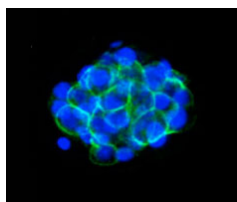


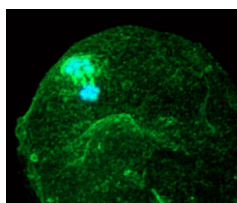
The APC of asymmetric divisions

Asymmetric cell divisions generate cell diversity during development, but what regulates the segregation of cell fate determinants during these divisions? Slack and co-workers have been examining the localization of Miranda (an adaptor for several neural cell fate determinants) to the basal cortex of *Drosophila* neuroblasts, which divide asymmetrically into an apical neuroblast and a basal ganglion mother cell. On p. 3781, the researchers report that this localization of Miranda requires the anaphase-promoting complex/cyclosome (APC/C), a new function for this mitotic regulator. They show that when APC/C activity is attenuated, Miranda accumulates near the centrosome instead of at the basal cortex. They also show that the C-terminal domain of Miranda is ubiquitinated, that removal of this domain disrupts Miranda localization similarly to APC/C attenuation, and that addition of ubiquitin to this C-terminal truncated protein restores its localization. As APC/C is an E3 ubiquitin ligase, the researchers speculate that APC/C normally adds a ubiquitin tag to Miranda that regulates its asymmetric localization in neuroblasts.



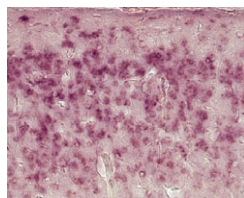
Found: earliest known specifier of the trophoblast

Specification in mammalian embryos begins in the 16-cell morula with the emergence of the trophoblast (TE, from which the placenta develops) and the inner cell mass (ICM, from which the embryo develops). Now, on p. 3827, Yagi and colleagues report that the transcription factor TEAD4 specifies the TE lineage at the start of mammalian development. The researchers show that *Tead4*, like the highly homologous *Tead2* gene, is first expressed in the mouse two-cell embryo. *Tead4*^{-/-} embryos develop to the morula stage, they report, but do not express TE-specific genes nor establish a TE lineage, and die before blastocyst formation and implantation. *Tead2*^{-/-} embryos, by contrast, develop into viable adults. *Tead4*^{-/-} embryos do, however, express ICM-specific genes and can produce embryonic stem cells, derivatives of the ICM. Furthermore, if *Tead4* is only disrupted after implantation, *Tead4*^{-/-} embryos complete development. Thus, the researchers conclude, *Tead4* is the earliest known TE lineage specifier, the expression of which, during zygotic gene activation, triggers the eventual differentiation of totipotent blastomeres into TE.



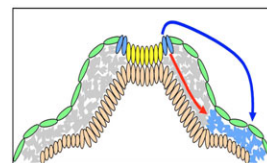
More to separate than chromosome separation

Fertilization triggers several events in oocytes, including resumption of the cell cycle and, in many organisms, exocytosis of cortical granules, the contents of which modify the extracellular covering of the zygote. Bembenek and co-workers now identify cortical granules in *C. elegans* for the first time and show that their exocytosis after fertilization is regulated by several cell-cycle components, most notably separate, which is required for chromosome segregation during anaphase (see p. 3837). The exocytosis of cortical granules in fertilized *C. elegans* oocytes, the researchers report, leads to the formation of an impermeable three-layered eggshell. Using RNAi knockdown, they show that separate is required for granule exocytosis and chromosome segregation. Then, using immunofluorescence and live-cell imaging, they show that, after fertilization, separate moves from filamentous structures into cortical granules. These, they report, are exocytosed during anaphase I. Together, these results lead the researchers to propose that separate helps to coordinate the cell cycle with the other events that occur during egg activation.



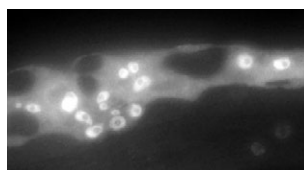
Divergent roles for reelin receptors revealed

The surface of the mammalian brain (the neocortex) contains six distinct layers of neurons. The extracellular matrix protein reelin regulates the migration of the neurons that form these layers. Reelin has two receptors: very low density lipoprotein receptor (Vldlr) and apolipoprotein E receptor 2 (ApoER2). Now, Hack and colleagues reveal divergent roles for these two receptors in the migration of cortical neurons (see p. 3883). In mice, the order of the cortical layers is inverted in reelin-knockout mutants and in ApoER2 Vldlr double-knockout mutants; the phenotype of single-receptor knockouts is much milder. To determine the specific role of each reelin receptor in neuronal migration, the researchers mapped the fate of newly generated cortical neurons in single and double receptor mutants. Their results indicate that the proper migration of late-generated neurons, which form the superficial layers of the neocortex, requires ApoER2. Vldlr, by contrast, mediates a reelin stop signal that prevents neurons migrating into the cell-poor marginal zone that covers the neocortex.



Nodal signals take an internal route

The left-right asymmetry of internal organs is established during mammalian development by a leftward fluid flow in the embryonic node cavity, expression of the secreted protein Nodal at the node, and subsequent asymmetric Nodal expression in the left lateral plate mesoderm (LPM). But, how is the Nodal signal transferred to the LPM? On p. 3893, Oki and co-workers controversially propose that Nodal travels directly to the LPM from the node by interacting with sulfated glycosaminoglycans (GAGs) in the intervening basement membrane-like structure. The researchers show that externally supplied Nodal does not signal to the LPM in cultured mouse embryos, which suggests that an internal route exists for Nodal signal transfer to the LPM. They discount that Nodal signals might be indirectly relayed by showing that the Nodal co-receptor Cryptic is not needed in the node for asymmetric Nodal expression in the LPM. Finally, they show that Nodal interacts with sulfated GAGs and that inhibition of their biosynthesis prevents Nodal expression in the LPM.



Runx oncogenic potential wormed out

Runx transcription factors, the DNA binding of which is enhanced by CBFβ, play important roles during development and may act as tumour suppressors and oncogenes. Disentangling what Runx proteins do in mammalian systems, where there are three Runx genes, has proved difficult, so researchers have turned to *C. elegans*, which has only one Runx homologue *rnt-1*. On p. 3905, Kagoshima and colleagues report that BRO-1, the worm CBFβ homologue, interacts with RNT-1 to promote self-renewal and proliferation of stem cells. They show that *bro-1* and *rnt-1* deletion mutants both lack some male-specific sensory rays because of failed cell divisions in the stem-cell-like seam cells from which the rays develop. BRO-1 increases the affinity and specificity of RNT-1–DNA interactions, they report, but can also act independently of RNT-1. Finally, co-overexpression of *rnt-1* and *bro-1* causes seam cell hyperplasia (effectively, a tumour). These new insights into the function of Runx/CBFβ in stem cells support the idea that this DNA-binding complex has oncogenic potential.

Jane Bradbury