GENE THERAPY

Proof of delivery

Treating any disorder of the brain poses a special challenge owing to the difficulty of getting drugs across the blood–brain barrier. New work shows that implanting the brains of animal models with genetically engineered neural progenitor cells (NPC) reduces some symptoms of Parkinson disease, and might benefit other neurodegenerative diseases.

Parkinson disease affects 1.5 million people in the United States and is caused by the irreversible loss of dopamine-producing neurons, which coordinate muscle movement and balance. We know that some molecules — such as glial-cell-line-derived neurotrophic factor, or GDNF — can promote the regeneration of lost neurons, but delivering these agents to the brain by using viruses as carriers, or by injecting the molecule straight into the brain, could pose a risk to health or be inefficient. The group, led by Soshana Behrstock and Clive Svendsen, has hit on the different strategy of modifying cells to express GDNF. The engineered cells — human NPCs that were derived from fetal brains — were then transferred into the area of the brain in which GDNF was needed in parkinsonian rats and ageing rhesus monkeys.

Remarkably, the protein produced by the cells remained active for up to 3 months and was transported to the substantia nigra, the brain region that degenerates in Parkinson disease. In addition, the cells migrated across the affected region and led to increased fibre sprouting and survival of the host neurons.

Given that the effects of GDNF are not specific to the cells that are damaged in Parkinson disease it is likely that these same cells can be used to treat other disorders, such as Huntington disease and amyotrophic lateral sclerosis (ALS). Whether this therapy can be attempted in humans will depend on devising a way to control the expression of GDNF in the engineered cells — in particular, to shut it off. The authors accomplished protein regulation in culture, but shut-off in animals proved more difficult and is being addressed in new experiments. Nevertheless, this work provides convincing evidence that stem cells are a valid route for targeting drugs to less accessible tissues such as the brain in a safe and efficient way.

Tanita Casci

ORIGINAL RESEARCH PAPER
Behrstock, S. *et al.* Human neural progenitors deliver glial cell line-derived neurotrophic factor to parkinsonian rodents and aged primates. *Gene Ther.* 15 December 2005 (doi:10.1038/sj.gt.3302679)
FURTHER READING Jakel, R. J. Using human neural stem cells to model neurological disease. *Nature Rev. Genet.* **5**, 136–144 (2004) | Svendsen, C. N. & Langston, J. W. Stem cells for Parkinson disease and ALS: replacement or protection? *Nature Med.* **10**, 224–225 (2004)
WEB SITE
Clive Svendsen's laboratory: http://www.waisman.wisc.edu/scrp/svendsen.html

YEAST GENOMICS

Shaping up the genome

Many yeast mutations result in qualitative changes in morphology, but can this be practically quantified for discovering gene function? Ohya *et al.* have devised a quantitative screen for morphological phenotypes and they show that these phenotypes correlate with function. They demonstrate how this information can be applied to the collection of yeast mutants to predict the roles of genes of unknown function.

The authors have previously produced a database of digital images of every non-essential yeast mutant. In each image the cell wall, the cytoskeleton and the nuclear DNA are stained simultaneously, allowing quantitative data to be extracted. From this they have now defined 254 statistically reliable parameters that reflect morphology at different stages of the cell cycle.

They found that 2,378 of the 4,718 available deletion strains differed from the wild type in at least one parameter, and that 247 of the 254 parameters identified differences in at least one strain. Importantly, 544 genes of unknown function showed a morphological phenotype, representing about half of the unassigned genes in the genome.

To test for correlations between morphology and function the authors used the Gene Ontology functional annotation of the genome. Each gene for which a function is known is assigned to one or more of 1,452 functional groups. They compared each of these groups with all 254 parameters and found that 260 of the functional groups showed significant correlation with at least one morphological phenotype.

Conversely, the authors tested each morphological class for enrichment with the genes that are associated with any one specific function. They found that 109 of the 254 morphological traits were associated with a functional annotation. Together, these results show that morphological data can be used to predict the functions of unassigned genes.

The power of such a method can be improved by studying more than one morphological trait at the same time. For example, the authors found two morphological traits that were associated with genes annotated as being involved in DNA repair. They then retrieved all the other non-essential genes in the genome that shared both traits and so identified several more candidate genes. These were then further characterized for sensitivity to the DNA-damaging reagent hydroxyurea. Interestingly, the morphological characteristics of wild-type cells that had been treated with hydroxyurea were similar to those of the untreated DNA-repair mutants. This indicates that correlations between chemically induced and mutant phenotypes could be used to predict the chemical targets of drugs. Wild-type cells that have been treated with a particular drug can be assessed for morphological traits, and the mutants with similar characteristics can be identified. It is likely that the molecular targets of the genes that are deleted in these mutants are the same as the targets of the drug.

The methods demonstrated in this study can now be systematically applied to all of the 544 genes of unknown function that show a morphological phenotype, and hopefully they will lead to the identification of function in many cases. This will further close the gap in our knowledge of the functions that are encoded by the yeast genome.

Patrick Goymer

ORIGINAL RESEARCH PAPER Ohya, Y. *et al.* High-dimensional and large-scale phenotyping of yeast mutants. *Proc. Natl Acad. Sci. USA* **102**, 19015–19020 (2006)

WEB SITE

***Saccharomyces cerevisiae* Morphological Database:** http://scmd.gi.k.u-tokyo.ac.jp

In the news

A CRIMINAL DATABASE EXPANSION PUSHES THE BOUNDARIES

"The DNA profiles of nearly four in 10 black men in the UK are on the police's national database — compared with fewer than one in 10 white men." (*The Guardian*, 5 January 2006) Several commentaries followed a Home Office report in which it was revealed "that 5.24% of the UK population now has a DNA profile held on the database. This compares with an EU average of 1.3% and 0.5% in the US." (*BBC News*, 5 January 2006)

When the expansion of the database started in 1999, the samples could only be taken from those charged with a crime. As of April 2004, the rules have been relaxed and the police can retain all samples, even if the donor has been cleared of a crime or the prosecution was dropped. "New Home Office figures estimate that by 2008, the samples of some 4.2 million people — seven per cent of the population — will be contained on a central criminal database." (*Daily Telegraph*, 5 January 2006).

The trouble with this expansion, especially given the racial bias of the database, is that there has been no national debate about it. The government has been accused of "compiling a national DNA database by stealth" (*Daily Telegraph*). Civil liberties groups have expressed concerns about the lack of safeguards to prevent misuse of this private information. The concern is not just over the risk of the data falling into the hands of insurers and employers but the reliability of the information — each database record is limited to 10 microsatellites. "Prof Sir Alec Jeffreys ... has suggested that this could allow false readings and said the number of DNA markers should be increased to 15." (*Daily Telegraph*)

Magdalena Skipper

GENE EXPRESSION

Where does all this noise come from?

Noise has stopped being a nuisance in biology, ever since it was realized that not only is it an inevitable by-product of any inherently variable molecular interaction, but that noise is in fact essential for development, evolution and disease. We know how to detect noise and measure its effects, but where does it come from? A new study has used computational modelling to answer precisely this neglected question.

Noise, or variability in gene expression, is of two kinds: 'intrinsic' noise derives from the natural variability in the way that molecules interact, whereas 'extrinsic' noise arises from random fluctuations in the environment, or the effect of regulatory inputs that are common to multiple genes. It is extrinsic noise that the authors wanted to pin down.

The approach was to generate five lines of yeast (*Saccharomyces cerevisiae*), each of which contains a different number of an identical galactose-inducible transgene, inserted at the same chromosomal location. The expression of the construct is measured, at the single-cell level, by GFP fluorescence, and the origin of variability is measured by analysing the scaling of the noise strength with the copy number of the transgene: if there is no extrinsic noise, then the coefficient of variation for the fluorescence (defined as the ratio of the variance to the mean squared) in a population of cells would be inversely proportional to the number of transgene copies and amount of inducer.

This assay revealed that the system is dominated by extrinsic variability, as the coefficient of variation was independent of transgene copy number. Mathematical models that link gene expression to population growth yielded two important insights. At high levels of inducer the variability in expression of the transgene is

SEX CHROMOSOMES

A more eXpressive chromosome

The fact that females have two X chromosomes and males only one is basic knowledge in mammalian genetics, but the way that this inequality between the sexes is dealt with keeps surprising us. A recent study tackles the issue of an important problem that male XY cells face — the fact that they carry just one copy of the X leaves them vulnerable to events that reduce the expression of genes on this chromosome. The recent study reveals an effective way of dealing with this: genes on the X — in both males and females — are simply expressed at twice the level of other genes.

Bumping up the expression of the X chromosome is not a new concept — it is well known to happen in male fruitflies. Nguyen and Disteche took a simple approach to investigating whether this also happens in mammals: they used microarrays to compare average expression levels for genes on the X with those on the autosomes. From over 1,500 microarrays, which represented a range of tissues from rodents, humans and other primates of both sexes, they showed that the average ratio of X:autosome expression is close to 1:1. This is not what would be expected if X-linked genes were expressed at levels comparable to genes on any one autosome: because of X inactivation in female mammals, male and female cells carry only one active copy of the X, compared with two for each autosome.

> "Our findings of X upregulation in mammals unify the concept of balanced expression in a given genome." (Nguyen & Ditreche, 2005)

Does this upregulation of expression on the X hold true for both sexes? Sex-specific microarray data showed that this is indeed the case: so not only is expression from the male X chromosome boosted, but the same applies to the active copy of the X in females. By contrast, no upregulation of the X was seen for spermatids and oocytes, showing that the X is expressed at similar levels to the single sets of autosomes in gametes from both sexes.

The authors also showed that X:autosome expression ratios become equalized early in embryogenesis,

influenced only by population dynamics (for example, by how a cell grows and when it divides, and the rate of gene expression). This corroborates the values seen in the experimental assay and is consistent with the existence of a lower level of variability (a 'noise floor') that a cell population can experience. However, at lower concentrations of inducer extrinsic noise has a greater role, which in this system was traced back to Gal4, a common, upstream activator of the *GAL1* promoter.

Although the details of this system are specific to the galactose-inducible gene network, the assumptions of the models used in this study are generally applicable, leaving the road open for exploring whether the same principles also hold for other eukaryotic systems.

Tanita Casci

ORIGINAL RESEARCH PAPER Volfson, D. & Marciniak, J. *et al.* Origins of extrinsic variability in eukaryotic gene expression. *Nature* 21 December 2005 (doi:10.1038/nature04281)
FURTHER READING Martinez Arias, A. & Hayward, P. Filtering transcriptional noise during development: concepts and mechanisms. *Nature Rev. Genet.* **7**, 34–44 (2006)

pointing to a rapid upregulation of X-linked expression after fertilization. The next challenge will be to work out how these higher levels of expression on the X are achieved and maintained.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Nguyen, D. K. & Disteche, C. M. Dosage compensation of the active X chromosome in mammals. *Nature Genet.* 11 December 2005 (doi:10.1038/ng1705)

DEVELOPMENTAL BIOLOGY

How to get your bearings

As development progresses, cells frequently need to assess positional information if organ and tissue formation are to occur normally. Exactly how cells monitor their position and integrate the relevant signals they receive is not well understood. Costa and Shaw now show that in *Arabidopsis thaliana* root epidermis, position-dependent cell-fate switching depends on alternative states of chromatin organization at a specific locus. The switch is rapid, ensuring a high level of developmental plasticity.

The root epidermis of *Arabidopsis* is made up of rows of hair and non-hair cells. This pattern is established in embryogenesis and propagated in the seedling root, but rather than being simply lineage-dependent, it relies on both positional information and the activity of GLABRA2 — a homeodomain transcription factor — in the future non-hair cells. Using three-dimensional fluorescence *in situ* hybridization (3D-FISH) of intact epidermis, the authors found that in hair cells, where *GLABRA2* is not expressed, chromatin around this locus is in a closed conformation; the converse was true for non-hair cells.

To explore the link between chromatin, *GLABRA2* expression and cell-fate specification, Costa and Shaw turned to *A. thaliana* mutants. Position-dependent expression of *GLABRA2* is controlled by WEREWOLF (WER) and CAPRICE (CPC), two Myb proteins. 3D-FISH and phenotypic analysis of *wer* and *cpc* mutants indicated that the closed chromatin conformation in hair cells requires CPC, but that open chromatin at the *GLABRA2* locus requires neither GLABRA2 expression nor cell-fate specification. Propagation of positional cues requires correct chromatin assembly — in *fasciata 2* (*fas2*) mutants, in which chromatin-assembly factor-1 is defective, the wild-type epidermal pattern is not established and *GLABRA2* is ectopically expressed.

Chromatin organization around *GLABRA2* is not irreversibly fixed. The authors used clonal analysis to expose cells of the same clonal origin to different positional cues and found that the *GLABRA2* locus was remodelled in response to the new position. The remodelling was surprisingly rapid — careful FISH analysis of two-cell clones revealed that the chromatin state is reset during mitosis and respecified in G1. So the cell-fate switch can take place without the need for completion of the cell cycle.

Costa and Shaw provide an elegant demonstration of how chromatin organization integrates positional information with gene-expression states. In the future, knowing the identity of the upstream players that are involved in this process will reveal how external cues are translated into changes at the chromatin level.

Magdalena Skipper

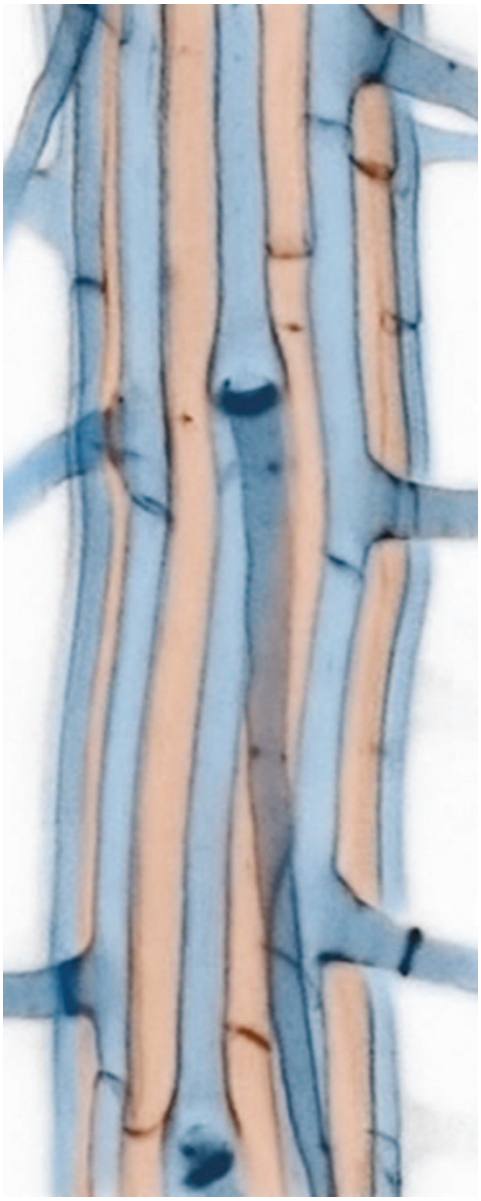


Image courtesy of Silvia Costa and Peter Shaw.

ORIGINAL RESEARCH PAPER Costa, S. & Shaw, P. Chromatin organization and cell fate switch respond to positional information in *Arabidopsis*. *Nature* 18 December 2005 doi:10.1038/nature04269

IN BRIEF

PALAEOGENOMICS

Multiplex amplification of the mammoth mitochondrial genome and the evolution of Elephantidae.

Krause, J. *et al. Nature* 18 December 2005 (doi:10.1038/nature04432)

Metagenomics to paleogenomics: large-scale sequencing of mammoth DNA.

Poinar, H. L. *et al. Science* 20 December 2005 (doi:10.1126/science.1123360)

These papers describe new approaches that make palaeogenomics — the study of genomes of extinct species — a viable strategy for understanding evolutionary relationships. The first study used multiplex PCR to amplify the entire mitochondrial genome of the Pleistocene woolly mammoth from tiny amounts of fossilized material. The trick is to carry out two initial amplifications that together cover the whole mitochondrial genome, followed by amplification of the initial reaction products to obtain sufficient DNA for analysis. The second paper focused on the nuclear genome of the mammoth. First, a particularly well-preserved specimen was identified from which a relatively large amount of DNA could be extracted. Using a recently developed approach that combines emulsion-based PCR and pyrosequencing, enough sequence information could be produced to potentially allow complete genome sequencing. Both studies used the sequence information obtained to refine existing knowledge of evolutionary relationships between the mammoth and extant elephant species.

STEM CELLS

The *RETINOBLASTOMA-RELATED* gene regulates stem cell maintenance in *Arabidopsis* roots.

Wildwater, M. *et al. Cell* **123**, 1337–1349 (2005)

This study provides evidence that pathways involved in stem-cell maintenance are conserved in animals and plants. In mammals, the retinoblastoma (RB) protein regulates the ability to re-enter the cell-cycle, a key feature of stem cells. Wildwater and colleagues showed that reducing the expression of an RB-related gene (*RBR*) in *Arabidopsis thaliana* root meristems increases stem-cell numbers, whereas its overexpression has the opposite effect. RBR is regulated by different upstream signals from those that regulate RB activity in mammals, which indicates that this mechanism of stem-cell regulation has been recruited independently in plants and animals.

PLANT GENOMES

Horizontal transfer of a plant transposon.

Diao, X. *et al. PLoS Biol.* **4**, e5 (2006)

Although the horizontal transfer of nuclear DNA between animal species is well-documented, findings in plants have previously been limited to the horizontal transfer of mitochondrial DNA. Diao and colleagues studied a subset of MULE transposable elements, which have a distribution among plant species that could be explained by horizontal transfer. The level of sequence similarity between such elements found in the genus *Setaria* and in rice was too high to be explained by vertical transmission, given the estimated time of divergence of the two lineages. This provides the first clear evidence for nuclear horizontal transfer in higher plants.

GENE REGULATION

No escape from micromanagement

MicroRNAs (miRNAs) have emerged as important regulators of gene expression — by binding to short homology stretches on their target mRNAs, miRNAs typically mediate target cleavage in plants and target degradation or translation inhibition in animals. Two papers now provide experimental and computational evidence for additional facets of miRNA regulation, which had previously been postulated: miRNAs modulate the output of many genes, confer robustness to gene expression and influence the evolution of many 3′ UTRs.

Using the mouse expression atlas, Farh and Grimson *et al.* showed that the expression of predicted mRNA targets was lower in tissues in which the corresponding miRNA was expressed. This is not surprising. However, they found that before differentiation and miRNA expression, target mRNA expression was higher. The conclusion from this observation, which is also made by Stark and Brennecke *et al.*, is that miRNAs "dampen the output of pre-existing messages to facilitate a more rapid and robust transition to a new expression program."

A combination of computational prediction and reporter assays revealed that the UTRs of many mRNAs contain potential miRNA binding sites that can mediate miRNA-dependent regulation despite not being evolutionarily conserved. mRNAs that contain these non-conserved sites tend not to be expressed in the tissues in which the corresponding miRNAs are found. Importantly, such sites tend to be underrepresented in genes that are highly expressed in a given tissue and that are involved in basic cellular functions. Genes that 'avoid' having miRNA binding sites have been dubbed 'antitargets' and their existence was proposed in 2004 by Bartel and Chen. Farh and Grimson *et al.*

DEVELOPMENTAL GENETICS

Back talk

Specification of the dorso–ventral axis in many vertebrates requires signalling through the transforming growth factor-β (TGF-β) and Wnt pathways. In zebrafish, dorsal specification begins soon after fertilization, but the nature of the determinants that establish the dorsal axis has remained unresolved. Signalling by Nodal, a member of a subclass of the TGF-β superfamily, is known to induce the formation of mesoderm and endoderm in vertebrate embryos. Now, the Nodal-related morphogen Squint (Sqt) has been identified by Gore *et al.* as a possible dorsal determinant.

Gore *et al.* first established that maternal *sqt* transcripts were localized asymmetrically in four-cell and eight-cell embryos and that this localization required cytoskeletal microtubules.

Knowing that elements in the non-coding 5′ and 3′ UTRs mediate the localization of several transcripts in the embryos of other species, Gore *et al.* generated deletions in the UTRs of *sqt* RNA. They found that the dorsal localization of *sqt* RNA required the 3′ UTR, and that *sqt* RNA could be directed dorsally in zebrafish embryos, by zebrafish as well as human 3′ UTR elements.

The authors showed that removal of sqt-containing cells can lead to the loss of dorsal structures, which indicates that dorsal specification is initiated by the four-cell to eight-cell stages stages. To confirm that maternal *sqt* does indeed have a role

predict that this effect on the evolution of UTRs is likely to be widespread, influencing the evolution of thousands of UTRs. For some messages that need to be co-expressed with miRNAs, the selection to avoid being targeted is so strong that their UTRs become very short. Stark and Brennecke *et al.* show that the most abundant among miRNAs targets are developmental genes and that housekeeping genes fall into the antitarget class.

The results show that the expression of targets and miRNAs is often mutually exclusive or at least anti-correlated, but that antitargets tend to be co-expressed with miRNAs. Stark and Brennecke *et al.* find that miRNAs tend to target genes that are expressed in neighbouring tissues. They refer to this phenomenon as mutual exclusion and argue that miRNAs function to prevent expression of unwanted mRNAs. This role would be especially useful during the transition between developmental fates, as it would prevent leaky transcription.

So miRNAs have emerged as important players in mRNA sequence evolution and guardians of robustness of developmental processes. As Stark and Brennecke *et al.* point out, we will need to study both the targets and antitargets to get a complete picture of this 'microregulation'.

Magdalena Skipper

ORIGINAL RESEARCH PAPERS Kai-How Farh, K. & Grimson, A. *et al.* The wiedespread impact of mammalian microRNAs on mRNA repression and evolution. *Science* **310**, 1817–1821 (2005) | Stark, A. & Brennecke, J. *et al.* Animal microRNAs confer robustness to gene expression and have a significant impact on 3′ UTR evolution. *Cell* **123**, 1133–1146 (2005)
FURTHER READING Bartel, D. P. & Chen, C. Z. Micromanagers of gene expression: the potentially widespread influence of metazoan microRNAs. *Nature Rev. Genet.* **5**, 396–400 (2004) | Mattick, J. S. RNA regulation: a new genetics? *Nature Rev. Genet.* **5**, 316–323 (2004) | He, L. & Hannon, G. J. MicroRNAs: small RNAs with a big role in gene regulation. *Nature Rev. Genet.* **5**, 522–531 (2004)

in dorsal specification, the authors injected embryos with *sqt* morpholinos to interfere with gene function. Intriguingly, they found that maternal *sqt* RNA localization was independent of β-catenin, a component of the Wnt-signalling pathway that is well known for its involvement in dorsal specification.

So Sqt, the maternally encoded morphogen, is a probable requirement for dorso–ventral axis specification in zebrafish. Interestingly, the fact that dorsal specification occurs in the presence of sequence elements of either zebrafish or humans seems to suggest that axis-specification pathways might be conserved among vertebrates.

Sharon Ahmad, Assistant Editor,
Nature Reviews Molecular Cell Biology

ORIGINAL RESEARCH PAPER Gore, A. V. *et al.* The zebrafish dorsal axis is apparent at the four-cell stage. *Nature* 15 Dec 2005 (doi:10.1038/nature04184)

IN BRIEF

EVOLUTIONARY GENOMICS

Animal evolution and the molecular signature of radiations compressed in time.

Rokas, A. *et al. Science* **310**, 1933–1938 (2005)

Evolutionary relationships among metazoans have been difficult to establish using phylogenomics. Rokas *et al.* could not overcome this problem even by increasing the numbers of gene sequences from a range of metazoans. Because the phylogeny of a fungal clade of roughly the same age could be resolved using the same data, the authors conclude that this inability to resolve phylogenetic relationships in the metazoa indicates a rapid radiation of metazoan species, consistent with fossil evidence for a 'Cambrian explosion' of animal diversity.

GENETICAL GENOMICS

Combined expression trait correlations and expression quantitative trait locus mapping.

Lan, H. *et al. PLoS Genet.* 6 December 2005 (doi: 10.1371/journal.pgen.0020006.eor)

Combining linkage mapping with the identification of co-regulated genes using microarrays enables the discovery of *cis*- or *trans*-acting expression QTLs (eQTLs). However, the small regulatory contributions of *trans*-acting eQTLs makes them hard to detect. This paper describes a two-step approach to overcoming this problem. Expression traits were first mapped using samples from mice that segregated for obesity and diabetes. Regions enriched for linkage that were in *trans* to expression traits with which they share a function were then identified, providing evidence for the existence of *trans*-acting eQTLs, even when the examination of individual traits would not have yielded statistical support.

EPIGENETICS

Hyperdynamic plasticity of chromatin proteins in pluripotent embryonic stem cells.

Meshorer, E. *et al. Dev. Cell* **10**, 105–116 (2006)

As pluripotent embryonic stem (ES) cells differentiate their genome undergoes global chromatin remodelling. The authors report that although histone H1 and the linker histones are highly dynamic in mouse ES cells, they become immobilized on chromatin as cells begin to commit to a particular lineage. Experimental manipulation of the binding rate led the authors to suggest that the hyperdynamic binding is functionally important for pluripotency and maintenance of the undifferentiated state.

HUMAN DISEASE

In vitro analysis of huntingtin-mediated transcriptional repression reveals multiple transcription factor targets.

Zhai, W. *et al. Cell* **123**, 1241–1253 (2005)

Transcriptional dysregulation has emerged as a potential important candidate mechanism for Huntington disease pathogenesis. Using a specifically developed *in vitro* transcriptional assay, Zhai *et al.* showed that several components of the basal transcription machinery are directly inhibited by mutant huntingtin (HD) protein in human cells. In the case of the RAP30 subunit of GTF2F1 (general transcription factor IIF, polypeptide 1) the effects of mutant HD can be alleviated by overexpressing RAP30.

DEVELOPMENTAL BIOLOGY

Regeneration swims into view

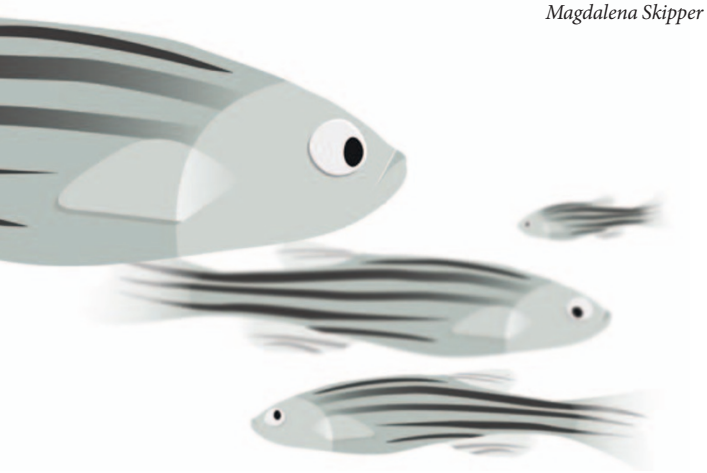
Newts can do it so why can't we? The ability to regenerate damaged tissues would have obvious medical applications. Although amphibians and, more recently, zebrafish have proved to be good models for regeneration studies, our limited understanding of the mechanisms that underlie this process has frustrated developmental biologists. Mark Keating and colleagues have now identified a new signalling factor — Fgf20 — that is required for the specific, early stages of zebrafish fin regeneration. Intriguingly, Fgf20 might be specifically required for regeneration.

The gene was identified from a forward genetic screen of adult fish for regeneration defects. One mutant, *dob*, showed a recessive regeneration defect 2 days after fin amputation. Although *dob* begins the regeneration process by forming an epithelium over the wound, the epithelium does not adopt the correct cuboidal morphology, which seems to be required for regeneration to proceed. None of the subsequent steps in fin regeneration, which involve cellular reorganization and proliferation, occurs in *dob* mutants.

The mutation was mapped to the *fgf20a* locus on chromosome 1. The missense mutation — an adenine to cytosine transversion at position 443 — converts a highly conserved tyrosine to a serine. By conducting a series of mutant *fgf20a* overexpression studies, the authors show that the mutation is likely to be a null.

So *fgf20a* — a new member of the FGF family — seems to be specifically required for the initiation stages of regeneration. Zebrafish *fgf20a* is expressed in mesenchymal cells, the cells that need to hyperproliferate during fin regeneration, whereas in other organisms, it is expressed in cancer cell lines and promotes myocardial proliferation and differentiation. It remains to be seen if Fgf20a will provide a handle on the regenerative potential of other vertebrates.

Magdalena Skipper



ORIGINAL RESEARCH PAPER Whitehead, G. G. *et al.* *fgf20* is essential for initiating zebrafish fin regeneration. *Science* **310**, 1957–1960 (2006)

Ethics Watch

TOOL-SHARING ISSUES IN COHERENT POPULATION-BASED RESEARCH

The Public Project in Population Genomics (P3G) has identified several important roadblocks in effective population-based genetic and genomic studies. In the January Ethics Watch article in this journal we focused on policy barriers. Here we focus on aspects of current practice and guidance that relate to the sharing of tools and other pre-competitive matters of mutual benefit to those who propose or carry out such large-scale studies.

There seem to be several systematic problems for those who wish to share freely the basic tools for the construction of large research databases for the study of gene–gene and gene–environment interactions (including socio-demographic data).

Some of these barriers stem from a failure to construct data or sample-collection handling frameworks that would make data sharing technically possible, whereas others arise from ethical concerns or guidelines on the use of information that are beyond the purposes for which the data were initially assembled.

The current failure to achieve semantic interoperability and common quality-assurance standards for data collection, entry, security and access could be mitigated by the creation of common lexicons and procedures that recognize equivalency. Such comparable data-sharing policies should not treat all genetic data as equally sensitive. Rather, they should differentiate between them according to the sensitivity of the information that is revealed by the analysis.

The sharing of finite biological samples requires explicit guidelines about who can access samples, and for what purposes. The sharing of immortalized cell lines also requires similar guidelines if public support is to be sustained. Moreover, concerns over property rights and ownership issues demonstrate the need for international principles that are specific to intellectual property-rights issues in large population databases.

No less urgent for the construction of this population-aimed toolbox is an appropriate ethical framework and level of ethical review. Although often not explicit in discussions on the development and management of such population-wide databases by ethics review boards, perceptions of potential legal liability for privacy (identifiability) or property claims are influential. Such anxieties might be addressed by the publication of aggregated data sets and by recourse to broad anti-discrimination laws. Indeed, adoption of 'genetic-specific' norms will only exacerbate the presaged stigmatization that is associated with genetic profiles of regions, communities and populations. The monogenic ethics model, as a basis for policies and tools, is inappropriate and inadequate to meet the practical and socio-ethical challenges that are inherent in population-based research. Uncritical adoption of such a model will hinder the realization of health gains in ways that would be widely regarded as unnecessary and undesirable by those who volunteer to contribute to these large-scale resources.

P3G's International Working Group on Ethics, Governance and Public Engagement favours a shift towards prospective harmonization and pre-competitive tool-sharing within a transparent governance framework that responds to and reflects the true nature of these resources for research.

Bartha Maria Knoppers and Alastair Kent

Bartha Maria Knoppers, Chair, Public Project in Population Genomics.

Alastair Kent, Chair, International Working Group on Ethics, Governance and Public Engagement, Public Project in Population Genomics.