WEB WATCH

Around the worm in 80 ways

- WormAtlas
  http://www.wormatlas.org/
- WormBase
  http://www.wormbase.org/

If your research involves *Caenorhabditis elegans* and you've ever dreaded the thought of ploughing through a never-ending pile of papers to understand that unfamiliar anatomical phenotype in your model, then WormAtlas could be the solution to your problems.

The site, which went live this year, aims to make the anatomy of *C. elegans* simple and accessible. WormAtlas is funded by a grant from the National Institutes of Health and is in close collaboration with WormBase, the definitive database for genes and proteins in *C. elegans*.

WormAtlas provides an illustrated handbook of worm anatomy and a description of staining and electron-microscopy methods, but where the site shines is the section entitled 'The slidable worm'. This site contains fine-structure images of cross-sections of the worm, a must for those research groups that do not have access to an electron microscope. This section is not yet complete, but its aim is to have 600–1,200 annonated electron-microscopy images in total.

The most frustrating aspect of what promises to be an invaluable resource is that many aspects are currently incomplete, including the illustrated handbook. Also, the site currently focuses on features of the wild-type adult anatomy, but it will eventually provide data on key mutant phenotypes, and the anatomy of the L1 larva and, where feasible, embryonic development. However, one future advantage of the Atlas will be that it is updateable, with submissions accepted in many formats, such as text and JPEG and TIFF images.

Simon Frantz

DEVELOPMENT

Hedgehog in growth…

Mutations that activate the Hedgehog (Hh) signalling pathway have been linked to tumour formation, but it's not been clear how. The discovery of a direct link between Hh signalling and key regulators of the cell cycle might now provide the answer.

Wei Du and colleagues were studying eye development in *Drosophila melanogaster*. The expression pattern of Hh during this process, just posterior to cells entering S phase, indicated that reception of the Hh signal might be needed for entry to S phase. To test this, the authors looked at what would happen if Hh signalling was blocked during eye development. They found that second mitotic wave cells with mutated *smoothened* (*smo*), a gene that is required for Hh signalling, do not enter S phase. By contrast, overexpression of Cubitus interruptus (Ci) — the transcription factor that mediates Hh signalling — drove G1-arrested cells to enter S phase.

One protein that promotes S phase is Cyclin D. During eye development, the highest expression of Cyclin D overlaps with that of Ci — so could Ci promote the expression of Cyclin D? Support for this idea came from the observation that levels of Cyclin D are reduced in *smo*-mutant clones, and also that overexpression of Ci induces high levels of Cyclin D messenger RNA and protein.

As well as promoting entry into S phase, Cyclin D induces cell growth. Du and co-workers therefore wondered whether Hh might also regulate growth, so they studied the effects of overexpressing either Ci or Patched (Ptc; an inhibitor of Hh signalling) in clones of undifferentiated wing-disc cells. Whereas Ptc overexpression clones were considerably smaller than controls, Ci overexpression clones were much larger, which indicates that Hh signalling not only promotes S phase, but that it also regulates cell growth.

Cyclin E also promotes S phase, and reduced or increased levels of this protein could be detected with loss of smo or overexpression of Ci, respectively. The authors then looked at how Hh signalling might induce the transcription of Cyclin E. They identified several sequences in the Cyclin E promoter with homology to the consensus Ci-binding site, and used chromatin immunoprecipitation to show that Ci indeed binds these sites *in vivo*. Hh signalling therefore seems to promote S phase by

SEX DETERMINATION

… and differentiation

A crucial event during early development of the testis is the specification of somatic cell lineages such as the Leydig cells. Little is known about the origin of fetal Leydig cells, or of the signals that induce them to differentiate. Now, however, reporting in *Genes and Development*, Blanche Capel and colleagues provide evidence that the Desert Hedgehog (DHH)/Patched 1 (PTCH1) pathway triggers Leydig cell differentiation.

Fetal Leydig cells are responsible for the initial masculinization of an embryo. They are first identifiable in the interstitium of XY gonads, where they express enzymes that are needed for the production of male sex hormones. There is some evidence that Leydig cell precursors migrate to the gonad from the mesonephros; but whatever their origin, most are present in the gonad by 11.5 days post coitum (dpc).

The PTCH1 protein is expressed in the interstitium of XY gonads at 12.5 dpc, which made Capel and co-workers wonder whether this receptor — and its ligand, DHH — might be involved in the differentiation of Leydig cells. To test this, they first studied the expression patterns of the *Ptch1*, *Dhh* and P450 side chain cleavage enzyme (*Scc*) genes (*Scc* is a marker for fetal Leydig cells). Expression of *Dhh* began at 11.5 dpc in XY gonads, as has been observed previously. At 12.5 dpc, most of the interstitial cells also expressed $Ptch^{LacZ}$ — but not *Scc*. However, by 13.5 dpc, most of the $Ptch^{LacZ}$-positive cells were also expressing *Scc*.

These expression patterns support the idea that DHH signalling is involved in the early development of Leydig cells. So Capel and colleagues next asked what effect the loss of this pathway would have on Leydig cell differentiation. They analysed the expression of *Scc* in $Dhh^{+/+}$, $Dhh^{+/-}$ and $Dhh^{-/-}$ XY gonads at 13.5–14.5 dpc. *Scc* staining was seen at the centre of $Dhh^{+/+}$ and $Dhh^{+/-}$ gonads at 13.5 dpc, yet it was absent from 70% of the $Dhh^{-/-}$ gonads at this stage. Even by 14.5 dpc, the $Dhh^{-/-}$ gonads showed only very sparse staining for *Scc*.

The authors next investigated why the lack of DHH signalling leads to defects in Leydig cell differentiation. One idea was that it might affect the migration of cells from the mesonephros to the gonad. However, two independent experimental approaches showed that this migration process was normal in $Dhh^{-/-}$ gonads. Another possibility was that DHH signalling is involved in the proliferation or