of stable growth arrest provoked by diverse stresses, including the enforced expression of cancer-promoting genes in cultured cells. This 'oncogene-induced senescence' (OIS)[5] is linked to known cancer pathways in cultured cells, notably the ARF–p53 and $p16^{INK4a}$–RB pathways (Fig. 1). But whether OIS is an authentic anticancer process *in vivo*, or simply an artefact of enforced oncogene expression in cells experiencing culture shock[6], has been controversial.

This issue is settled by the new papers[1–4], which show that OIS occurs *in vivo* in several diverse precancerous tissues from both human and mouse. In addition, the work identifies much-needed markers of senescence, and further delineates the molecular underpinnings of this key tumour-suppressing process. A compelling feature of these studies is the consistency of OIS in response to a variety of cancer-causing mutations in different human tumour types and mouse-model systems. At the same time, the reports reveal that the molecular circuitry of OIS may be wired differently among tumour types.

Michaloglou *et al.* (page 720)[1] worked with cultures of human melanocytes (pigmented skin cells) and nevi (skin moles, the benign precursors of malignant melanoma). They found that nevi harbouring mutations of the BRAF protein (mutations that are frequently found in melanomas) have robust expression of senescence markers and do not seem to proliferate. In melanoma cells, however, senescence is extinguished and proliferation accelerated.

Curiously, the tumour suppressor $p16^{INK4a}$ — a known activator of senescence that is deleted in melanoma cells — showed spotty expression in nevi, and experimental depletion of $p16^{INK4a}$ failed to increase BRAF-induced senescence in melanocyte cultures. Mutated BRAF in melanocytes also failed to induce the ARF and p53 tumour suppressors, two proteins integral to the activation of senescence in many systems. These results expose serious gaps in our understanding of the genes and pathways that function to constrain the transformation of nevi into lethal melanomas.

Exploring the evolution of prostate cancer, Chen *et al.* (page 725)[2] discovered senescence in early-stage prostate abnormalities in humans and in mice engineered to sustain prostate-specific deletion of the PTEN tumour-suppressor gene. However, in contrast to the situation in melanocytes, prostate OIS is dependent on p53, and co-deletion of PTEN and p53 cancelled senescence, promoting full-blown prostate cancer. Parallel studies using mouse models to dissect the role of the *Ras* oncogene in the lung and pancreas[3] and in lymphoid cells[4] reinforced similar principles. So, although previous work has established that the role of p53 as a tumour suppressor depends on its ability to mediate apoptosis, these papers emphasize that p53 can also mediate senescence in primary tumours.

Collado *et al.* (page 642)[3] address a crucial need for better *in vivo* markers of OIS. So far, the gold standard has been the detection of an enzymatic activity associated with senescence (that of SA-β-gal)[7]. Although SA-β-gal has been used successfully to analyse human and mouse samples, this marker is not molecularly well-defined and demonstrates background activity in certain organs. Collado *et al.* employed an ingenious microarray screen to identify a small set of genes, the expression of which correlates strongly with senescence induced by the ERK protein. (ERK mediates the effects of certain cancer-causing mutations.) The correlations with gene expression are not seen when ERK is induced in the absence of senescence. These markers of OIS include protein-encoding genes and at least three RNA-encoding genes that are relevant to mouse tumour models of different tissues. These markers might predict OIS in precancerous abnormalities in humans.

Braig *et al.* (page 660)[4] provide a penetrating biochemical view of senescence. Their experiments were guided by the observation of unusual foci of tightly packed DNA in senescent cells[8]. These foci possessed features of a form of silenced DNA called heterochromatin,

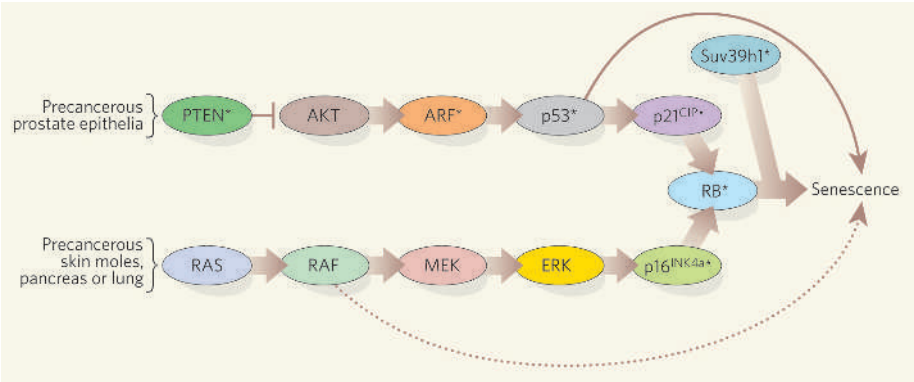

Figure 1 | A senescence wiring diagram. Oncogene-induced senescence has been linked to two major cell-signalling pathways that are often disrupted in cancer: the ARF–p53 and the 16^{INK4a}–RB pathways. Aberrant cancer-associated signals in premalignant cells activate these pathways and force would-be tumours into senescence, preventing progression to cancer. Although formerly thought to be molecularly homogeneous, senescence is now shown to differ depending on the cancer-promoting mutation and cell type. For example, ARF-independent senescence in human melanocytes (pigmented skin cells) may not require long-lasting expression of $p16^{INK4a}$ or p53 (ref. 1), whereas ARF-induced senescence in the prostate occurs in response to mutation of AKT (ref. 2). Moreover, a biochemical dissection of the process shows that the Suv39h1 histone methyltransferase seems to act downstream of RB activation in RAS-induced senescence in lymphoma[4]. Asterisks denote proteins that are tumour suppressors.

and were characterized by specific methylation of some of the histone proteins around which the DNA is packed. The Suv39h1 protein is known to methylate histones, and binds physically to the RB tumour suppressor[9,10]. So Suv39h1 seemed a reasonable candidate for a mediator of the senescence-promoting functions of RB.

Accordingly, Suv39h1 activity was shown to be required for *Ras*-induced OIS in lymphocyte cells. And in Suv39h1-deficient lymphomas, RB was not able to promote senescence as it normally does. These data suggest that Suv39h1 functions in concert with RB to alter DNA packaging in a manner that is required for senescence.

The findings of Braig *et al.* emphasize that OIS is an active process requiring specific molecular events that are sometimes perturbed, with malignant consequences. The authors reasoned that OIS would be inhibited by blocking histone deacetylases (HDACs) and DNA methyltransferases (DNMTs) because the activities of these enzymes seem to potentiate the ability of Suv39h1 to induce the formation of heterochromatin. Indeed, they found that lymphoma progression in a mouse model is accelerated by treatment with inhibitors of HDACs and DNMTs.

These findings are of added significance given the emerging application of 'epigenetic' therapies — targeted, for instance, at HDACs and DNMTs — in cancer and chronic diseases such as sickle-cell anaemia. The work raises the spectre that such therapies would provoke adverse consequences if they inhibited the senescence-mediated suppression of would-be cancer cells. Nonetheless, DNMT inhibitors have shown remarkable clinical activity in the bone-marrow disease myelodysplasia, and HDAC inhibitors have exhibited promising anticancer profiles in early trials.

Several issues regarding senescence remain to be addressed. Does senescence really mean life imprisonment for a precancerous cell, or is parole possible — that is, can senescence be reversed under some conditions? For example, could senescence in benign nevi be quelled, leading to melanoma, by further exposure to sunlight? The preliminary data here are mixed: some forms of senescence, such as that mediated by p53 in mouse cells[11,12], can be reversed by inactivation of p53 and/or RB, whereas other types, for example that mediated by $p16^{INK4a}$ in human cells[12], cannot. Moreover, what eventually happens to senescent cells *in vivo*? Do they accumulate with age or are they culled through some unknown mechanism? The fact that certain markers of senescence mount up with age suggests that senescent cells do accumulate to some extent.

Perhaps most importantly, these reports provide additional evidence that senescence is molecularly heterogeneous, requiring different pathways in different cell types, and in response to different oncogenic insults. A more precise molecular understanding of OIS is clearly needed. Just as apoptotic mechanisms are being used for therapeutic benefit, so a greater understanding of the stimuli that induce and enforce OIS will allow oncologists to exploit this crucial tumour-suppressor mechanism in cancer prevention and treatment. ■

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EARTH SCIENCE

Trouble under Tonga?

George Helffrich

Earthquakes occur in cool, foundering tectonic plates deep within the Earth. But seismic data from the southwestern Pacific indicate that the minerals that make up the plates at depth don't behave as if they are cool.

Is there something wrong with our understanding of basic seismological features of Earth's mantle, the seismic discontinuities at depths of 410 km and 660 km? A report by Rigobert Tibi and Douglas A. Wiens, just published in the *Journal of Geophysical Research*[1], provides cause for thought about this possibility.

First, however, some context. Earth's surface consists of a mosaic of rigid tectonic plates, many of which have a hard life. They form at rock-melting temperatures at mid-ocean ridges, sally across ocean basins and then sink out of sight in trenches, where they collide with another plate in a subduction zone. At the end of their life cycle, however, they leave a Cheshire-cat-like reminder of their former presence in the form of a sheet of earthquakes that extends, in many cases, from the surface down to about 700 km deep in the Earth. Here the grin of earthquakes fades.

The earthquakes in subducted plates happen because these plates are as much as 1,000 °C colder than their surroundings and