A journey into the nucleus

Conference on Nuclear Structure and Dynamics

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The EMBO Conference on Nuclear Structure and Dynamics took place between 1 and 5 September 2007, in Montpellier, France, and was organized by G. Cavalli, C. Cremer, S. Gasser, T. Pederson, F. Uhlmann and R. van Driel.

Keywords: nuclear periphery; genome function; chromatin and chromosome dynamics; DNA replication; DNA repair; RNA metabolism

Conference on Nuclear Structure and Dynamics brought together 240 scientists to discuss the interplay between nuclear structure and genome function. The scope of the meeting was broad, and the speakers covered various topics and experimental approaches. Here, we highlight some of the main issues that were discussed at the conference.

The nuclear periphery

Various types of chromatin are segregated in the nucleus. Heterochromatin—which is gene-poor, rich in proteins that promote gene silencing and characterized by low levels of transcriptional activity—is typically located near the nuclear envelope and around the nucleolus. For this reason, the nuclear periphery has been traditionally regarded as a repressive compartment for gene expression. However, recent studies have shown that the association of actively transcribed genes with nuclear pores gives rise to high levels of expression (for example, Taddei *et al*, 2006). By using the DNA adenine methyltransferase identification (DamID) technique, B. Van Steensel (Amsterdam, The Netherlands) identified approximately 1,300 lamin-associated domains (LADs) in human cells and showed that such chromatin regions are characterized by low gene density. LAD borders are flanked by promoters or by CCCTC-binding factor (CTCF)-binding sites that potentially act as insulators. B. Kalverda (Amsterdam, The Netherlands) analysed sequences associated with nuclear-pore proteins in *Drosophila* cells. In contrast to the lamin-interacting DNA, the nucleoporin-interacting sequences contain highly expressed genes, and are enriched in transcription factors and active histone marks. These results confirm that the nuclear periphery is a heterogeneous compartment that contains active genes. Kalverda also suggested that some of the interactions that have been detected between active genes and nucleoporins might occur in the nuclear interior, which would suggest that some nucleoporins have intranuclear roles.

Several studies analysed the effect of peripheral gene positioning. D. Spector (Cold Spring Harbor, NY, USA) presented a live-cell system for targeting a synthetic gene to the nuclear lamina. Relocation to, and association with, the lamina was not an obstacle for gene expression. Both the transcription and splicing machineries were recruited to the lamin-associated gene (Fig 1), and the kinetic behaviour of

EMBO reports (2008) 9, 228–233; doi:10.1038/embo.2008.18

Introduction

The basic processes that are responsible for the maintenance and expression of the genome are relatively well understood at the biochemical level, but we still have much to learn about how these processes occur in their physiological context—the cell nucleus—and how they are regulated and coordinated. The second EMBO

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Submitted 4 December 2007; accepted 24 January 2008;
published online 15 February 2008

Fig 1 | Recruitment of splicing factors to a targeted and activated genetic locus at the nuclear lamina. Targeting cells were transiently transfected with pTet-On and yellow fluorescent protein (YFP) fused to the splicing factor SF2/ASF (green), induced for 12 h with cumate to express the targeting-fusion protein lacI-mCherry-lamin B1 (A,D, arrows), and then incubated in the absence of Dox (–; A–C) or presence of Dox (+; D–F) for 5 h to induce transcription of the locus. In the Dox (–) condition, YFP-SF2/ASF was not recruited (B,C, arrows) and cyan fluorescent protein (CFP)-SKL protein was not observed (C). In the Dox (+) condition, YFP-SF2/ASF was recruited (E, arrow) and localized with the locus (F, arrow), and CFP-SKL protein was observed at cytoplasmic peroxisomes (F, blue). Scale bar, 5 μ m. Image courtesy of D. Spector.

transcriptional induction at the nuclear periphery was similar to that observed for the same gene at a more internal location (Kumaran & Spector, 2008). W. Bickmore (Edinburgh, UK) showed that tethering chromosomes to the nuclear lamina reduced the level of gene expression but that it was compatible with transcription. Transcriptional inhibition was more severe for genes originally located internally than for genes that originally had relatively peripheral positions, which suggests that the regulation of each gene is fine-tuned in the context of its specific chromatin environment. Together, these findings indicate that the nuclear periphery *per se* is not a repressive compartment. This idea was illustrated by T. Cremer (Munich, Germany), who has studied the organization of the nuclei of rod photoreceptor cells in some nocturnal mammals. In these cells, heterochromatin is concentrated in the centre of the nucleus, whereas euchromatin occupies a thin shell along the nuclear border, presumably to improve vision in low-light conditions. Such organization of the nucleus is, however, an exception.

The remarkable stability of the nuclear architecture might be related to the fact that the components of the nuclear periphery are involved in many processes, as discussed by R.D. Goldman (Chicago, IL, USA) with regard to the lamins. Mutations in the lamin genes cause several diseases and that responsible for the most common form of Hutchinson–Gilford progeria, *LAD50*, affects mitosis, nuclear shape and the clustering of nuclear pores. Lamin mutations also downregulate histone methylation and cause a loss of heterochromatin. G. Pegoraro (Bethesda, MD, USA) studied the molecular mechanisms that lead to ageing-related chromatin defects and identified the retinoblastoma-binding proteins RBBP4 and RBBP7 as crucial components in this process. Elimination of RBBP4 and RBBP7 causes rearrangements of the heterochromatin and increased DNA damage, similar to that observed in aged individuals and in progeria patients.

Chromatin mobility and ‘co-’

The role of chromatin positioning in transcription regulation draws attention to changes in the positioning of chromatin regions. A.S. Belmont (Urbana, IL, USA) has constructed cell lines that carry up to hundreds of copies of 200kb BAC transgenes that can be used to trace transcriptional activation. He observed chromatin decondensation, although the level of compaction of the transcribing chromatin remained greater than the 30nm chromatin fibre. He also observed repositioning of activated genes towards the nuclear interior and, for some of the transgenes—such as heat-shock protein 70 (*HSP70*)—association of the nascent RNA with splicing speckles. This observation raises an important question: do activated genes move to pre-existing nuclear speckles or are the speckles assembled where nascent transcripts are generated? The results presented by Spector (Kumaran & Spector, 2008) suggest that the latter is the case.

In another *in vivo* study, M. Dundr (Chicago, IL, USA) showed that stably integrated arrays of U2 small nuclear RNA genes are relocated from the interior to the periphery of chromosome territories on transcriptional activation. Dundr analysed the recruitment of the U2 arrays towards Cajal bodies and showed non-random movements over distances of 2–3 μ m. Both Dundr and Belmont reported that actin is necessary for the relocation of the activated loci.

Results presented by P. Fraser (Cambridge, UK) and F.J. Iborra (Oxford, UK) suggest that the functional importance of the relocation of transcriptionally activated chromatin to the nuclear interior is in regard to the establishment of associations between the transcribed genes, transcription factories and nuclear speckles. Iborra presented a model for the building of transcription factories based on stochastic collisions and self-assembly of neighbour polymerases. Both speakers emphasized that the limited number of transcription factories compels many genes to share a factory. They observed both co-transcription of collinear genes (interactions ‘*in cis*’) and

non-random interchromosomal associations (spatial interactions 'in trans'), which suggests the existence of transcriptional networks in the nucleus.

Distant chromatin interactions have recently emerged as an extremely important and somewhat controversial topic (Fraser & Bickmore, 2007; Teller *et al*, 2007; Cavalli, 2007; de Laat, 2007). Spatial contacts between distant chromatin regions have been identified as an important factor in co-transcription and co-regulation. These contacts can be relatively stable (co-transcription) or transient (co-regulation). E. Heard (Paris, France) showed through a study of Xist-induced chromosome inactivation that complex transient interactions between the two X-inactivation centres might allow XX embryonic stem cells to sense their XX status and to coordinate monoallelic Xist expression, resulting in X inactivation (Augui *et al*, 2007). A. Pombo (London, UK) reported that the association of genes with transcription factories occurs independently of the position of the genes in the chromosome territories. She also reported that the transcribed genes loop out of the chromosome territories after transcriptional activation. She suggested that transcription factories promote distant chromatin interactions and regulate the extent of intermingling between territories. Distant chromatin interactions have also been studied by W. de Laat (Rotterdam, The Netherlands) using a technique defined as chromosome conformation capture (3C) on chip, or 4C (Simonis *et al*, 2006; Zhao *et al*, 2006). He concluded that transcriptional activation of the β -globin gene causes a shift from an inactive to an active chromatin environment, and that most of the long-range interactions are a consequence of general chromosome folding patterns that have no functional significance. Experimental repositioning of genes in the nucleus might help to clarify the role of long-range interactions in gene expression, and the use of 4C will be an important tool to understand the extent of these gene contacts. These techniques have been recently developed and their improvement is likely to increase their power. This was illustrated by G. Cavalli (Montpellier, France), who presented an improvement of 3C that allows the detection of spatial contacts between chromatin sites as little as 3 kb apart. By using this approach, Cavalli showed that chromatin insulators form loops that can target regulatory elements in the vicinity of gene promoters and affect their regulation. Further adaptation of this method promises to allow detailed analyses of the conformation of chromatin regions within small individual loci and in large chromosomal domains.

RNA, chromatin and transcription regulation

We are far from understanding the molecular mechanisms that link transcription, RNA and chromatin structure; however, several talks provided new insights into this rapidly developing field of research. In fission yeast, the centromeric repeats are transcribed and processed into small interfering RNAs that direct heterochromatin formation (reviewed by Bühler & Moazed, 2007). D. Moazed (Boston, MA, USA) presented a mechanism by which repressive histone methylation marks can spread along the chromosome. His results suggest that oligomerization of Tas3, one of the components of the RNA-induced transcriptional silencing complex, is required for RNA-based spreading. A. Morillon (Gif-sur-Yvette, France) has found a new regulatory mechanism for transcriptional silencing of the Ty1 transposon in the budding yeast *Saccharomyces cerevisiae*. In this case, silencing is mediated by histone methylation events that require an antisense RNA, the abundance of which is regulated

by cytoplasmic exoribonucleases. Although RNA interference does not occur in budding yeast (Aravind *et al*, 2000), these results show that chromatin regulatory mechanisms mediated by non-coding RNA are active in *S. cerevisiae*.

Another regulatory process that involves RNA is dosage compensation. In *Drosophila*, dosage compensation is achieved by a twofold upregulation of the genes located in the male X chromosome through a mechanism that involves hyperacetylation by the male-specific lethal (MSL) complex, which contains two non-coding RNAs. A. Akhtar (Heidelberg, Germany) has searched for MSL-interacting proteins in an attempt to understand how MSL is targeted to the X chromosome. She has identified, among others, Nup153 and Mtor, which are two proteins implicated in mRNA export (Mendjan *et al*, 2006). The occupancy profiles of Nup153 and Mtor on the X chromosome partly overlap with that of the MSL complex, but we still do not know how these proteins act.

N. Visa (Stockholm, Sweden) has studied the expression of the Balbiani ring genes of the dipteran *Chironomus tentans* and has shown that proteins associated with the nascent pre-mRNA recruit a histone acetyltransferase that contributes to keeping the genes active (Sjölander *et al*, 2005). Interestingly, β -actin is involved in the recruitment of the acetyltransferase to the messenger ribonucleoprotein (mRNP) complex. Visa reported that the chromatin remodeller Brahma is also associated with nascent mRNA, and proposed that recruitment of chromatin factors by RNA constitutes an efficient mechanism that targets chromatin factors to active genes during transcription elongation.

In the nucleolus

I. Grummt (Heidelberg, Germany) has proposed that actin has a role in the nucleolus. She previously studied the association of β -actin and nuclear myosin I (NMI) with RNA polymerase I (Philimonenko *et al*, 2004), and reported that drugs that prevent actin polymerization inhibit ribosomal DNA transcription both *in vivo* and *in vitro*. Furthermore, transcription is inhibited by a polymerization-deficient actin mutant, and the motor activity of NMI is required for efficient ribosomal DNA synthesis. Grummt proposed at the meeting that polymeric actin and NMI work as a motor to drive transcription (Ye *et al*, 2008).

By using electron spectroscopic imaging, T. Pederson (Worcester, MA, USA) identified regions of the nucleolus that are deficient in RNA and, on the basis of bimolecular fluorescence complementation studies, speculated that these sites contain complexes of cell-cycle regulatory proteins including nucleostemin, p53 and murine double minute 2 (MDM2). Interestingly, knockdown of nucleostemin releases p53 from the nucleolus and induces a G1 arrest (Ma & Pederson, 2007).

A. Lamond (Dundee, UK) reported how stable isotope labelling with amino acids in cell culture (SILAC) can be used to determine subnuclear protein distribution in quantitative terms (Andersen *et al*, 2005). This 'localization proteomics' revealed that the composition of the nucleolus is highly dynamic and that newly synthesized nucleolar proteins are continuously turned over in the nucleus.

Reprogramming the nucleus

Eukaryotic genomes are duplicated from thousands of replication origins that are clustered within megabase-sized domains and sequentially activated throughout the S phase (Aladjem, 2007). The spatio-temporal pattern of DNA replication is one of the

Fig 2 | Coordination of DNA replication and gene expression. Topoisomerase 1 (Top1) prevents genomic instability in S phase by promoting ribonucleoprotein assembly by the splicing factor ASF/SF2 and preventing the formation of DNA–RNA hybrids (R-loop), which are toxic for replication forks. DNA-combing analyses show that progression of sister replication forks, sequentially pulse-labelled with IdU (red) and CldU (green), is slower and more asymmetrical in mouse Top1(–) cells.

best characterized examples of higher-order organization of the nucleus. I. Hiratani (Tallahassee, FL, USA), investigated whether this replication pattern changes during cell differentiation. He performed a genome-wide analysis of the timing of replication during the differentiation of mouse embryonic stem cells, and observed a reduction in the number of the domains and an increase in their size. This process, which Hiratani calls ‘consolidation’, does not affect the correlation between replication timing, gene activity and subnuclear localization. Instead, differentiation of embryonic stem cells results in an alignment of replication timing domains to isochore sequence properties of chromosomes—for example, GC content and long interspersed nuclear element (LINE) density. This reveals a global reorganization of replication domain structure during stem-cell commitment.

Another interesting question is whether changes in replication timing or localization are a cause or a result of changes in gene expression. By using heterokaryons, A. Fisher (London, UK) found that mouse embryonic stem cells are able to dominantly reprogramme human B cells so that a human embryonic stem-cell-specific gene-expression profile is established and stably maintained. Reprogramming begins before nuclear fusion and depends on at least the transcription factor Oct4. Whether this process requires progression through the cell cycle is an important question that was addressed by O. Cuvier (Montpellier, France). He reported that the de-differentiation of erythrocyte nuclei in *Xenopus* egg extracts involves the resetting of replication origins in mitosis, through a topoisomerase II

(Top2)-dependent mechanism (Lemaitre *et al*, 2005). Cuvier also showed that Top2 is required for the termination of DNA replication, and for the removal of any residual origin recognition complex (ORC) and replication protein A (RP-A) from the chromatin. This reaction involves the Top2-dependent recruitment of Pin1, an inhibitor of the anaphase-promoting complex. Cuvier proposes that origin resetting at mitosis is a prerequisite for the reprogramming of the functional organization of the nucleus during differentiation. T. Hirano (Tokyo, Japan) pointed out the possibility that termination of DNA replication is also regulated by a specific class of condensins that are enriched at late-replicating regions. F. Uhlmann (London, UK) reported that, in budding yeast, condensins are loaded at the same sites as cohesins but are not redistributed by the transcription machinery (Lengronne *et al*, 2004).

Maintenance of genome integrity during S phase

Another important role of topoisomerases in the coordination of DNA replication and gene expression was reported by P. Pasero (Montpellier, France). By using DNA combing, he showed that replication forks frequently stall and break in human and mouse cells depleted in either Top1 or the splicing factor ASF/SF2. Interestingly, this phenotype is suppressed by transcription inhibitors and by RNase H, which degrades DNA–RNA hybrids formed during transcription. These results show that RNP assembly and DNA replication must be tightly coordinated to prevent genomic instability (Fig 2).

G. Almouzni (Paris, France) reported how replication fork progression and histone dynamics are coordinated. She showed that the histone chaperone Asf1 forms a complex with the minichromosome maintenance (MCM) helicase and is required for DNA unwinding at the fork. Asf1 acts as a histone donor/acceptor to facilitate disruption of parental nucleosomes ahead of the fork, and to transfer histones onto newly replicated DNA. As Asf1 also binds to new histones, it might have a crucial role in the coordination of DNA unwinding and histone dynamics involving recycling and *de novo* deposition (Groth *et al.*, 2007).

R. Laskey (Cambridge, UK) has shown that the acetyltransferase MCM3AP represses DNA replication by acetylating MCM3, a subunit of the MCM complex. He showed that induction of MCM3AP expression by tumour necrosis factor- α and interleukin-6 induces cell death in transformed cells, but not in primary cells. Intriguingly, the pro-apoptotic *MCM3AP* gene overlaps an anti-apoptotic gene, germinal-centre-associated nuclear protein (*GANP*), which might represent a defence against accidental immortalization.

Recruitment of DNA repair complexes in the nucleus

Several speakers discussed how DNA-damage signalling and repair complexes are assembled *in vivo*. E. Soutoglou (Bethesda, MD, USA) reported that a full DNA-damage response can be activated in the absence of DNA lesions, simply by tethering sensor proteins to DNA. Their approach has also proved useful in investigating the hierarchy of repair factor recruitment.

Nucleotide excision repair (NER) complexes are sequentially assembled on DNA lesions by passive diffusion and random collision. R. van Driel (Amsterdam, The Netherlands) emphasized the fact that textbook models of NER complex assembly are misleading because they are mostly based on qualitative information. He presented predictive models of NER derived from quantitative *in vivo* measurements. These models integrate the binding, dissociation and enzymatic rates of all partners involved in NER.

W. Vermeulen (Amsterdam, The Netherlands) asked whether the kinetics of NER complex assembly determined for cultured cells can be extrapolated to living tissues. By using fluorescence recovery after photobleaching (FRAP), he has analysed the dynamics of yellow fluorescent protein (YFP)-tagged XPB—a subunit of the repair/transcription factor TFIIH—in mice. He observed a remarkable difference in TFIIH mobility between proliferating and terminally differentiated cells, which probably reflects different modes of transcription initiation. He also reported that different point mutations of XPD, another TFIIH subunit, have different effects on TFIIH recruitment and activity *in vivo*.

New technologies

The results presented here make it abundantly clear that significant conceptual advances are intimately linked to technical breakthroughs. C. Cremer (Heidelberg, Germany) and J. Sedat (San Francisco, CA, USA) presented new microscopes that go beyond the Abbe limit of resolution of conventional optical microscopy. Cremer discussed the spatially modulated illumination (SMI) microscope, an instrument that allows high axial size resolution in the 40–100 nm range and three-dimensional measurements of positions in the 2 nm range. Sedat presented the OMX, a microscope that provides high resolution (100 nm lateral, 350 nm axial) and rapid multi-channel three-dimensional imaging of live samples. Both Cremer and Sedat presented images that showed the outstanding

performances of these new instruments. The combination of such new microscopy approaches with methods of spectrally assigned localization microscopy should make three-dimensional analysis of nuclear nanostructures possible at macromolecular effective optical resolution.

Significant advances in the detection of single RNA molecules in live cells were also presented. R.H. Singer (Bronx, NY, USA) reported a recent analysis of gene expression in real time, based on the use of the MS2 coat-protein system and fluorescence microscopy (Darzacq *et al.*, 2007). This approach allows the direct visualization of single mRNP particles, and provides direct information on the kinetics of transcription and RNA movement.

J. Dejjardin (Boston, MA, USA) presented a new method to purify specific chromatin domains by hybridization with locked nucleic acid probes and the subsequent identification of associated proteins by mass spectrometry. Dejjardin has purified human telomeres and identified several new telomere-associated factors. Dejjardin proposed that one of these factors, the orphan receptor COUP-TF2, might contribute to telomere maintenance in the absence of telomerase by targeting them to promyelocytic leukaemia bodies.

Concluding remarks

In summary, the conference presented many new results and provided an excellent environment for discussions. It became clear that our knowledge of the structure and dynamics of the nucleus is expanding rapidly. In particular, the use of genome-wide techniques such as DamID, ChIP-on-chip and 4C should soon provide detailed maps of the spatial organization of the genome inside the nucleus. The keynote lecture given by J. Gurdon (Cambridge, UK) was an encouraging illustration of how much our understanding of the regulation of the genome has improved in recent years, and judging from the contents of the meeting, much more is to come in the near future.

ACKNOWLEDGEMENTS

We thank the organizers, in particular G. Cavalli, for putting together such a stimulating and timely conference. We also thank the speakers for permission to cite their work, and we apologize to the many participants whose excellent contributions could not be mentioned owing to space limitations. We thank G. Farrants for language editing. The authors' work is financed by grants from the Swedish Research Council and the Swedish Cancer Society (N.V.), from the Fondation Recherche Medicale (equipe FRM), Centre National de la Recherche Scientifique (CNRS), Agence Nationale de la Recherche (ANR) and Institut National du Cancer (INCa; P.P.), and from the Bundesministerin für Bildung und Forschung (BMBF) NGFN II-EP (grant 0213377A) and the Munich Center for Integrated Protein Science (CIPSM; I.S.).

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