WEB WATCH

Incyte into the stars

Want to know more about the big names who regularly feature on those seminal papers? Well, look no further, because Incyte Genomics has collected a series of in-depth conversations on its web site, "with committed, passionate scientists who are shaping the world of genomics". Those featured include Gerry Rubin, Mina Bissell, David Botstein and Walter Gilbert.

So what can you expect of these interviews? Well, after the obligatory, praise-filled introduction to the featured scientist's career and achievements, the Incyte interviewers do actually pose some hard-hitting questions and, in some instances, have received some refreshingly candid answers. For example, how did Gerry Rubin's colleagues react to his collaboration with Craig Venter to sequence the fly genome? Rubin replies, "A good friend whom I've known for over 20 years said, 'I hated you for three months … but then I got over it.' I don't think that everyone has gotten over it." And Mina Bissell, on how her upbringing and curiosity helped her to find original answers to biological questions, says "I grew up having political debates with my father … I was raised to question things, … and I have always gotten myself into a bit of trouble by doing things that aren't quite predictable."

What I liked about these interviews was that — if you don't have time to read the whole thing — you can browse a list of questions each interviewee was asked to select interesting topics. The more recent interviews also carry a box of choice quotes from the featured scientist. So, if you want to find out what David Botstein thinks about patents or how Walter Gilbert relaxes, visit www.incyte.com.

Jane Alfred

DEVELOPMENTAL BIOLOGY

Tackling gradients

Morphogens are secreted molecules that impart positional information to cells within a tissue in a concentration-dependent manner. A central question has been how developing cells translate the different concentration thresholds of the morphogen into distinct cell fates. Two reports in *Cell* now tackle an equally important problem. By analysing the morphogens Sonic hedgehog (Shh) and Wingless (Wg), these papers identify two distinct mechanisms by which the concentration gradient of a morphogen is formed and maintained.

In the *Drosophila* embryo, Wg expression and that of the transcription factor Engrailed (En) in adjacent rows of cells are required for segmentation of the embryo along its anterioposterior (AP) axis. After egg deposition, Wg distribution changes from being symmetric to asymmetric — it can diffuse for several cell diameters anteriorly, but for only one row of cells posteriorly, where it meets the *en*-expressing domain. Dubois *et al.* show that this asymmetry is caused by a fourfold increase, anteriorly relative to posteriorly, in the lysosomal degradation of Wg. They discovered this by following the subcellular fate of Wg in transgenic flies that produced a horseradish peroxidase (Hrp)–Wg fusion protein. In cells posterior to its source, Wg is targeted to the degradative compartment — the degradative vesicles of these cells showed strong Hrp activity. Indeed, when the lysosomal and endocytic pathways were disabled (genetically or chemically) Wg signalling was upregulated. Wg degradation might be modulated by signalling through the Epidermal growth factor receptor (Egfr) because Rhomboid — an activating member of the Egfr pathway that is expressed at the posterior of each *en*-expressing domain — is required for efficient Wg degradation, perhaps by regulating the transfer of Wg to the degradative compartment.

In the vertebrate limb, Shh is required for the AP patterning of digits — high levels of Shh specify the posterior digits (4 and 5), whereas progressively lower levels specify more-anterior digits. The active signalling form of Shh is produced by the cleavage of its amino-terminal portion and its covalent attachment to the carboxyl terminus by a cholesterol moiety. Lewis *et al.* show that, in the vertebrate limb, this cholesterol modification of Shh is required for its long-range action. Mice that express a truncated form of Shh that cannot be cholesterol modified and have no endogenous wild-type Shh develop only the most-posterior digits. Additionally, the anterior expression of Shh target genes is lost. This indicates that cholesterol modification of Shh is required for its correct distribution because unmodified Shh never reaches the anterior of the limb field. The authors believe that this cholesterol modification doesn't simply enable Shh to progress through the field, but also prevents it from diffusing too far. Its transport might be favoured by interactions with heparan-sulphate-proteoglycans; conversely, the cholesterol moiety might restrict the movement of Shh by favouring its interaction with Patched — its receptor. In the absence of cholesterol, Shh is sequestered but not transported, hence the limited range of activity of the non-modified form.

The morphogen concept was proposed 50 years ago, and although we are still far from understanding how morphogenetic gradients are regulated, these two papers bring us a step forward. But many questions remain. What is the molecular mechanism behind the function of cholesterol in Shh regulation? How might Rhomboid regulate the transfer of Wg from the lysosome to the degradative vesicles?

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPERS Dubois, L. *et al.* Regulated endocytic routing modulates Wingless signalling in *Drosophila* embryos. *Cell* **105**, 613–624 (2001) | Lewis, P. M. *et al.* Cholesterol modification of Sonic hedgehog is required for long-range signalling activity and effective modulation of signalling by Ptc1. *Cell* **105**, 599–612 (2001)
FURTHER READING Teleman A. A. *et al.* Shaping morphogen gradients. *Cell* **105**, 559–562 (2001)