

senescence in oncogenically primed cells.

Lin *et al.*² genetically eliminated the Skp2 protein, which normally mediates degradation of a number of proteins, including p21 and p27 (ref. 8). Consistent with the viability of mice with reduced G1 CDK activity, mice lacking Skp2 are also viable and fertile despite having moderately raised levels of p21 and p27 (ref. 8). Lin *et al.* find that, in the absence of Skp2, cancer-prone cells expressing the Ras oncoprotein or partially lacking the tumour-suppressor protein Pten become more sensitized to senescence. The survival of mice carrying only one copy of the *Pten* gene (*Pten*^{+/-} mice) is severely compromised owing to the spontaneous development of several cancers, most notably in the lymph nodes, adrenal glands and prostate. Intriguingly, Lin and colleagues find that mice deficient in both Pten and Skp2 (*Pten*^{+/-}; *Skp2*^{-/-}) are strongly protected from cancer².

The authors report similar results in mice lacking Pten in the prostate, and those deficient for another tumour suppressor, Arf. In both cases, when deficiency in these tumour suppressors was combined with low Skp2 levels, strong resistance to cancer was observed. Importantly, analysis of the tissues protected from cancer, particularly the lymph nodes and prostate, showed abundant senescent cells and a low proliferation rate within the pre-tumoral tissues. By contrast, the comparable tissues from mice expressing normal Skp2 levels contained either no senescent cells (lymph nodes) or only low levels of them (prostate).

Campaner *et al.*³ focused directly on CDK2-deficient mice. In agreement with Lin and colleagues' data, they found that oncogenic stress, in this case exerted by the Myc oncoprotein, caused the cells of mice lacking CDK2 to become sensitized to senescence. In normal mice, oncogenic expression of Myc in B lymphocytes (white blood cells) led to a strong apoptotic response, which, despite its protective potential, was not sufficient to prevent the eventual development of lymphoma. By contrast, Myc expression in CDK2-deficient mice resulted not only in apoptosis but also in increased levels of senescent cells in the pre-tumoral spleen, where B lymphocytes are abundant. This double anti-oncogenic response was accompanied by a lower number of proliferative cells and delayed development of lymphoma. The authors also present conceptually similar data in the islets of Langerhans in the pancreas, to show that the effect they observed also occurs in other tissues.

Both studies^{2,3} demonstrate that it is feasible to lower the critical point for senescence in oncogenically primed mouse cells. Consequently, these cells senesce at the pre-tumoral stage rather than at the subsequent pre-malignant stage (Fig. 1). The earlier and more sensitive induction of senescence translates into better protection from cancer without interfering with the normal functioning of the organism.

These data^{2,3} lead to an even more exciting question: if early tumorigenic cells can be sensitized to undergo senescence, what about fully malignant cells? Malignant cells evade senescence because they generally lack proper CKI function, and so retain G1 CDK activity. It is therefore conceivable that, by inhibiting G1 CDKs, senescence can be induced in malignant cells. The authors of both papers take a first step in exploring this possibility.

Lin *et al.*² show that human prostate cancer cells lacking Pten senesce when treated with a small-molecule drug that indirectly blocks the activity of Skp2 (by inhibiting the Nedd8-activating enzyme⁹), and the same drug can decrease the growth of tumours introduced into mice.

Campaner *et al.*³ report that two small-molecule inhibitors of CDK2 can induce senescence in human leukaemia cells that are overexpressing Myc, but not in those expressing

normal Myc levels. The challenge ahead is to test whether these preclinical studies in mice can be translated into more effective cancer therapies. ■

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EVOLUTIONARY BIOLOGY

Pregnant fathers in charge

Anders Berglund

Pipefish and related species provide rare examples of extreme male parental care. Controlled breeding experiments allow the resulting conflicts of interest between female, male and offspring to be explored.

In sea horses, pipefishes and sea dragons, it is the males that undergo pregnancy. The father broods the female's eggs, and in many species this takes place in a specialized pouch where the babies are protected and can receive oxygen and nutrition^{1,2}. In some pipefish species the father's commitment is so great that males cannot reproduce as fast as females, and males become a limiting resource for females^{3,4}. Females then compete for males, and traits that aid females in this competition may evolve. This reversal of the usual sex roles has been well documented in several pipefish species^{3,5}. But there remains the crucial question of why the brood pouch evolved to start with. There are probably many answers, and an intriguing possibility is tackled by Paczolt and Jones (page 401 of this issue)⁶ — what if the pouch allows a male to resolve a conflict of interest for his own benefit?

The conflict is a family one — between parents and offspring and between mothers and fathers. All mothers and offspring would of course benefit from getting as much care for eggs as possible from the father. But this might bear on the father's reproductive prospects: spending all his valuable resources on one brood might compromise his future interests. Instead, a father could benefit from spending more on offspring with good prospects (that is, offspring from a mother that already has invested substantially in the eggs), and less on

low-quality eggs from low-quality mothers; he may even want to use the low-quality eggs as food for himself, to gain resources for future offspring with better prospects. According to Paczolt and Jones⁶, both eventualities occur: by means of selective abortion and resorption, pipefish fathers can manipulate eggs to their own ends but to the detriment of low-quality mothers and their eggs.

In their experiments, Paczolt and Jones mated males of the gulf pipefish, *Syngnathus scovelli*, to one female each. They allowed the males to complete their pregnancies and give birth, and then mated each male to a new female. Females varied in size, which in this species may reflect quality — males were more reluctant to mate with smaller females and discriminated against them⁶. In a related species, the broad-nosed pipefish *Syngnathus typhle* (Fig. 1), larger females produce more and larger eggs that give rise to higher-quality offspring^{7,8}.

The idea of mating each male to one female after another was to establish a reproductive history for the males, and see whether a previous brood affected what happened to a subsequent one. Indeed it did: Paczolt and Jones found that if the first brood came from a large female, survival in the second brood decreased, implying that those males had few resources left to invest. Similarly, if offspring survival was low in the first clutch, the second survived better, implying that males

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Figure 1 | Courting couple. A male (front) and female of the species *Syngnathus typhle* engage in a nuptial dance. Like other pipefish, including the species (*S. scovelli*) studied by Paczolt and Jones⁶, it is the father that broods the resulting eggs.

can save resources for future broods.

It could be that larger females are better at manipulating males to invest more in their eggs, but this explanation seems less likely than one invoking male control. The eggs of small females never did very well, not even when those females were preceded in mating by another small female, which suggests that the pattern of brood survival is due to a male adaptive strategy of cryptic choice (choice after mating). So pipefish fathers invest more in offspring from preferred mates. Can they also exploit non-preferred females by using their eggs as a source of nutrition? Possibly they can: in related *Syngnathus* species, nutrients move not only from father to offspring¹ but also from offspring to father⁹.

Evidently, cryptic male support for eggs from preferred females for mating would benefit these females' offspring; that is, one might expect post-copulatory sexual selection to reinforce pre-copulatory selection. A different possibility is that fathers might compensate for the shortcomings of low-quality mothers by investing more in their eggs. Something similar has, for instance, been shown in the broad-nosed pipefish, where mothers made up for the shortcomings of low-quality fathers by providing them with eggs with extra protein¹⁰. Perhaps the sex that makes the choice of partner is more likely to invest differentially in the offspring of high-quality partners, whereas the chosen sex is more likely to adopt the compensatory strategy of providing extra support for those of low-quality partners.

From Paczolt and Jones's observations⁶ it seems that male gulf pipefish opt for differential allocation of support, and a simulation model using realistic reproductive parameters

confirmed that this strategy can be adaptive. Males that were reluctant to mate with small females and exhibited cryptic (post-copulatory) choice in favour of large females had a higher fitness than males not adopting cryptic choice — the higher fitness taking the form of more offspring being produced.

The pipefish brood pouch may serve several functions. It provides safety and nutrition for offspring, and it may serve as an attractant signal for females. But also, as is evident from Paczolt and Jones's study, it grants fathers better control over reproduction — males may use their role as carers not only to nurture the eggs but also to favour those from high-quality females and disfavour and/or exploit those of low-quality females. What at first sight seems an egalitarian partnership between males and females, both investing heavily in their young, looks more like brooding sexual conflict. ■

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CELL BIOLOGY

Actin filaments up against a wall

Cécile Sykes and Julie Plastino

The front of motile cells is thought to be pushed out by branched filaments of actin protein abutting the cell membrane. New work challenges this textbook view, showing that actin branches grow away from, or obliquely to, a surface.

Monomers of the protein actin assemble into a filamentous scaffold that propels the cell forward, and that can also power the movement of intracellular pathogens and transport vesicles, as well as biomimetic objects such as beads and liposomes^{1,2}. The complex formed by actin-related proteins 2 and 3 (the Arp2/3 complex) is a 'nucleator' of actin polymerization, which causes branching in this scaffold. The existing model for actin-mediated movement proposes that the fast-growing (barbed) ends of actin filaments are directed towards a surface, such as the cell membrane, where polymerization is catalysed. Writing in *Current Biology*, Achard *et al.*³ turn this model on its head by providing a real-time readout of single-filament dynamics in a network growing on a surface. They show that when the growing filament-ends encounter a wall (in this case, a rod or a bead, but by analogy a cell membrane), they orient away from it.

The previous view of actin-based motility came from three main observations. First, in solution, the Arp2/3 complex is activated by nucleation-promoting factors (NPFs) of the WASp/Scar family; consequently, it nucleates new actin filaments as branches at a 70° angle on the sides of the 'mother' filaments, and near the growing barbed end^{4,5}. Second, live imaging shows that new actin material is incorporated near the leading-edge membrane of motile cells and near the surface of moving biomimetic objects^{6–8}. Third, electron microscopy of

fixed cells suggests that branches are oriented towards the cell membrane⁹. Together, these observations led to the interpretation that, at an NPF-coated surface, forward-facing branches form, elongating by actin-monomer addition to the barbed ends abutting the surface and so pushing the surface forward.

Achard *et al.*³ call this view into question. The authors coated glass rods with an NPF, and incubated them with the ingredients for actin-filament formation: the Arp2/3 complex and a mixture of actin and profilin (a protein that binds to actin monomers), to ensure that filament elongation occurred only at barbed ends. Their trick was to use a fluorescently labelled form of actin that bleaches quickly; the newly polymerized filament-ends fluoresce, whereas older parts of the network are less visible. The authors then observed this biomimetic system using TIRF (total internal reflection fluorescence) microscopy, which limits background fluorescence.

Surprisingly, they saw that all of the filaments' barbed ends were directed away from the rod surface. On adding a capping protein, which stops filament elongation, barbed ends were still oriented away from the surface, although the region containing the growing filaments was closer to the surface. The authors also found that explosive Arp2/3-dependent actin polymerization was initiated by actin-filament seeds, or 'primers'. This is consistent with the results of experiments performed in