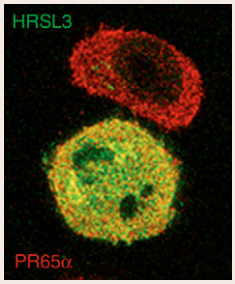
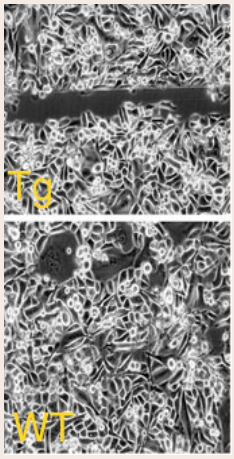
In this issue

by Jane Bradbury



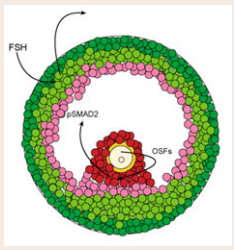
REVving up cancer

Inactivation of tumour suppressors is an essential step during tumorigenesis. Permanent genetic alterations inactivate *p53* and other class I tumour suppressor genes; reversible mechanisms, which could provide targets for cancer therapy, inactivate class II tumour suppressors. Now, Christine Sers and colleagues reveal how the type II tumour suppressor HRSL3 (also called H-REV107-1) might regulate the growth and survival of ovarian cancer cells (see p. 1393). HRSL3 is expressed in most normal tissues but downregulated in many human tumours. The authors show that it sequesters a regulatory subunit of protein phosphatase 2A (PP2A) away from the enzyme's catalytic subunit – HRSL3 interacts through its N-terminal proline-rich region with the α-isoform of regulatory subunit A of PP2A. Overexpression of HRSL3 (but not of a mutant lacking the interaction domain) reduces PP2A activity in ovarian cancer cells and induces their apoptosis. Furthermore, the HRSL3-PP2A interaction inhibits the dephosphorylation of the atypical Ca^{2+}-dependent protein kinase PKCζ by PP2A. The authors suggest, therefore, that HRSL3 regulates a signalling pathway that drives tumorigenesis in the ovary.



Wound healing goes to Rac and ruin

During wound healing, increased proliferation of epidermal keratinocytes and their migration across the wound repairs the damaged epithelium. The signalling mechanisms that regulate skin re-epithelialization are poorly understood but there have been hints that the small GTPase Rac1 is involved. Ingo Haase and colleagues now provide the first clear evidence that Rac1 is required for normal epidermal wound healing in vivo in mammals (see p. 1480). Transgenic mice expressing dominant-negative Rac1 (N17Rac1) in epidermal keratinocytes (and mice with an epidermis-specific deletion of Rac1) have a normal epidermis, they report, but repair skin wounds slowly. The authors show that the proliferation and migration of N17Rac1-expressing keratinocytes are both inhibited in vitro, and that the migration defects of these cells are particularly pronounced on collagen. Finally, they report that decreased persistence of lamella protrusions may underlie these migration defects. Overall, these results indicate that Rac1 plays an important role in skin wound healing by regulating keratinocyte proliferation and migration.

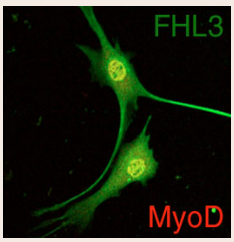


Opposing gradients make follicles fit for function

Ovarian follicles, the structures where oocytes develop, contain two types of granulosa cell: cumulus cells surrounding the oocyte promote its development through reciprocal interactions and later expand to facilitate ovulation; mural granulosa cells lining the follicle have an endocrine function. Both cell types develop from one precursor cell but how? The answer, report John Eppig and co-authors on p. 1330, is opposing gradients of pituitary-derived follicle-stimulating hormone (FSH) and oocyte-stimulated SMAD2/3 signalling. Oocyte-derived members of the TGFβ superfamily are key regulators of ovarian function. The authors show that cumulus cells contain more phosphorylated SMAD2, which transduces TGFβ signals, than do mural granulosa cells. Oocytectomy or treatment of cumulus-oocyte complexes with an inhibitor of SMAD2/3 activation, they also report, reduces the levels of cumulus cell markers, blocks cumulus expansion, and allows FSH to induce mural cell transcripts. Thus, they suggest, opposing gradients of FSH signals from outside the follicle and oocyte-stimulated SMAD2/3 signals from within specify the two cell types that provide the developmental and endocrine functions of the ovarian follicle.

Virtual actin networks match reality

Actin polymerization is thought to drive the formation of lamellipodia and other protrusions at the leading edge of migrating cells. Lamellipodia contain a dense actin network but, although the assembly of such networks has been reconstituted in vitro, their dynamic and structural properties in lamellipodia are poorly understood. On p. 1491, Sébastien Schaub, Jean-Jacques Meister and Alexander Verkhovsky remedy this by comparing experimental and simulated images of actin networks. They create virtual actin networks by assuming that the nucleation of new branched filaments and their capping occurs at random along the lamellipodia's leading edge (a dendritic nucleation mechanism). Images of these simulated networks, report the authors, closely resemble electron microscopic and fluorescence images of the lamellipodia of fish keratocytes and can be used to estimate the length and orientation of actin filaments in these structures. Importantly, the close correspondence between the real and virtual images indicates that dendritic nucleation alone may account for the formation of actin networks in lamellipodia; no bundling proteins seem to be required.



LIMbering up to make muscle

Throughout life, myoblast differentiation maintains and repairs muscle. The transcription factor MyoD, which is regulated by MyoD-interacting proteins, initiates myogenesis by controlling the temporal expression of myogenin and other muscle-specific regulatory genes. Now, Christina Mitchell and colleagues identify FHL3 as a MyoD-interacting protein that negatively regulates myogenesis (see p. 1423). FHL3, which is highly expressed in skeletal muscle, contains four and a half LIM domains, which mediate protein-protein interactions. The authors show that overexpression of FHL3 in the muscle cell line C2C12 retards myotube formation and decreases the expression of myogenin but not MyoD. By contrast, knocking down FHL3 by RNAi enhances myoblast differentiation and increases myogenin expression, again without altering MyoD expression. FHL3, the authors report, binds to MyoD and functions as its potent negative co-transcriptional regulator. They propose, therefore, that, when new muscle is needed, FHL3 is excluded from the nucleus, which relieves its negative regulation of MyoD and allows myogenesis to proceed.

Development in press

Stonewalling stem cell differentiation

Organisms must maintain appropriate numbers of various stem cells. Too few can cause infertility or defective tissue regeneration; too many may increase the risk of cancer. Stem cells are maintained mainly by preventing the expression of differentiation factors – sometimes through chromatin-mediated transcriptional repression. In a paper published in *Development*, Maines and co-workers report that female germline stem cells (GSCs) in Drosophila are maintained by the DNA-associated protein Stonewall (Stwl). They show that *stwl*-mutant GSC clones are lost through differentiation and that overexpression of *stwl* increases the number of GSCs. Because *stwl* mutants act as suppressors of variegation (they prevent patchy gene silencing within tissues), which is characteristic of mutations in certain genes that affect chromatin remodelling, the authors propose that Stwl is involved in chromatin-dependent gene repression. Finally, they show that Stwl represses the expression of many genes; some of these contain putative binding sites for Pumilio, a translational inhibitor that, together with Nanos, represses the translation of key differentiation factors in GSCs. Thus, the researchers conclude, two overlapping mechanisms block GSC differentiation.

Maines, J. Z., Park, J. K., Williams, M. and McKearin, D. M. (2007). Stonewalling *Drosophila* stem cell differentiation by epigenetic controls. *Development* **134**, 1471-1479.