IN THE NEWS

Gene doping: a new threat for the Olympics?

Forget the next generation of steroids or growth hormones and imagine the following headline from the Beijing 2008 Olympics: "Top Molvanian athlete misses a gene doping test." (See Cilauro, S. *et al*. *Molvania: A Land Untouched by Modern Dentistry* (Jetlag Travel Guide S., 2004).)

The story that this might be possible broke following the announcement from the University of Pennsylvania that inserting *IGF-1* into rat muscles improved their muscle performance. Even if possible in humans, who would want to receive such a genetic boost? According to Lee Sweeney, who has been inundated with calls ever since he published this work, there might be many: "…anyone who doubts that athletes would alter their genes to win gold need only speak with him" (*PRWeb*).

And there are other hints of how muscles could be strengthened. For example, the *New England Journal of Medicine* reported on the mutation that explains the extraordinary strength of a child: "…by the time he was 4, he could lift almost seven pounds with each hand" (*The Globe and Mail*).

The World Anti-Doping Agency (WADA) is worried, especially that gene doping will be difficult to detect. "WADA is researching and developing new genetic approaches, such as imaging and molecular methods, to detect evidence of genetic enhancement, but even these might not be enough" (*PRWeb*).

Whereas some think that gene doping raises important ethical issues (see *Nature Reviews Genetics'* ethics watch in July 2003 by Thomas Murray from The Hastings Center), others such as Julian Savulescu from Oxford University think otherwise: "Genetic enhancement is not against the spirit of sport, it is the spirit of sport" (*Australian Broadcasting Corporation*).

Magdalena Skipper

EPIGENETICS

Silent transmission

In mammals, DNA and histone methylation together provide an effective, long-term mechanism for silencing gene expression, but how specific methylation patterns are 'remembered' during cell division is unclear. In a recent paper, Sarraf and Stancheva showed that this depends on the coupling of the two types of methylation during DNA replication.

At sites of constitutive heterochromatin and transcriptionally silenced promoters, silencing is mediated by methylation of DNA at CpG dinucleotides and of histone H3 at lysine 9 (H3-K9). During DNA replication, the methyltransferase DNMT1 interacts with the replication machinery to ensure that DNA methylation patterns are faithfully copied. By contrast, little is known about how histone methylation is reproduced. One model proposes that this is somehow coordinated with DNA methylation, but evidence has so far been lacking.

By co-immunoprecipitation, Sarraf and Stancheva showed that MBD1 — a protein that specifically binds methyl-CpG groups — associates with a complex that contains an H3-K9-specific methyltransferase activity, providing a possible link between DNA and histone methylation. The other components of the complex were identified as the H3-K9-specific methyltransferase SETDB1 and CAF1, a protein involved in chromatin assembly. So, MBD1 bound to methylated DNA could recruit SETDB1 and, through its interaction with CAF1, promote H3-K9 methylation at specific sites during chromatin assembly.

Consistent with this, the three proteins were shown to form a complex *in vivo* specifically during DNA replication. The authors also showed how DNA replication is coupled to the activation of the CAF1–MBD1–SETB1 complex. CAF1 is only transiently associated with MBD1 and SETDB1 during S-phase and this depends on MBD1 being displaced from DNA. Specific inhibition of replication elongation showed that this displacement depends on the progression of the replication complex. This seems to knock MDB1 off the DNA strand, allowing it to bind CAF1 and promote

RNA SILENCING

Small RNAs take the tube

A new study published in *Plant Cell* reveals that, rather than being limited to the cells that produce them, small RNAs in plants can hitch a ride in the phloem to exert their effects on gene expression over long distances.

In plants, mRNAs are transported between tissues in the network of phloem tubes that carry sap. In addition, the antiviral effects of RNA interference (RNAi) can spread over long distances from the site of infection, indicating that the small interfering RNAs (siRNAs) that block viral gene expression might be transported in a similar way.

To find out whether small RNAs are carried in the phloem, Lucas and colleagues analysed sap from several plant species and identified a population of small RNAs of 18–25 nucleotides, corresponding to the sizes of known small regulatory RNAs. Comparing the sequences of these RNAs with plant databases revealed a range of potential targets, indicating that both siRNAs and microRNAs (miRNAs) that are involved in regulating plant gene expression are carried in the phloem.

To prove that small RNAs can move from their site of expression into the phloem — and are not just expressed in phloem cells — Lucas and colleagues expressed a viral coat protein transgene (*CP*) in the leaves of a species of squash. A corresponding siRNA was detected in the phloem sap from these plants, but not from a silencing-defective strain that expressed the same transgene. To confirm that small RNAs in phloem are genuine sap components, and not contaminants from surrounding tissues, the authors carried out heterografting experiments. They expressed the *CP* transgene in one plant (the stock) and grafted on part of another plant that did not express the transgene (the scion). Identifying *CP* siRNA in the sap of the scion confirmed that this molecule must have been transported in the phloem from the stock plant.

The authors also confirmed that RNAi signalling triggered by viral infection, rather than artificial expression of a viral transgene, can be transmitted in the phloem sap.

H3-K9 methylation on newly formed chromatin.

How does this relate to the silencing of specific genes? Sarraf and Stancheva identified several genomic MBD1-binding sites, including a CpG island in the *p53BP2* promoter region. In HeLa cells, *p53BP2* is usually transcriptionally silent, and the authors showed that this depends on both DNA methylation and methylation at H3-K9. Treatment with an inhibitor of DNA methylation or with small interfering RNAs against either MDB1 or SETDB1 led to loss of methylated H3-K9 at the *p53BP2* promoter and induced the expression of the gene. Similarly, reducing levels of DNA methylation or MBD1 expression resulted in loss of methylated H3-K9 at 23 other genomic MBD1-binding sites.

So, interactions between the DNA and histone methylation machinery seem to be important for maintaining patterns of epigenetic modification on a widespread basis. This provides one way of ensuring that transcriptional silencing is transmitted accurately through ongoing rounds of cell division, an essential requirement for normal mammalian development.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPER

Sarraf, S. A. & Stancheva, I. Methyl-CpG binding protein MBD1 couples histone H3 methylation at lysine 9 by SETDB1 to DNA replication and chromatin assembly. *Mol. Cell* **15**, 595–605 (2004)

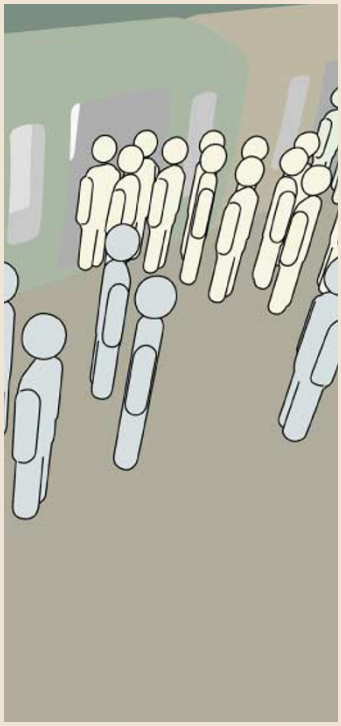
WEB SITE

Irina Stancheva's laboratory:
http://www.bms.ed.ac.uk/services/staff/stancheva/index.htm

They infected a species of pumpkin with the *Cucumber yellows closterovirus* (CuYV) and showed that sap from these plants contained CuYV-specific siRNAs.

So, as previously suspected, the transport of siRNAs through the phloem allows plants to mount a systemic response to viral infection. The finding that miRNAs are transported in a similar way also raises an intriguing possibility — that this allows the long-range control of plant gene expression. Future studies should provide insights into how plants use this transport system to coordinate physiological processes between tissues.

Louisa Flintoft



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Yoo, B.-C. *et al.* A systemic small RNA signaling system in plants. *Plant Cell* **16**, 1979–2000 (2004)

WEB SITE

William Lucas's laboratory:
http://plb.ucdavis.edu/labs/lucas/

IN BRIEF

HUMAN GENETICS

Neural basis of genetically determined visuospatial construction deficit in Williams syndrome.

Maeyer-Lindenberg, A. *et al. Neuron* **42**, 623–631 (2004)

Little is known about the genetic basis of cognition — the phenotypes are difficult to characterize and model organisms are of limited help. These authors took advantage of Williams syndrome, which is caused by a well-characterized deletion on chromosome 7q11.23 that causes highly specific impairment of the ability to visualize an object as a set of parts or to construct a replica. Using a combination of neuroimaging and path analysis, they define a systems-level phenotype that will be invaluable in future mapping of genetic determinants of this cognitive function.

EVOLUTION

Evolvability is a selectable trait.

Earl, D. J. & Deem, M. W. *Proc. Natl Acad. Sci. USA* **101**, 11,531–11,536 (2004)

Evolution allows organisms to adapt to their environment, but can the propensity to evolve — evolvability — also be an object of selection? A positive answer to this question is suggested based on the fact that evolvability depends on mechanisms of genetic change, such as recombination, that are themselves selectable. Using computer simulations, Earl and Deem show that evolvability is indeed selected for when systems are subjected to constant, but random, environmental change.

CHROMATIN BIOLOGY

Histone deimination antagonizes arginine methylation.

Cuthbert, G. L. *et al. Cell* **118**, 545–553 (2004)

Lysine methylation is well known for its role in transcription regulation, but there are many other histone modifications that are important for the regulation of gene expression; one of them — deimination, which converts arginine into citrulline — is now described by Cuthbert and colleagues. They identify a specific enzyme responsible for this modification and show, through *in vivo* targeting experiments, that it represses gene induction by arginine methylation, thereby uncovering a novel mechanism of regulating gene expression at the epigenetic level.

EVOLUTION

The ring of life provides evidence for a genome fusion origin of eukaryotes.

Rivera, M. C. & Lake, J. A. *Nature* **431**, 152–155 (2004)

Constructing the phylogenetic tree of life has been plagued by problems caused by genome fusions and horizontal gene transfer. Rivera and Lake used complete genome sequences from selected eukaryotes and prokaryotes in a newly developed method that reconstructs ancient genome fusions. They propose that the eukaryotic genome resulted from a fusion of two diverse prokaryotic genomes. The eukaryotic genome is therefore at the deepest level that links prokaryotes and eukaryotes — the tree of life is in fact a ring.