Meeting report

Order out of chaos in the nucleus

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A report on the 'Nuclear architecture and control of gene expression' minisymposium at the first meeting of the European Life Scientists Organisation (ELSO), Geneva, Switzerland, September 2-6, 2000.

The organization of the cell nucleus, and how this relates to gene expression and DNA replication, is a subject of intensive research. Indeed, the topic is becoming ever more important as we enter the era of genomics (or is it post-genomics already?). After all, surely we cannot hope to comprehend the functioning of entire genomes until we understand the behaviour of DNA - indeed the ecology of DNA - inside the nucleus. The first minisymposium of ELSO 2000 was dedicated to this topic. Although entitled 'Nuclear architecture and control of gene expression', the symposium included talks on DNA replication as well as gene expression. One of the recurring themes was the dynamic nature of DNA in the nucleus. On the 'macro' scale, DNA (or more strictly chromatin) is distributed in a particular spatial pattern in any given cell type, with some regions of high DNA concentration and some (relatively) DNA-free zones. This pattern is surprisingly stable and reproducible between different cells from the same cell line, but it can differ dramatically between cell lines (Daniele Zink, Institut für Anthropologie und Humangenetik, Munich, Germany). This is certainly suggestive of functionally important organization, particularly when one considers that the spatial pattern must be re-established after each mitosis. Further evidence for the non-random distribution of DNA is the finding that homologous chromosome pairs can associate with each other during mitosis; in yeast, two alleles of a given locus appear to lie close to each other in the nucleus in 20-30% of cases (Susan Gasser, Swiss Institute for Experimental Cancer Research, Lausanne, Switzerland).

The above examples indicate that DNA must be physically moved in the nucleus in a controlled manner. How this is achieved, in terms of molecular mechanisms, remains elusive, although steps forward have been made. Peter Becker (Adolf-Butenandt-Institut, Munich, Germany) presented further work on one important ATPase motor involved in chromatin dynamics: the chromatin accessibility complex (CHRAC). This has the ability to 'slide' nucleosomes along DNA, creating order out of the chaos of linear DNA in each nucleus. This property involves interaction of CHRAC with the amino-terminal tail of histone H4. Other revealing insights into DNA relocation are provided by studies on a lymphocyte-expressed zinc-finger protein, Ikaros. Several lines of evidence suggest that Ikaros protein recruits inactive genes to heterochromatic regions of the nucleus. Amanda Fisher (MRC Clinical Sciences Centre, Hammersmith Hospital, UK) presented further evidence in support of this model, and resolved an important question: which comes first, relocation or gene silencing? The answer (at least for one gene) was found by an elegant experiment that examined where the gene is sited immediately after transcription ceased. And the answer? The gene is found away from the heterochromatin. This suggests that Ikaros-mediated relocation of DNA within the nucleus comes after silencing, and is used to stabilise the 'off' state of a gene. Further experiments suggest that this stabilization is used particularly when that 'off' state is to be inherited by daughter cells after mitosis.

It has been known for many years that silencing of genes is (often) associated with the removal of acetyl groups from histones. Indeed, the Ikaros protein referred to above is associated with histone deacetylases. Acetylation, however, is not the only histone modification of relevance to gene activity: phosphorylation and methylation are also prevalent. An example of the latter modification was discussed by Tony Kouzarides (Wellcome/CRC Institute, Cambridge, UK), who mapped a methylation site to Lys9 of histone H3 and showed an association of methylation at this site with gene repression. The lysine methyltransferase can be recruited by the retinoblastoma (Rb) repressor protein and

the modified lysine in turn recruits the HP1 chromodomain protein, a component of heterochromatin. These studies, however, do raise a broader question. Why so many histone modifications? One explanation is that some modifications are probably part of the same pathway. For example, Kouzarides proposed that the acetylated histones of an 'active' gene are deacetylated as a prerequisite to methylation at the same lysine residue. Another possibility is that there is more than one category of 'on' or 'off', differing in such characteristics as stability and heritability. Relating these properties to nucleosome modifications and to trafficking within the nucleus remains a significant challenge.