

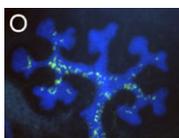
### Epithelial migration: Scribble and Pak lead in turn

Several developmental stages, including dorsal closure (DC), involve epithelial fusion events during which cell-cell adhesions disassemble, cells migrate and, when migration is complete, cell-cell adhesions reassemble. On p. 2023, Nicholas Harden and colleagues reveal how the Scribble complex (which contains Scrib, a polarity regulator) and Pak (a Cdc42/Rac effector kinase; Cdc42 and Rac regulate actin-based membrane extensions during cell migration) interact to shift epithelial cells between adhered and migratory states in *Drosophila*. In mammalian cells, Scrib recruits Cdc42, Rac and Pak to the leading edge (LE) membrane during cell migration. Similarly, in *Drosophila* Pak localisation in the follicular epithelium is Scrib dependent. Importantly, however, the researchers show that during DC, Scrib is lost from the LE during epidermal migration, and, at the end of DC, integrin-localised Pak recruits the Scrib complex to the LE, thereby restoring apicobasal polarity and cell-cell adhesion. They suggest, therefore, that bidirectional interactions between the Scrib complex and Pak might modulate epithelial plasticity during DC and in other developmental situations.



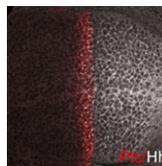
### Ecdysteroid synthesis 'Black Box' illuminated

In insects, the steroid hormone ecdysone controls the timing of moulting and metamorphosis. Some enzymes involved in ecdysone biosynthesis from dietary cholesterol have been identified but not those for the conversion of 7-dehydrocholesterol to 5 $\beta$ -ketodiol, the so-called 'Black Box'. Now, Ryusuke Niwa, Tetsuro Shinoda and co-workers report that *non-molting glossy (nm-g)/shroud (sro)* encodes a short-chain dehydrogenase/reductase that functions in this ecdysteroid biosynthesis Black Box (see p. 1991). The researchers first isolated *nm-g* by positionally cloning the silkworm *nm-g* mutant gene. This mutant has low ecdysteroid levels and developmentally arrests as a larva. Next, they discovered that the *Drosophila* mutant *sro*, which is a *Drosophila* Halloween-class embryonic lethal mutant, is caused by the loss of function of an *nm-g* orthologue. Finally, they report that the application of ecdysteroids or 5 $\beta$ -ketodiol, but not that of cholesterol or 7-dehydrocholesterol, reverses *nm-g/sro* mutant phenotypes. Thus, the researchers conclude, *Nm-g/Sro* is an essential, but as yet uncharacterised, component of the ecdysteroid biosynthesis Black Box.



### Etv branches out in developing kidneys

During kidney development, Ret receptor tyrosine kinase signalling promotes the cell movements that give rise to the ureteric bud (UB), which branches to form the renal collecting system, from the Wolffian duct. The ETS transcription factors *Etv4* and *Etv5* act downstream of *Ret* in this process, but how? Frank Costantini and colleagues now report that during mouse kidney development, *Etv4* and *Etv5* mediate the formation of the UB tip domain where branching occurs and which induces surrounding mesenchyme to form nephrons (see p. 1975). To examine *Etv4* and *Etv5* function during kidney development, the researchers analysed the contribution of compound mutant cells to chimeric kidneys. They report that, like *Ret*<sup>-/-</sup> cells, *Etv4*<sup>-/-</sup>;*Etv5*<sup>+/-</sup> cells contribute to some trunks of the initial UB branches but to few tips; *Etv4*<sup>-/-</sup>;*Etv5*<sup>-/-</sup> cells make an even smaller contribution to the UB. Together, these results suggest that *Etv4* and *Etv5* play a cell-autonomous role in the Ret-promoted, Wolffian duct cell rearrangements, and importantly, that they also act downstream of other signals that drive kidney morphogenesis.

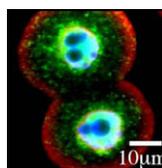
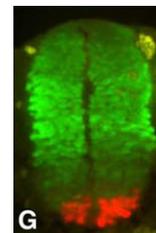


### Hedgehog signalling regulation: from outside to in

The Hedgehog (Hh) family of secreted signalling proteins specify distinct cell fates in a concentration-dependent manner throughout development. In this issue, two papers provide new information about how Hh signalling is regulated.

On p. 2033, Xinhua Lin and colleagues examine the regulation of Hh signalling in *Drosophila* by two cell-surface proteins – the glypican Dally-like (Dlp) and the Ig/fibronectin superfamily member Interference hedgehog (Ihog). Because Hh proteins carry lipid modifications, they associate with the cell membrane. Consequently, a key issue in Hh signalling is how Hh proteins are secreted and form concentration gradients. Here, the researchers show that the core protein of Dlp interacts with Hh and that this interaction is essential for the function of Dlp in Hh signalling. Overexpression experiments indicate that, in wing discs, Dlp enhances Hh signalling strength but reduces its signalling range. By contrast, Ihog overexpression in wing discs extends the Hh signalling range. In cultured imaginal disc cells, low Ihog levels increase Hh signalling, whereas high levels decrease it. These and other results suggest that Dlp acts as a Hh co-receptor, whereas Ihog acts as an exchange factor that retains Hh on the cell surface, while competing for Hh with the Hh receptor.

On p. 2001, Baolin Wang and colleagues investigate how the stability and processing of Gli2 and Gli3, transcriptional regulators that mediate Hh signalling in vertebrates, are regulated. Full-length Gli2 (Gli2<sup>FL</sup>) strongly activates Hh signalling but a small fraction is C-terminally processed to a repressor (Gli2<sup>REP</sup>). By contrast, Gli3<sup>FL</sup> weakly activates Hh signalling but is mainly C-terminally processed. Thus, mechanisms that stabilise, destabilise and process Gli2 and Gli3 ensure a prompt response to Hh signalling. The researchers show here that suppressor of fused (Sufu, an inhibitor of Gli transcriptional activities) is essential for the stabilisation of Gli2<sup>FL</sup> and Gli3<sup>FL</sup> but not of Gli2<sup>REP</sup> and Gli3<sup>REP</sup>, whereas Spop (a substrate-binding adaptor for the cullin3-based ubiquitin E3 ligase) promotes Gli2<sup>FL</sup> and Gli3<sup>FL</sup> degradation. The researchers also unexpectedly discover that Gli3<sup>REP</sup> can function independently of Sufu. Overall, these results provide new insights into how Sufu and Spop regulate Gli2 and Gli3 stability and processing to affect the transcriptional response to Hh signalling.



### Hosting factors for reprogramming

Animals can be cloned by transferring a somatic cell nucleus into an enucleated oocyte, but the reprogramming of such nuclei to totipotency to create clones seems to depend on the cell-cycle and differentiation state of both the donor and recipient cell. Now, on p. 1953, Dieter Egli and Kevin Eggan reveal that somatic nuclear reprogramming is not cell cycle dependent but does require nuclear transcriptional factors from the recipient cell. The researchers investigated reprogramming efficiency by examining the development of embryos that were produced by combining donor nuclei and recipient cells at various cell cycle and developmental stages. Many stages of the cell cycle are compatible with nuclear reprogramming, they report, provided sufficient host nuclear factors (including the transcriptional regulator Brg1) are retained in the enucleated recipient cell. Furthermore, cell cycle synchrony between the donor and the recipient is not strictly required at the time of nuclear transfer for successful reprogramming. These results, which reveal that reprogramming is remarkably flexible, might help to improve the efficiency of somatic cell nuclear reprogramming.

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