MATERIALS SCIENCE

Film review

Free-standing nanofilms are a wonder of membrane technology. Although it's no easy matter to produce them, once made these quasi-two-dimensional objects display fascinating behaviour, combining macroscopic surface area with nanoscopic depth.

A remarkable example is reported by Toyoki Kunitake and colleagues in *Nature Materials* (R. Vendamme *et al.* doi:10.1038/nmat1655; 2006). They have prepared an ultrathin film that is barely visible to the naked eye, but is so flexible it can be drawn through a micropipette hole 30,000 times smaller than its width (pictured).

Despite its flimsy appearance, the film can support a liquid body 70,000 times heavier than its own weight, and withstand significant deformation. It is also stable to various environmental and mechanical stresses. Even more impressively, the film breaks records for size in being several centimetres across, yet only around 35 nanometres thick.

This apparently incompatible combination of strength and thinness is a result of the film's hybrid composition. It consists of an organic polymeric network, which makes it pliable and deformable, interpenetrated by zirconia (zirconium dioxide), which confers strength and stability. To prepare the nanofilm, the two materials are generated simultaneously from their precursors on a spin-coating plate. The chemical processes involved are quite different: the polymer forms by light-induced crosslinking of its monomers, whereas the zirconium precursor reacts with residual traces of water in the film's polyvinyl alcohol substrate. Nevertheless, the components intertwine to give nanofilms with properties that make them useful as sensors, actuators and separation membranes.

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species[9]. This leaves the extent of overlap between statistical and ecological significance as an interesting and open question.

We can go further: on what basis did Darwin make his assertion about the discreteness of species? This question is distinct from debates about the definition of species in nature. Blackberries reproduce asexually, and it is impossible to agree on how many 'species' there are; but, nonetheless, we all know a 'blackberry' when we see one and do not wonder if it is actually a raspberry. Great tits, blue tits and coal tits are all quite distinct when considered as a set, but are surely just more-or-less continuous variants on a tit theme when compared with flamingos. Bacteria that are vastly different genetically are all called *Legionella* because they clump along the single niche axis that matters to us: they all cause Legionnaire's disease.

So what is the correct or meaningful frame of reference when thinking about the ecological nature of species? As well as providing stimulating theoretical results, Scheffer and van Nes[1] have revitalized the fundamental question of how we should look at the ecological identity of species. ■

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STEM CELLS

Good, bad and reformable

Viktor Janzen and David T. Scadden

The ability of stem cells to continuously supply vast numbers of cells is magnificent, but it can be devastating if it runs amok, as in some tumours. So what makes a normal stem cell turn bad, and can it be redeemed?

The stem cell is a bit like the griffin of mythology — half lion, half eagle; grand and powerful, but potentially monstrous in effect. These essentially unspecialized cells can renew their own population while supplying cells that mature (differentiate) into the specialized cells necessary for all tissues. Although this ability to reproduce and self-renew is sublime when functioning properly, its disorder creates masses of dysfunctional replicating cells. Indeed, stem-cell-like cells have been found in a range of human tumours. Not all cancer is due to a stem cell gone bad, but some cancer-initiating cells are probably stem cells, and the rest acquire the stem-cell feature of self-renewal. This raises the troubling spectre that normal stem cells and cancer stem cells might share the molecular features essential to their nature. So attempting to treat cancer by disrupting the functions of the cancer stem cells might also disturb normal stem cells — potentially fatally.

In this issue, however, Yilmaz *et al.* (page 475)[1] and Zhang *et al.* (page 518)[2] report that there may be key molecular distinctions between the normal and malignant stem cell that might be of use in designing therapies that target malignant stem cells, while sparing normal stem cells.

The investigations centred on a protein called PTEN (for 'phosphatase and tensin homologue'), a known tumour suppressor and an intracellular modulator of several major cell-signalling pathways. Notably, PTEN inhibits signalling through the AKT pathway that responds to growth factors (Fig. 1a). Growth factors bind to specific receptors on the cell surface and induce a cascade of cellular modifications in which phosphate groups are added to a series of proteins. Essentially, the activation signal is passed along the pathway like a baton in a relay race until it reaches the final 'effector' proteins that carry out the pathway response: for example, changing the expression of particular genes or halting the cell cycle. When the growth factor binds to its receptor, the enzyme PI3K is activated, and it is this step that PTEN inhibits. Activation of PI3K leads to phosphorylation and activation of the AKT protein, which in turn can potentially phosphorylate more than 9,000 proteins. Two key downstream AKT effectors, called mTOR and FOXO, are implicated in cancer development.

Yilmaz *et al.*[1] and Zhang *et al.*[2] used PTEN-deficient mice to examine how a lack of this protein affects cell proliferation, programmed cell death and cell localization in haematopoietic stem cells (which produce blood and immune cells) (Fig. 1b). Previous work had shown that PTEN deficiency increases the proliferation of stem or progenitor cells (a slightly more differentiated cell type) in the fetal mouse brain. It also increases self-renewal

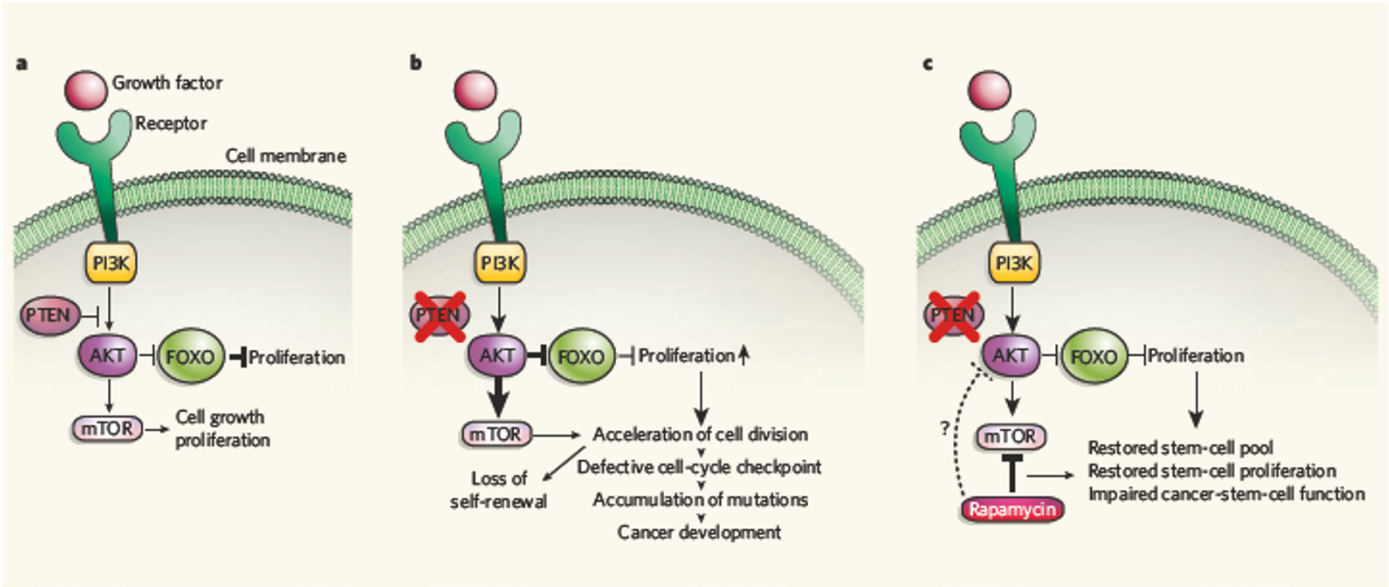

Figure 1 | PTEN regulates signal transduction and cancer development. **a**, PTEN negatively regulates PI3K activity in the AKT signalling pathway that is activated by growth factors. This keeps cell division from becoming excessive. **b**, Yilmaz *et al.*[1] and Zhang *et al.*[2] find that, in the absence of PTEN, the proliferation of haematopoietic stem cells increases and leukaemia develops. This is presumably because hyperactivity of AKT leads to activation of mTOR with a subsequent increase in cell division. The checkpoints that would usually halt division of aberrant cells are overridden, so that there is an accumulation of mutations and eventually malignancies develop. Hyperactive AKT would also suppress FOXO, again causing hyperproliferation. In stem cells lacking PTEN, this proliferative stress leads to exhaustion of stem-cell numbers as self-renewal is reduced. **c**, The drug rapamycin inhibits the activity of mTOR. Treatment of PTEN-deficient mice with rapamycin markedly restores stem-cell function and prevents the development of leukaemia[1]. Rapamycin may also exert its effects through a direct inhibition of AKT activity.

of these cells and decreases their dependence on growth factors *in vitro*[3,4]. In the haematopoietic system[1,2], the proliferation of stem cells also increased, but it was associated with three distinct effects on the homeostasis of the stem-cell pool. First, the cells changed their location, being found more commonly in the blood or spleen and becoming less able to take up residence in the bone marrow[2]. Second, PTEN-deficient stem cells had a skewed pattern of differentiation into types of white blood cell. Third, the stem cells became progressively fewer in number[1,2].

If the cells are dividing more, how do they become depleted? When stem cells divide, the two daughter cells have three possible fates. Both may be stem cells, both may be differentiating cells, or one daughter may remain a stem cell while the other differentiates. The balance between the different outcomes varies depending on the circumstances. For example, during early development the stem-cell pool expands, but after organ formation is complete the stem-cell population is generally stable, with the emphasis being on producing the mature cells needed for tissue maintenance. The result of stem-cell division must therefore be modifiable, to adjust the balance between reproduction of stem cells and production of differentiating cells. So stem-cell proliferation and stem-cell expansion are not synonymous terms, and there is growing evidence that the proliferative programme is distinct from the molecular programme of self-renewal. Indeed, downstream of PTEN are molecules such as $p21^{Cip1/Waf1}$ that influence stem-cell proliferation without necessarily invoking self-renewal[5,6]. The effects of PTEN on $p21^{Cip1/Waf1}$ may be mediated by FOXO regulatory proteins that influence the expression of a range of crucial genes for stem-cell function, including cell division and tolerance of oxidative stress[7,8]. Perturbing PTEN may thus result in non-renewing cell divisions or death of stem cells.

Yilmaz *et al.*[1] and Zhang *et al.*[2] found that the absence of PTEN not only caused the gradual loss of normal stem cells, but also changed their differentiation characteristics, allowing leukaemia to develop. The leukaemia included high numbers of cells that functioned as cancer stem cells[1]. How can a defect that reduces self-renewal in normal stem cells also result in cancer stem cells with a capacity to self-renew?

The mechanism was not explored in these papers. But to examine whether some of the tumour-related effects are mediated through specific elements of the AKT pathway, Yilmaz *et al.*[1] looked at the role of the AKT effector mTOR. This enzyme is inhibited by the drug rapamycin (Fig. 1c), and treating the PTEN-deficient mice with rapamycin not only prevented the development of leukaemia, but also inhibited established leukaemia from progressing by profoundly reducing the numbers of cancer stem cells. These latter cells therefore remained sensitive to the pathway modulated by PTEN and targeted by rapamycin. Moreover, addition of rapamycin led to the recovery in the numbers of normal stem cells. How rapamycin, which alters only some of the many downstream effects of PTEN and AKT, could redress all the consequences of the lack of PTEN is intriguing. There are indications that rapamycin may feed back to AKT, inhibiting its activation and thus its many downstream targets[9]. So it may be that rapamycin can alter even mTOR-independent members of the PTEN pathway, such as FOXO (Fig. 1c). If so, a drug that selectively targets a portion of the pathway might have broader beneficial effects.

Yilmaz *et al.*[1] and Zhang *et al.*[2] have thus shown that the loss of PTEN has distinct effects on malignant and normal stem cells that might be exploited by a therapeutic drug. This molecular defect in PTEN-deficient mice enabled the preferential emergence of diseased stem cells, but also provided a drug target to selectively enhance normal over malignant cells. The message is therefore one of hope: a single molecular defect can make a whole stem-cell pool go bad, but in this case a single targeted therapy might restore the good and impair the bad: even the griffin may be tamed. ■

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