Meeting report

The epigenetics of the cell

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A report on the 42nd Annual Meeting of the American Society for Cell Biology, San Francisco, 14-18 December 2002.

Visions for the post-genomic world

The American Society for Cell Biology takes public policy issues very seriously. At the Society's 42nd annual meeting, one key concern was research funding. Elias Zerhouni, the new Director of the US National Institutes of Health (NIH; Bethesda, USA) addressed issues of funding, the direction of science and the way in which it must be practised in the future. He began by explaining the problem he has to explain to the US Congress - why is it that a 100% increase in NIH funding will only result in a 40% increase in the number of grants? The difference is mainly due to the increasing costs (the average grant has gone from $255,000 in 1998 to $370,000 in 2003) and the multi-year commitments; despite this problem, Zerhouni is proud that the funding level remains at about 30% of submitted grant proposals, and that about one third of newly funded grants are for new investigators. He also recognizes the threat to the future of science if we don't adequately nurture young scientists. "You don't become a thoroughbred," he said, "by longevity." Only about 4% of NIH-funded researchers are 35 or under, creating a difficult situation for many young workers. Only half the NIH grantees have their grants renewed after four years, and only about 4% of grantees have been funded for over twenty years.

Turning to the current and future state of biomedical research, Zerhouni defined the unifying concepts as 'omics' (genome-scale studies of all kinds), signaling, apoptosis, trafficking within the cell, and cell-cycle control. He identified the "mathematicization" of biology and has observed an increasing emphasis on epigenetics - differential gene expression and its controls. He maintained that we cannot address the complexity of these problems with today's methods and with today's organization of research teams. We are in a race against time, with pressure for more rapid translation of research into clinical reality, and more attention to research on 'molecular prevention' and behavioral modification. His four priorities for the NIH are revolutionary methods, new pathways to discovery, multidisciplinary research teams, and re-engineering of clinical research.

Nuclear motors

Primal de Lanerolle (University of Illinois, Chicago, USA) described an interesting role for actins and myosins in the regulation of transcription. It has been known for more than 20 years that actin is present in the nucleus, and the recent demonstration by De Lanerolle and colleagues of the presence of an unconventional myosin (myosin I) in the nucleus has suggested that actin and myosin I function together as a molecular motor in the nucleus; but the role of these molecules, if any, in transcription has not been clear. To address this question, De Lanerolle and colleagues injected antibodies against actin into the nucleus of mammalian cells and found that an antibody to non-muscle β-actin inhibited transcription by RNA polymerase II. In a variety of experiments using western blots, de Lanerolle showed that some β-actin co-purified with RNA polymerase II; and the antibody to β-actin inhibited transcription even in reconstituted transcription complexes. Evidently one of the functions of actin is in the formation of pre-initiation complexes: it was found in these complexes and was shown to co-immunoprecipitate with the TATA-binding protein (TBP). De Lanerolle also speculated that actin and myosin I are involved in transcriptional elongation. Although unconventional myosins do not form filaments, myosin I has a positively charged domain that binds to negatively charged lipids and possibly to DNA. De Lanerolle speculated that the tail of myosin binds to DNA filaments and that the myosin head then interacts with actin in the transcription complex, performing an astoundingly similar role to that of sarcomeric actin and myosin in muscle contraction.

RNA regulates the genome

Time and again, model organisms have provided key insights into cellular processes that have later been recognized in higher eukaryotes such as humans. When a maize geneticist mentioned 'paramutation' at a human genetics meeting less than a decade ago, there was some skepticism; now, phenomena known as post-transcriptional gene silencing in plants and quelling in the fungus *Neurospora* are appearing under the name RNA interference (RNAi) in mainstream yeast and mammalian molecular biology. At this meeting, Marjori Matzke (Austrian Academy of Sciences, Salzburg, Austria) explained how RNA-directed DNA methylation (RdDM) regulates gene expression in *Arabidopsis*. Whereas RNAi involves the cleavage of a target mRNA mediated by double-stranded RNA, RdDM acts at the transcriptional level. RNA-DNA base-pairing near the promoter acts as a signal for methylation of cytosines in the DNA region, silencing gene expression. The process methylates virtually all cytosines in the region, not just the CpG dinucleotides that are characteristically affected by mammalian DNA methyltransferases. The mechanism is poorly understood, but members of Matzke's laboratory are screening mutants and have begun to catalog the proteins involved in RdDM. Experiments have shown that two genes, encoding the methylase MET1 and the histone deacetylase HDA6, are required for maintenance of RdDM methylation. The *de novo* methylase involved in RdDM has not yet been identified, but MET1 is a strong candidate. RdDM hasn't yet made its debut in mammalian genetics, but Matzke pointed out that non-CpG methylation is important in very early mammalian development.

The dosage-compensation complex

In the nematode *Caenorhabditis elegans*, hermaphrodites have two X chromosomes while males have only one, and expression of X-linked genes is made equivalent in the two sexes by a two-fold downregulation of the two X chromosomes in hermaphrodites. In mammals, on the other hand, one of the two X chromosomes is inactivated in each cell in females; and in *Drosophila melanogaster*, the single X chromosome in males is upregulated two-fold to attain dosage compensation; non-coding RNAs are known to be involved in both mammals and insects. Now that RNA interference is all the rage, it is surprising that no non-coding RNA molecule has yet been associated with the dosage-compensation process in *C. elegans*. We might be in a better position to find such an RNA, however, when we understand better the loci on the X chromosome that might be essential for dosage compensation. Gyorgyi Csankovszki, from Barbara Meyer's laboratory (University of California, Berkeley, USA), is elucidating some of the *cis*-acting elements along the *C. elegans* X chromosome that might be involved. Meyer's laboratory has described at least seven proteins that are essential for formation of the dosage compensation complex on the hermaphrodite X chromosomes; some of these are also involved in other chromosomal processes, including meiosis and mitosis.

In mammals, X inactivation nucleates at a single site, called the X-inactivation center, that harbors the locus for the non-coding RNA *XIST* (for X-inactive-specific transcript). Csankovszki explained that a similar point of origin for dosage compensation on the *C. elegans* X chromosome has not yet been described. On the *Drosophila* X chromosome, there appear to be many such points of origin, at least two of which are loci for the non-coding RNA molecules *Rox1* and *Rox2*, which are required for dosage compensation. Until Csankovszki's work, we did not know whether there were one, a few or many similar points of nucleation for dosage compensation in *C. elegans*. Using animals with small duplications of the X chromosome, she showed that some regions were able to recruit the dosage-compensation complex, whether they were free-floating or attached to autosomes, while others could not. (As *C. elegans* chromosomes are holocentric, all fragments have centromeric activity and so are not lost as they would be in other organisms.) Additional work will be required to determine whether or not gene expression is appropriately regulated in the duplicated regions. This work strongly suggests that there are, indeed, multiple sites for the nucleation of dosage compensation in *C. elegans*, but that they are spaced some distance apart. With a refined experimental system, Csankovszki and her colleagues will be able to identify specific DNA sequences that recruit the dosage-compensation complex and that may serve as initiation points for dosage compensation. One or more of the *cis*-acting regions involved in *C. elegans* dosage compensation might, in fact, be transcribed into a hypothetical non-coding RNA that could be analogous to *XIST*. We may be on a fast track to a very exciting convergence of mammalian, insect and worm X-chromosome regulatory mechanisms.

RNA-mediated regulation of gene expression may be the hot topic of the day, but it is only the latest part of a growing body of evidence that while the genome may give us the raw ingredients of life, it is surely the 'epigenome' that gives us the spice. At no time has it been more apparent that the cell biologists will be the chefs. Abstracts of the meeting are available at the American Society for Cell Biology website [http://www.ascb.org] or as a supplement to *Molecular Biology of the Cell,* volume 13.