WEB WATCH

Your cup of *ZF-espresso*?

- http://zf-espresso.tuebingen.mpg.de

Zebrafish has quickly established itself as an important model not only for developmental biologists, but also for those studying human disease. To satisfy the growing need for analysis of data from large-scale, high-throughput experiments, Robert Geisler's group at the Max Planck Institute in Tuebingen has developed an online database for zebrafish expression-profiling data — *ZF-Espresso*.

The database is being developed as part of the ZF-MODELS project, an Integrated Project that is funded by the European Commission. The aim of *ZF-Espresso* is to give biologists access to publicly available expression-profiling data. Experiments from different investigators can be compared and combined in a single expression profile. It is also possible to search for genes with similar expression profiles across experiments.

The information is organized under three headings: Select Conditions, Select Probes and Draw Expression Profile. The user can select from a list of experimental conditions and a list of microarray (or qPCR) probes. Because the probes have been mapped to UniGene IDs comparisons can be made across microarray platforms. Line and bar graphs and dot and distribution plots help to visualize expression profiles. The data (from the spreadsheet view) can also be downloaded and imported for further analysis.

ZF-Espresso launched only a couple of months ago. Eventually, it will include all the zebrafish expression-profiling data from public repositories. The plan is to add links to external image databases, provide raw and processed data and to add statistical tools for cross-experiment validation. It is based on freely available PHP and MySQL software and will be easily adaptable for other organisms.

Magdalena Skipper

DEVELOPMENTAL BIOLOGY

Shapely organs require clear orientation

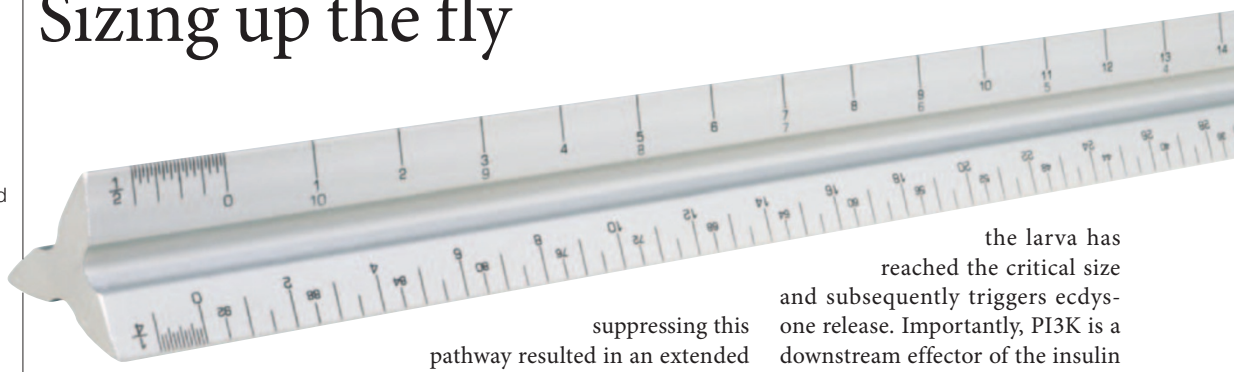
Cell migration and orientated cell division contribute to the spatial distribution of cells. Careful analysis of fly wild-type and mutant embryonic organ precursors for orientation of cell division implicates such orientation in determining organ morphology and points to planar cell-polarity genes as important players in this process.

The authors analysed the orientation of cell divisions in marked clones within imaginal discs — the epithelial, embryonic precursors of adult fly organs. They found a correlation between the orientation of cell divisions and the shape of the clones (and ultimately the adult organs); the correlation persisted throughout development.

Planar cell-polarity genes are known to define the polarity of cells within an epithelium, and flies that carry mutations in members of this family, such as *dachsous* and *fat*, have abnormally shaped organs. The authors show that this

DEVELOPMENTAL BIOLOGY

Sizing up the fly



The final size of an organism depends on both its rate and duration of growth — but how are these variables controlled and coordinated? A recent flurry of studies in the fruitfly has pieced together some important parts of this puzzle.

In *Drosophila melanogaster*, growth takes place over three larval stages, during which enough food needs to be consumed to survive the rest of development. Larvae at the third stage must reach a critical size to undergo pupariation, a process that marks the transition to metamorphosis and is triggered by the release of the steroid hormone ecdysone from the prothoracic gland (PG).

Caldwell and colleagues showed that expressing constitutively active components of the RAS signalling pathway in the PG led to a reduction in final body size. By contrast, suppressing this pathway resulted in an extended duration of the larval stages and an increase in body size. Monitoring the expression of ecdysone-responsive transgenes revealed that activated RAS in the PG leads to premature ecdysone release. So, the RAS pathway regulates body size by regulating ecdysone production, and therefore the duration of growth.

However, the same study indicated that RAS signalling is not the only pathway that regulates body size. Expression of activated phosphatidylinositol 3-kinase (PI3K) was found to decrease body size independently of RAS activity. The authors postulated that this effect of PI3K is mediated through its ability to increase the size of PG cells, which would increase ecdysone production and terminate larval growth prematurely. This is consistent with a study by Mirth and colleagues, which showed that the PG assesses when the larva has reached the critical size and subsequently triggers ecdysone release. Importantly, PI3K is a downstream effector of the insulin signalling pathway, which is known to couple fly body size to the availability of nutrients, and these findings provide new insights into the underlying mechanisms.

A paper by Colombani and colleagues reports similar effects on body size after genetic manipulation of PI3K in the PG. Interestingly, this study also establishes a new role for ecdysone in regulating animal growth rate, through a general repression of insulin signalling in peripheral tissues. So, insulin and ecdysone seem to antagonize each other's effects on growth rate, and thereby regulate body size.

Finally, Shingleton and colleagues investigated whether insulin signalling exerts the same effect on body size at all larval stages. Using a temperature-sensitive mutation in the insulin receptor (*Inr*) gene they showed that disrupting this

dismorphology is associated with changes in the orientation of cell division.

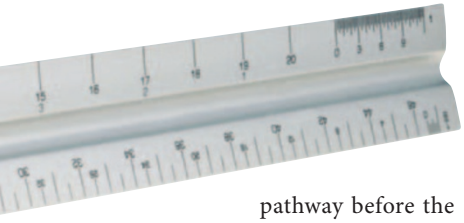
This work might have uncovered a general mechanism of organ morphogenesis: there is a correlation between the orientation of cell division and the shape of different organs and, importantly, planar cell-polarity genes are well-conserved throughout evolution. We now need specifically targeted experiments to confirm this possibility.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER

Baena-López, L. A. *et al.* The orientation of cell divisions determines the shape of *Drosophila* organs. *Curr. Biol.* **15**, 1640–1644 (2005)



pathway before the critical size is reached extends total development time, but has no effect on the final size of the fly. The opposite was true when INR signalling was blocked after the critical size had been attained.

These studies represent important steps in understanding how body size is regulated in the fly. They might also have implications for understanding the coordination of nutrient availability and developmental transitions in mammals, where steroid hormones and insulin signalling also have key roles in regulating growth.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPERS Caldwell, P. E., Walkiewicz, M. & Stern, M. Ras activity in the *Drosophila* prothoracic gland regulates body size and developmental rate via ecdysone release. *Curr. Biol.* 20 September 2005 (doi:10.1016/j.cub.2005.09.011) | Mirth, C., Truman, J. W. & Riddiford, L. M. The role of the prothoracic gland in determining critical weight for metamorphosis in *Drosophila melanogaster*. *Curr. Biol.* 20 September 2005 (doi:10.1016/j.cub.2005.09.017) | Colombani, J. *et al.* Antagonistic actions of ecdysone and insulins determine final size in *Drosophila*. *Science* 22 September 2005 (doi:10.1126/science.1119432) | Shingleton, A. W. *et al.* The temporal requirements for insulin signaling during development in *Drosophila*. *PLoS Biol.* **3**, e289 (2005)

HUMAN EVOLUTION

Brains under pressure

It has taken us many millions of years to evolve the big sophisticated brains that we are so proud of. But it's unlikely to be the best we will ever have. New work shows that two genes that are involved in brain development arose at culturally crucial times during human history and indeed might still be evolving.

It makes sense that genes involved in brain morphology, like so many other developmental genes, are subject to natural selection. Bruce Lahn's initial investigation into the subject was reported last year, when he and his colleagues found that two genes that regulate brain size — microcephalin (*MCPH1*) and abnormal spindle-like microcephaly associated (*ASPM*) — have been under strong selective pressure in the human evolutionary lineage since we split off from the chimpanzee lineage. New work has looked more closely at these two genes to see whether there are signs of more recent selection.

To do this, the distribution of haplotypes for the two genes was studied in a panel of ~90 cell lines that are representative of human diversity. In both cases, one haplotype stood out as being present in a large proportion of cell lines — a frequency that could not be explained by random or demographic factors and therefore might have been driven up in abundance by positive selection. The population distribution of polymorphisms at the two loci and the extent of linkage disequilibrium around each candidate positively selected region support this idea and also point to the occurrence of a recent selective sweep that still continues.

A statistical analysis that is based on estimating the past mutation rate of the genes placed the emergence of the high-frequency alleles at ~37,000 years ago for *MCPH1* and ~5,800 years ago for *ASPM*. These dates coincide with significant periods in recent human history: the first to the emergence of cultural traits such as music, art and symbolism, and the second to the building of the first cities in Mesopotamia.

The young age of the frequent *ASPM* variant makes it likely that brain evolution is still continuing. As the authors themselves point out, however, the results should not be overinterpreted. For example, as we cannot tell what force is driving the positive evolution of gene variants, we cannot ascribe it to variation in cognitive function (both genes are also expressed outside the brain). For the same reasons, we should be wary of reading any adaptive significance into the current geographical distribution of *MCPH1* and *ASPM* alleles.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPERS Evans, P. D. *et al.* *Microcephalin*, a gene regulating brain size, continues to evolve adaptively in humans. *Science* **309**, 1717–1720 (2005) | Mekel-Bobrov, N. *et al.* Ongoing adaptive evolution of *ASPM*, a brain size determinant in *Homo sapiens*. *Science* **309**, 1720–1722 (2005)

FURTHER READING Gilbert, S. L. *et al.* Genetic links between brain development and brain evolution. *Nature Rev. Genet.* **6**, 581–590 (2005) | Bamshad, M. & Wooding, S. P. Signatures of natural selection in the human genome. *Nature Rev. Genet.* **4**, 99–111 (2003)

WEB SITE

Bruce Lahn's home page: http://www.genes.uchicago.edu/fri/lahnres.html

DISEASE MODELS

Of mice and men

For the first time, researchers have generated a mouse strain that also carries a single copy of human chromosome 21. O'Doherty *et al.* have overcome technical obstacles to create this new trans-species model of human Down syndrome, which is the result of chromosome 21 trisomy.

Previous attempts to model Down syndrome in mice have involved either introducing individual human transgenes or creating trisomies of mouse chromosomes. The one-gene-at-a-time approach does not correctly model the 3:2 gene dosage that is found in trisomy, and the mouse trisomies are only approximations to the human condition because genes that lie on human chromosome 21 lie on several mouse chromosomes.

Using injection into female mouse embryonic stem cells, the authors created an aneuploid strain that contains 92% of the gene content of human chromosome 21. The strain had several characteristics of Down syndrome such as heart defects and decreases in long-term synaptic potentiation and memory, neuronal density and T-lymphocyte activation, but only minor facial defects.

The model is a starting point for the study of the specific dosage effects of individual genes, although the precise consequences of heterologous interactions between human and mouse proteins need to be investigated.

Patrick Goymer

References and links

ORIGINAL RESEARCH PAPER

O'Doherty, A. *et al.* An aneuploid mouse strain carrying human chromosome 21 with Down syndrome phenotypes. *Science* **309**, 2033–2037 (2005)

FURTHER READING Antonarakis, S. E. *et al.* Chromosome 21 and Down syndrome: from genomics to pathophysiology. *Nature Rev. Genet.* **5**, 725–738 (2004) | Patterson, D. & Costa, A. C. S. Down syndrome and genetics — a case of linked histories. *Nature Rev. Genet.* **6**, 137–147 (2005)