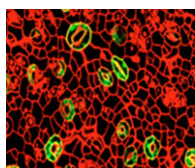


Intestinal stem cells bust a gut without *Apc*

Loss of *Apc*, a tumor suppressor gene conserved from flies to mammals, results in gastrointestinal tumour initiation in humans. Now, on p. 2255,

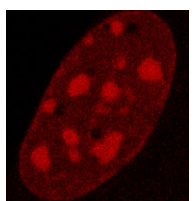
Craig Micchelli and colleagues identify an intriguing novel role for *Apc* in regulating the proliferation of *Drosophila* intestinal stem cells (ISCs). The authors demonstrate that reducing *Apc* function interferes with midgut homeostasis and leads to hyperplasia and multilayering of the midgut epithelium. Inducing small groups of labelled cells that lack *Apc* function in the adult midgut reveals that *Apc* is required specifically in the midgut ISC lineage for homeostasis. *Apc* loss does not affect ISC self-renewal or fate specification, but does increase ISC proliferation. In addition, activating Wnt signalling in ISCs results in phenotypes similar to those caused by *Apc* mutations, whereas reducing Wnt signalling suppresses the hyperplasia triggered by the loss of *Apc*. Based on these data, the authors conclude that Wnt signalling partly mediates the effects of *Apc*, and propose that *Drosophila* ISCs might be a useful model for investigating gastrointestinal tumour initiation.



Stomata's grassy claim to FAMA

Stomata are tiny pores in the epidermis of most land plants that allow regulated gas exchange between the environment and the plant interior, as well as water evaporation. In *Arabidopsis*, stomatal development

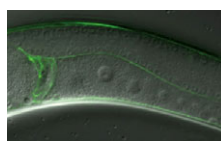
requires the sequential function of the three related basic helix-loop-helix transcription factors FAMA, MUTE and SPEECHLESS (SPCH), but how is it controlled in other plants? On p. 2265, Dominique Bergmann and co-workers report that orthologues of all three transcription factors exist in rice and maize, and that the function of FAMA is evolutionarily conserved. The authors first identify *Arabidopsis* FAMA, MUTE and SPCH homologues in rice and maize through in silico analysis and then analyse their function by studying their expression and through mutation, complementation and overexpression approaches. FAMA function is conserved between *Arabidopsis* and grasses; in both cases, deleting *FAMA* prevents stomatal differentiation and morphogenesis. MUTE and SPCH functions, however, differ between grasses and *Arabidopsis*. Future work should shed further light on the regulation of stomatal development in grasses and other agriculturally important plants.



How DNMT1 mediates between repair and death

Disrupting the function of the maintenance methyltransferase DNMT1 during *Xenopus* development leads to apoptosis and embryonic lethality, but what initiates apoptosis? Richard Meehan and

colleagues now reveal that DNA mismatch repair (MMR) pathway components mediate this apoptotic induction (see p. 2277). First, the authors ruled out that DNMT1 methylase activity triggers the apoptosis. Instead, they show that overexpressing the methyl-CpG binding protein MBD4 or the MMR pathway protein MLH1 causes p53-dependent apoptosis, and that co-depleting either MBD4 or MLH1 rescues DNMT1-depleted embryos. They demonstrate that MBD4 interacts directly with DNMTs from various species. In mouse cells, MBD4 recruits MLH1 to methylated DNA sites that also contain DNMT1, and localised UV irradiation of nuclei triggers the recruitment of all three factors to sites of DNA damage. Based on these and other data, the authors suggest that chromatin-associated DNMT1, MBD4 and MLH1 can respond to DNA lesions either by repairing them or by triggering apoptosis through the release of an MBD4-MLH1 complex.



Opposing signalling centres balance oocyte growth

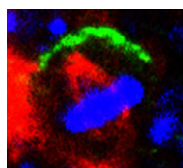
In animals, oocyte development arrests at the first meiotic prophase. Oocyte maturation then

resumes in response to specific triggers, which, in *C. elegans*, take the form of the major sperm protein (MSP, an ephrin signalling antagonist). Now, two studies by David Greenstein and co-workers shed light on how MSP triggers oocyte maturation, and identify crucial roles for Notch signalling and G α _s-adenylate cyclase (G α AC) in both oocyte growth and maturation.

In their first study (see p. 2211), these researchers report that all germline MSP-dependent oocyte meiotic maturation events require G α AC signalling in the somatic sheath cells of the gonad, but not in the germ cells themselves. They demonstrate that the MSP-mediated events that occur in the germline, including MPK-1 MAP kinase activation, which triggers meiotic maturation, and cortical microtubule reorganisation, which probably promotes meiotic spindle assembly, depend on G α AC signalling. Gap junctions appear to function downstream of G α AC signalling, as mutations in gap junction protein-encoding genes suppress G α AC-associated defects. G α AC signalling also promotes MSP-dependent oocyte growth and cytoplasmic streaming.

In their second study (on p. 2223), these investigators go on to show that GLP-1/Notch signalling in the somatic distal tip cells (DTCs) regulates MSP-dependent oocyte growth and cytoplasmic streaming. Mutations in *glp-1* lead to large oocytes, and, by using genetic mosaic analysis, in which the fates of clonally derived cells that are genetically distinct from the surrounding tissue are traced, the authors show that germline *glp-1* regulates normal oocyte growth. The DTC-expressed GLP-1 ligands LAG-2 and APX-1 probably mediate this regulation, as DTC ablation or LAG-2 and APX-1 co-depletion result in enlarged oocytes. Moreover, *glp-1* mutations lead to higher rates of cytoplasmic streaming and to delayed oocyte cellularisation, as long as certain gap junction proteins and core apoptotic pathways are functional. These results indicate that GLP-1/Notch signalling restricts oocytes to their normal size in the presence of MSP signalling.

Taken together, these findings suggest that two major signalling centres in the adult *C. elegans* hermaphrodite gonad – GLP-1/Notch distally and MSP proximally – function in opposition to regulate meiotic maturation and oocyte growth, a regulatory interaction that might be conserved in other species.



Keeping neuroblast self-renewal in check

Drosophila larval brain neuroblasts normally divide asymmetrically to generate another self-renewing neuroblast and a more fate-restricted cell; failure of

asymmetric division results in neuroblast overgrowth that can resemble some vertebrate brain tumours. Now, Hongyan Wang and colleagues identify Protein phosphatase 2A (PP2A) as a novel tumour suppressor that can limit neuroblast self-renewal (see p. 2287). The authors report that defects in, or the depletion of, PP2A cause larval neuroblast overgrowth, which occurs at the expense of normal neuronal differentiation. PP2A also regulates neuroblast polarity, with the defects caused by PP2A disruption resembling those of *polo* mutant embryos. Polo is a kinase that phosphorylates and thereby activates the cell fate determinant Numb, and the authors determine that PP2A regulates Numb activity by promoting Polo expression. Based on these and other findings, the authors propose that PP2A acts upstream of Polo and Numb to block excessive neuroblast self-renewal. Whether this function of PP2A is conserved in other stem cell systems awaits future investigation.