apoptosis. These mutants coimmunoprecipitated poorly with ASPP1, although they seemed to interact well with ASPP2.

Might ASPP inactivation offer a selective advantage to tumours that have wild-type *TP53*? In a panel of 58 breast tumours with matched normal tissue, most of the *TP53* wild-type tumours had reduced expression of either *ASPP1* or (less commonly) *ASPP2*, whereas most of those with mutant *TP53* had normal *ASPP* expression levels.

Cleopatra had an accomplice — the asp — to help her die, and now, it seems, p53 also uses an ASPP to nudge cells towards death. The discovery of this family explains why the promoters of many of p53's target genes, particularly the pro-apoptotic ones, have weak p53 binding sites. By modulating p53's ability to bind at these promoters, the cell can control the decision to live or die. The precise mechanism by which ASPPs boost p53's killing power, and the tantalizing possibility of sensitizing tumours to chemotherapy or radiotherapy by reactivating *ASPP* expression, are exciting avenues for future research.

Cath Brooksbank

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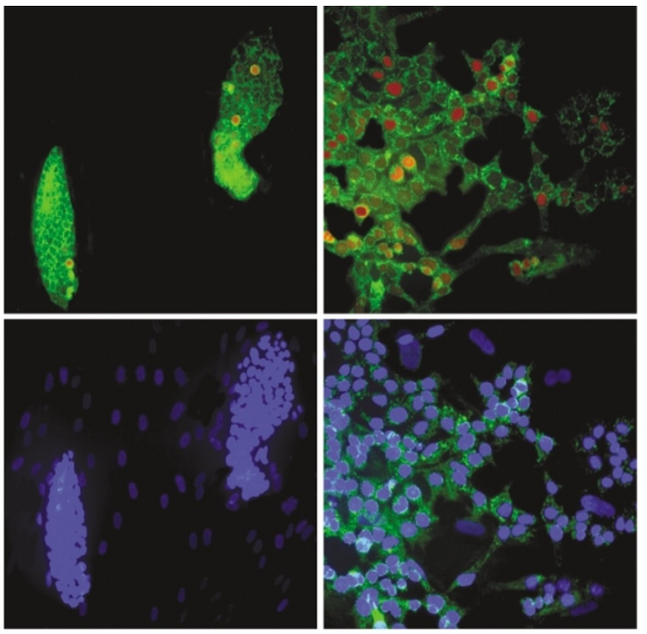

Preneoplastic cells grow more vigorously on senescent human fibroblasts compared with presenescent ones. The image shows the more robust proliferation (red) of preneoplastic epithelial cells (green) on lawns of presenescent (left) and senescent (right) fibroblasts. The cell nuclei are stained in blue. The smaller epithelial nuclei stain more intensely than the larger fibroblast nuclei. Courtesy of Judith Campisi.

SENESCENCE

The worm that turns

It has long been known that the incidence of cancer increases as we age owing to the accumulation of mutations. But now Judith Campisi and colleagues, reporting in the 9 October issue of *Proceedings of the National Academy of Sciences*, show that another mechanism contributes to tumorigenesis as we grow old. Cellular senescence, which protects us from cancer when we are young (oncogenic stimuli can induce cellular senescence), slowly turns against us to promote tumour growth.

Cellular senescence causes remarkable changes in gene expression, and senescent fibroblasts secrete proteins — such as growth factors and enzymes — that can alter the microenvironment and could affect the growth of the epithelial cells that surround them. To investigate this, the authors incubated normal, preneoplastic and neoplastic epithelial cells with presenescent and senescent fibroblasts. Senescent fibroblasts could stimulate the growth of neoplastic and preneoplastic cells, but not of normal epithelial cells. The growth difference between cells incubated with senescent and presenescent cells was seen within just 4 days (see picture).

So, how do senescent cells stimulate epithelial cell growth? The two possibilities were through factors secreted by the senescent fibroblasts or through direct cell–cell interaction. To test this, the authors grew preneoplastic epithelial cells and senescent fibroblasts in chambers that were separated by a membrane, which prevented cell contact but allowed diffusion of soluble factors. A 2–3-fold increase in cell growth was seen with the senescent cells compared with the presenescent cells, indicating that soluble factors secreted from senescent cells can stimulate cell growth. But are secreted matrix proteins also involved? Senescent and presenescent fibroblasts were grown on culture dishes where they deposited extracellular matrix proteins. The fibroblasts were removed and preneoplastic cells were plated on top. Again, the matrix deposited by the senescent cells stimulated 3–4-fold more growth than the presenescent cells. The authors calculated that secreted factors account for at least 50% of the growth stimulation by senescent cells, but that cell–cell interaction is also involved.

So, if senescent cells can stimulate growth of preneoplastic cells, might they be able to induce tumorigenesis *in vivo*? Campisi and colleagues injected epithelial cells, either alone or with senescent fibroblasts, into immunocompromised mice. Injection of preneoplastic human epidermal keratinocytes (HaCATs) alone did not induce tumour formation by 40 days, but 7/15 mice that were also injected with senescent cells had developed tumours. MDA231 cells, a human breast cancer cell line, were also injected into mice either alone or with senescent fibroblasts. In this case, small tumours had formed by 45 days in 2/5 mice injected with MDA231 cells, but when combined with senescent cells, more mice (4/5) developed tumours, and the tumours were significantly larger. So, senescent fibroblasts can stimulate tumorigenesis in mice.

Why should a process that evolved to protect us have such dire consequences later in life? The authors suggest that selection for the process has unforseen and unselected effects in aged organisms. Deleterious mutations accumulate in cells as they age, so the probability that mutant cells will be in close proximity to senescing cells increases, thereby reinforcing the tumorigenic process. Cancer cells have therefore found yet another way of coming out on top.

Emma Greenwood

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