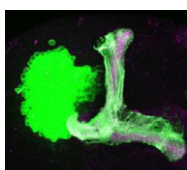


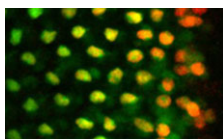
### MicroRNAs: they're a knock-out

MicroRNAs (miRNAs), a class of short non-coding RNAs, regulate target messenger RNAs post-transcriptionally by inhibiting their translation or promoting their degradation. The specific roles of miRNAs are only now beginning to be uncovered, but have we inadvertently learned more about their function than we realise? On p. 3989, Calvin Kuo and co-workers report that most of the vascular phenotypes previously attributed to disrupting the mouse gene *Egfl7*, which encodes an endothelial extracellular matrix molecule, are actually caused by disruption of the endothelial miRNA *miR-126*, which resides within the seventh intron of *Egfl7*. *miR-126* deletion inhibits VEGF-dependent signalling. Importantly, *miR-126* appears to have been unintentionally disrupted in the generation of two knockout mouse models designed to investigate *Egfl7* function. As over half of all known miRNAs are embedded in introns of protein-coding genes, and as the mouse genome possibly contains over 1000 miRNAs, this study highlights the importance of considering the potential dysregulation of miRNAs in the design and interpretation of knockout studies.



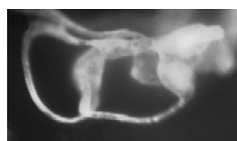
### Smad-free TGF $\beta$ signalling: mushrooming evidence

The canonical TGF $\beta$  signalling pathway, which controls many developmental processes, involves ligand binding to a type 2 receptor kinase. This then phosphorylates a type 1 receptor, which activates a Smad-dependent pathway that controls gene transcription. Now, however, Julian Ng reports that TGF $\beta$  signals regulate axonal development in *Drosophila* mushroom body neurons through Smad-independent mechanisms (see p. 4025). Loss of the type 1 TGF $\beta$  receptor Baboon (Babo) causes axon overextension in these neurons, reports Ng, whereas Babo overexpression causes premature axon termination. Babo, he shows, acts independently of Smads, signalling instead through the actin cytoskeleton regulators Rho1 and Rac (Rho GTPases) and LIM kinase 1 (LIMK1). Furthermore, Babo acts upstream of the *Drosophila* type 2 TGF $\beta$  receptors Wishful thinking and Punt, which regulate axon growth independently through LIMK1-dependent and -independent mechanisms. Finally, Ng shows that Babo also regulates the development of other *Drosophila* neurons independently of Smads, raising the possibility that non-canonical TGF $\beta$  signalling might also function in other developmental situations.



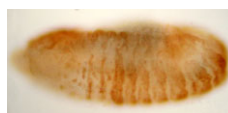
### Photoreceptor specification gets rough

During *Drosophila* eye development, a single founder photoreceptor (R8) is specified in the eye imaginal disc for each of the compound eye's structural units. However, groups of disc cells express the proneural gene *atonal* (*ato*), which is required for eye development, so what restricts the R8 potential to single cells? On p. 4071, Pepple and co-workers propose a new two-step model to explain this mysterious process. The researchers show that ectopic R8s develop from R2 and R5 photoreceptor precursors independently of ectopic *Ato* in *rough* mutants (*rough* encodes a transcription factor that represses *ato*) and that *Rough* normally represses the R8-specific transcription factor *senseless* (*sens*) in these two precursors. Because R8 differentiation requires the repression of *rough* by *Sens*, these results suggest that *sens* activation by *Ato* and lateral inhibition together establish a transient pattern of R8s that is 'locked' by a repressive feedback loop between *rough* and *sens*, a strategy that could allow the successful integration of a repressive patterning signal with developmental plasticity during eye development.



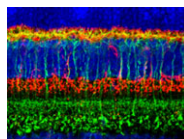
### A balancing act in the inner ear

The generation of complex three-dimensional structures is one of the most remarkable feats of embryonic development, but in many cases little is known about how such structures are achieved. Now, Lisa Goodrich and colleagues report that the formation of the mouse inner ear, which houses the sensory organs for hearing and balance, requires a previously unrecognised feedback loop between the morphogen netrin 1 (Ntn1) and the immunoglobulin superfamily protein Lrig3 (see p. 4091). During a mutagenesis screen, the authors found that the lateral canal (a component of the inner ear) of *Lrig3* mutant mice is truncated. This, they report, is due to the accelerated fusion of the opposing walls of a precursor structure known as the lateral pouch, which is caused by ectopically expressed Ntn1 triggering basement membrane breakdown. The authors demonstrate further that cross-repressive interactions between Lrig3 and Ntn1 define the fusing and non-fusing domains of the lateral pouch during lateral canal morphogenesis, and propose that this interaction constitutes a novel mechanism for Ntn1 regulation.



### Pho-nomenal transcriptional memory

During *Drosophila* development, Polycomb (PcG) and trithorax (*trxG*) group proteins maintain DNA regions in transcriptionally silent and active states, respectively, by forming complexes that modify chromatin. Surprisingly, Fujioka and colleagues now report that the DNA-binding PcG protein Pleiohomeotic (Pho) maintains both active and repressed transcriptional states of *even skipped* (*eve*; a *Drosophila* gene with a conserved role in the regulation of nervous system gene expression) through a single site (see p. 4131). The researchers identify a Pho-dependent sequence at the 3' border of the *eve* locus. They then show that, while this element maintains repression in nervous system cells in which *eve* is silenced during early development, it unexpectedly maintains an active transcriptional state in other cells. Both negative and positive transcriptional maintenance depend on Pho binding and on *pho* gene activity. From these and other results, the researchers suggest that the differential regulation of a core DNA-binding complex that contains Pho and other factors facilitates the transcriptional memory of both active and repressed states during development.



### Neurons escape death with $\gamma$ -protocadherins

During central nervous system development, excessive numbers of neurons are initially generated, before approximately half of them undergo programmed cell death (PCD), often during synapse formation. The factors that regulate central neuron survival and synaptic specificity remain largely unknown, but now, Joshua Sanes and colleagues (see p. 4141) report that the protocadherin- $\gamma$  (*Pcdh- $\gamma$* ) gene cluster, which encodes a family of 22 adhesion molecules, is important for the survival of developing neurons, but not for the specificity of their synaptic connections. By selectively inactivating the *Pcdh- $\gamma$*  cluster in the mouse retina, the authors demonstrate that the PCD of certain retinal cell types is accentuated by the loss of  $\gamma$ -Pcdhs, whereas the formation of appropriate synapses and of complex functional circuits remains unaffected. Importantly, these findings suggest that  $\gamma$ -Pcdh-mediated regulation of neuronal survival is independent of synaptic connectivity. These results are complemented by a study on p. 4153 by Joshua Weiner and co-workers, who report that  $\gamma$ -Pcdhs promote the survival of mouse spinal interneurons in a non-cell-autonomous fashion.