WEB WATCH

Model resource

- http://www.ebi.ac.uk/biomodels

A step towards the greater use of computational models in biology was taken when the world's first database of annotated biological models went online on 11 April 2005.

The Biomodels Database has been designed to allow biologists to store, search and retrieve published mathematical models of biological systems. The free-to-use database aims to provide access to published, peer-reviewed, quantitative models of biochemical and cellular systems.

So far, there's been no 'official' way for biologists to readily share such models, but they can now produce and freely distribute their models using the widely accepted, open-source Systems Biology Markup Language (SBML). Once entered into the database, models are annotated and linked to relevant data sources, such as publications or other databases, by human curators.

The database is the result of a collaboration led by the European Bioinformatics Institute (part of the European Molecular Biology Laboratory) in the United Kingdom and the SBML team from the United States. Other contributors come from the United States, Japan and South Africa.

The developers' hope is that, ultimately, scientists will be encouraged to deposit their published models in the Biomodels Database, making them freely available to all.

The database is currently open to the submission of models — the curators will then pick them up for syntax and semantic curation and submit them to the database itself. At present, they accept only SBML Level 2 Version 1, but say that they will soon expand to Level 1, then CellML, and eventually to other formats.

David Stevens

WOUND HEALING

Rebuilding barriers

Mammals have skin; insects have cuticle — both function as barriers. It goes without saying that simple wounds in these integuments must be fixed, and William McGinnis' group has defined an evolutionarily conserved pathway, involving the Grainy head (Grh) transcription factor and extracellular signal-regulated kinase (ERK), through which this is achieved.

The authors studied two genes — *Ddc* and *ple* — in *Drosophila melanogaster*. *Ddc* encodes dopa decarboxylase and *ple* encodes tyrosine hydroxylase; both proteins are involved in generating the integument of insects. After wounding late *D. melanogaster* embryos, *Ddc* and *ple* transcripts began accumulating in epidermal cells near the wound within 30 minutes, indicating that they were directly targeted by wound-induced signalling. A sequence from –1.4 kb to the transcriptional start of *Ddc* was required for this response. A tagged reporter construct containing this sequence was activated in a decreasing graded response surrounding the wound, indicating that a signal produced at the injury site probably activated the wound response enhancer dose dependently.

MOLECULAR MOTORS

Coordinated movement

Microtubule-dependent molecular motors are responsible for the long-distance intracellular transport of organelles. Kinesins move organelles towards the plus end of microtubules — that is, towards the cell periphery — whereas dyneins move them towards the minus end. But how is this bidirectional transport of organelles achieved *in vivo*? Is there an ongoing tug-of-war or are the functions of these motors coordinated? Selvin and colleagues provide answers in *Science*.

They used a technique known as FIONA (fluorescence imaging with one nanometre accuracy) to observe green-fluorescent-protein-labelled peroxisomes being moved by microtubule motors inside live *Drosophila melanogaster* S2 cells. This technique provides a 1.5-nm accuracy and a 1.1-msec time resolution (the latter is a 400-fold improvement on previous methods). They inhibited actomyosin-dependent movements to ensure that only microtubule motors were being observed, and used RNA interference to show that kinesin-1 and the dynein heavy chain move peroxisomes in these cells. They also verified that the effects of microtubule lattice movements on peroxisome transport were minimal — that is, the movements observed were related to motor-driven movement.

FIONA revealed a step size of ~8 nm for kinesin-1 and the dynein heavy chain, which concurs with the results of *in vitro* assays. In addition, the step size remained constant. This indicates that there is no tug-of-war, which would cause the step size to decrease. Instead, it seems that the motors might be turned on and off, so that they don't pull the peroxisome simultaneously. Furthermore, the speed of the *in vivo* peroxisome movement indicates that, at any one time, several kinesins or dyneins (up to 11 in both cases) can work together to produce speeds that are 10 times greater than those seen *in vitro*. The faster movements have the same step size; the steps just occur with greater rapidity.

So, how is motor coordination achieved? Answering this question

This wound response enhancer didn't require the activity of signalling pathways involved in innate immunity (which protect against infections through wounding), nor did it require the zygotic functions of Jun N-terminal kinase (JNK), Jun or Fos, which are involved in dorsal closure during embryogenesis. What, then, binds to the enhancer region?

One protein isoform encoded by *grh* — Grh-N — is expressed in barrier epithelia, and zygotic mutations in *grh* result in a phenotype similar to *Ddc* and *ple* mutants. The authors therefore tested a potential function for Grh-N in activating the –1.4-kb *Ddc* wound response element. The –1.4-kb *Ddc* reporter was only weakly activated in aseptically wounded *grh*-mutant embryos, and such wound sites couldn't regenerate normal cuticle.

As well as two evolutionarily conserved sites that bind the Grh transcription factor, the *Ddc* wound response enhancer contains several other consensus binding sites for other transcription factors, including activator protein-1 (AP-1) and ETS, as well as a GGGGGATT motif. A 3-kb fragment of *ple* also includes such sites, and strongly activates reporter expression around wounds.

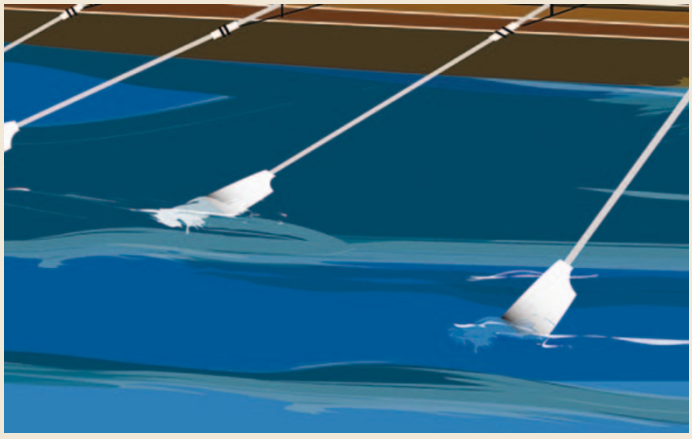
McGinnis and colleagues also noticed an increase in phosphotyrosine staining and ERK activation in cells near aseptic wounds. ERK was activated in sites surrounding embryonic wounds within 30 minutes of injury. ERK was still activated in *grh* mutants, but inhibiting ERK activation decreased the activation of the *Ddc* wound response reporter. So ERK might somehow transduce the wound signal to Grh, and the aim is to find out how. Once Grh binds to, and activates, *Ddc* and *ple* near wounds, crosslinking molecules that repair the epithelial barrier kick into action. In another study in *Science*, Ting *et al.* report that a mouse orthologue of *grh*, *Grainy head-like-3* (*Grhl3*), is needed to form and maintain the epidermal barrier in mice. One target of Grhl3 is the gene for transglutaminase-1, an enzyme that, like the *Ddc* and *ple* gene products, is involved in crosslinking epidermal proteins.

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Mace, K. A., Pearson, J. C. & McGinnis, W. An epidermal barrier wound repair pathway in *Drosophila* is mediated by *grainy head*. *Science* **308**, 381–385 (2005)

FURTHER READING Ting, S. B. *et al.* A homolog of *Drosophila* grainy head is essential for epidermal integrity in mice. *Science* **308**, 411–413 (2005)



is the challenge for the future. It will be interesting to determine exactly how the movements of kinesin and dynein are coordinated, as well as how several kinesins or dyneins can work together to bring about the rapid movement of cargo.

Rachel Smallridge

References and links

ORIGINAL RESEARCH PAPER Kural, C. *et al.* Kinesin and dynein move a peroxisome *in vivo*: a tug-of-war or coordinated movement? *Science* 14 Apr 2005 (doi:10.1126/science.1108408)

FURTHER READING Mallik, R. & Gross, S. P. Molecular motors: strategies to get along. *Curr. Biol.* **14**, R971–R982 (2004)

WEB SITE

Paul Selvin's laboratory: http://www.physics.uiuc.edu/People/Faculty/Selvin/

IN BRIEF

CELL CYCLE

PPM1D dephosphorylates Chk1 and p53 and abrogates cell cycle checkpoints.

Lu, X., Nannenga, B. & Donehower, L. A. *Genes Dev.* 3 May 2005 (doi:10.1101/gad.1291305)

The ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia and Rad-3 related (ATR) kinases phosphorylate various targets, including p53 and Chk1, following DNA damage. Lu *et al.* reported that the serine/threonine phosphatase PPM1D/Wip1, which is induced by p53, dephosphorylates Chk1 and p53. Overexpression of PPM1D inhibited both S-phase- and G2–M-damage-induced checkpoints, so PPM1D might restore cell-cycle homeostasis after completion of DNA repair.

SIGNALLING

JNK extends life span and limits growth by antagonizing cellular and organism-wide responses to insulin signalling.

Wang, M., Bohmann, D. & Jasper, H. *Cell* **121**, 115–125 (2005)

In *Drosophila melanogaster*, calorie restriction extends lifespan by relieving the inactivation by insulin/insulin-like growth factor signalling (IIS) of Foxo to allow Foxo target-gene activation. Foxo also translocates to the nucleus in response to oxidative stress. The authors showed that Jun N-terminal kinase (JNK) signalling, which in *D. melanogaster* confers tolerance to oxidative stress and extends lifespan, induces Foxo nuclear localization and Foxo-dependent stress-response genes by antagonizing IIS. JNK also downregulates the production of *D. melanogaster* insulin-like peptide-2, thereby inhibiting IIS.

MORPHOGENS

Lipoprotein particles are required for Hedgehog and Wingless signalling.

Panáková, D. *et al. Nature* **435**, 58–65 (2005)

How do lipid-anchored Wingless/Wnt and Hedgehog (Hh) induce long-distance target-gene expression? Panáková *et al.* showed that Wingless and Hh, as well as glycosylphosphatidylinositol (GPI)-linked proteins, associate and colocalize with the lipoprotein lipophorin, which is needed for lipid transport and long-range Hh and Wingless function. Lipid-linked morphogens and GPI-linked proteins are therefore moved (rather than simply released) by binding to lipoprotein particles.

DEVELOPMENT

FGF signal interpretation is directed by Sprouty and Spred proteins during mesoderm formation.

Sivak, J. M., Petersen, L. F. & Amaya, E. *Dev. Cell* **8**, 689–701 (2005)

These authors identified two Sprouty and two Spred genes in *Xenopus laevis*, and showed that, in the early embryo, they inhibit distinct pathways mediated by fibroblast growth factor. The Sprouty proteins inhibit the activation of protein kinase Cδ, Ca^{2+} signalling and morphogenesis, whereas the Spreds inhibit the activity of mitogen-activated protein kinase and mesoderm specification. Their differential expression provides a putative mechanism to coordinate mesoderm formation and cell movements.