Design (and) principles of nuclear dynamics in Stockholm

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The structural organization of the nucleus and its content has drawn increasing interest in recent years, as it has become evident that the spatial and temporal arrangement of the genome and associated structures plays a crucial role in transcriptional regulation and numerous other functions. Shining light on the dynamic nature of this organization, along with the processes controlling it, were the topics of the Wenner-Gren Foundations international symposium "Nuclear Dynamics: Design (and) Principles." The meeting, organized by Pietro Coppola, Maria Vartiainen, Neus Visa, and Ann-Kristin Ovstlund-Farrant, brought over 60 participants, including 20 international speakers, to Stockholm, Sweden from August 19–22, 2015 to share the latest developments in the field. Given the unpublished nature of many of the talks, we have focused on covering the discussed topics and highlighting the latest trends in this exciting and rapidly evolving field.

One of the major challenges in understanding nuclear structure and dynamics is that the function, interaction, and regulation of many key components remain insufficiently characterized. This particularly applies to many of the proteins that make up the nuclear envelope, which play crucial roles in connecting the nucleus to the cytoskeleton and also mediate the structure and organization of the nuclear interior by dynamically interacting with chromatin and structural and regulatory proteins. The structural organization of the nucleus and its content has become evident that the spatial and temporal arrangement of the genome and associated structures plays a crucial role in transcriptional regulation and numerous other functions. Shining light on the dynamic nature of this organization, along with the processes controlling it, were the topics of the Wenner-Gren Foundations international symposium "Nuclear Dynamics: Design (and) Principles." The meeting, organized by Pietro Coppola, Maria Vartiainen, Neus Visa, and Ann-Kristin Ovstlund-Farrant, brought over 60 participants, including 20 international speakers, to Stockholm, Sweden from August 19–22, 2015 to share the latest developments in the field. Given the unpublished nature of many of the talks, we have focused on covering the discussed topics and highlighting the latest trends in this exciting and rapidly evolving field.

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puzzle researchers. One major challenge has been the limited availability of tools to faithfully visualize nuclear actin without perturbing its structure and function. Christian Baarlink from Robert Grosse’s group (Philipps University of Marburg, Germany) presented a promising new approach that is based on a nuclear targeted anti-actin chromobody and that enables following nuclear F-actin formation and dynamics in living cells upon cell spreading and during the cell cycle. This antibody-based technique labels endogenous nuclear actin, thereby circumventing the need (and potential pitfalls) to ectopically express fluorescently labeled actin. Furthermore, the nuclear actin chromobody does not alter the concentration of nuclear actin or stabilize assembled nuclear F-actin; the latter had been described previously as a potential challenge when using fluorescently labeled nuclear LifeAct- and utrophin-derivatives at higher concentrations. While novel nuclear actin reporters can provide new insights into the structural organization of nuclear actin, Maria Vartiainen (University of Helsinki, Finland) highlighted the need to develop tools to specifically manipulate actin in the nucleus to study its function, without perturbing cytoplasmic actin networks, which are essential for a large number of cellular processes. She presented her laboratory’s efforts on this front, showing that manipulating the activity of importin-9, which is the nuclear import receptor for actin, can be used to decrease nuclear actin in both cultured cells and in model organisms. In addition, she shared recent insights from her studies to identify nuclear actin-binding partners, which suggest that nuclear actin could influence the genome beyond gene expression.

The emerging concept of nuclear actin and nuclear myosin I (NM1) as key regulators of gene expression that coordinate global chromatin dynamics with gene-specific activities and directly affect the functional architecture of the cell nucleus was further supported by new studies from Piergiorgio Percipalle (Karolinska Institute, Sweden) and his group. Using genome-wide analysis on the global occupancy of NM1 across a mammalian genome, they found that NM1 binds to both intergenic and genomic sequences and is enriched at transcription start sites of a large number of protein-coding genes. In the absence of NM1, RNA polymerase II transcription was reduced, and increased levels of repressive epigenetic marks were prevalent, suggesting that NM1 may cooperate with actin to promote permissive chromatin states required to activate RNA polymerase II transcription at the gene promoter. Using chromatin immunoprecipitation and deep sequencing (ChIP Seq) to investigate the association of β-actin with a mammalian genome, they discovered that β-actin binds intergenic and genic regions across the mammalian genome associated with both protein-coding and rRNA genes. The distributions of β-actin, NM1, and the subunits of the B-WICH chromatin remodeling complex, WSTF and SNF2h were directly correlated within the rRNA genes; β-actin-deficient mouse embryo fibroblasts had decreased levels of rRNA synthesis and drops in Pol I and NM1 occupancies across the rRNA gene. These defects could be rescued by re-introduction of wild-type β-actin, but not with actin mutants that have polymerization defects. Based on these novel results, Percipalle proposed a novel genome-wide mechanism, where the polymerase-associated β-actin synergizes with NM1 to coordinate permissive chromatin with Pol I transcription, cell growth and proliferation.

Nuclear actin and myosin were also the topic of the next 2 speakers. Xuetong (Snow) Shen (MD Anderson Cancer Center, USA) made the case for using the actin-containing chromatin remodeling complex, INO80, in yeast as a defined genetic and biochemical system to study nuclear actin mechanisms. Presenting recent results from his group, he showed that actin is an essential subunit of the INO80 complex and acts as a monomer to regulate chromatin interactions. Furthermore, taking advantage of the easy-to-manipulate yeast genetics, the Shen laboratory identified multiple actin mutations that preferentially affect nuclear functions, suggesting that nuclear actin may function through mechanisms that are distinct from cytoplasmic actin. Wilma Hofmann (University of Buffalo, USA) shared her group’s latest insights into the function of nuclear myosin. They used a combination of mutagenesis coupled with structural analysis to identify and characterize the elements that govern the nuclear functions of various myosin IC isoforms. Furthermore, they found that nuclear translocation of myosin IC isoforms is regulated differentially by intracellular calcium, and that changes in intracellular calcium levels affect transcriptional activity of myosin IC. These findings add intracellular calcium as an important new regulatory element that can control nuclear myosin IC functions.

Focusing on the human nucleolus, Brian McStay (National University of Ireland, Ireland) presented new findings regarding the nucleolar organizer regions (NOR) and their genomic architecture. Nucleoli form around ribosomal gene (rDNA) arrays with NORs. A technical problem in whole genome sequencing is that the p-arms of the 5 nucleolar organizer region (NOR) bearing acrocentric chromosomes are absent from the current human genome assembly, which makes them ‘invisible’ in most standard RNA-seq assays and hence understudied. Brian McStay made the case that a NOR distal element, localized to the periphery of the nucleolus, anchors the rDNA that extends into the nucleolar interior, and he discussed the possibility that this chromosomal context is involved in the genomic stability of rDNA arrays. His group found that targeted introduction of double strand breaks (DSBs) into rDNA resulted in ATM-dependent inhibition of their transcription by RNA-polymerase I, and that this effect was coupled with movement of rDNA from the nucleolar interior to the anchoring points at the periphery. The reorganization rendered rDNA accessible to repair factors, allowing DSBs to appear to be repaired by the homologous recombination pathway independent of cell cycle stage.

The ‘Where’ and ‘Why’ of Nonsense-mediated mRNA decay (NMD) in human cells were the topic of Lynne Maquat’s (University of Rochester Medical Center, USA) talk. She provided corroboration for her laboratory’s human-cell fractionation and mRNA half-life studies performed in the mid-90s, which indicated that NMD is largely restricted to newly synthesized mRNAs. Collaborating with Robert Singer (Albert Einstein College of Medicine, USA), she showed that individual β-globin mRNA molecules that harbor a premature termination codon (PTC) undergo NMD within 60 seconds of reaching the...
CRISPR Detection Repeat

Arrayed to unravel the dynamics of pre-mRNA splicing as it and Maria Carmo-Fonseca (Instituto de Medicina Molecular Lis-

bon, Portugal) presented a new approach that they have imple-
mented to unravel the dynamics of pre-mRNA splicing as it takes place on actively transcribing genes. Using a combina-
tion of 2 separate RNA tags, the MS2 tag as well as the lambda tag, they performed direct measurements of intron dynamics in single pre-mRNA molecules in live cells. Their results reveal that splic-
ing can occur within seconds after transcription of the 3′ splice site. In collaboration with Nick Proudfoot’s laboratory (University of Oxford, UK), they have also developed bioinformatics approachs to analyze nascent RNA complexes immunoprecipi-
tated by RNA Pol II antibodies, and identified a subset of introns that are excised immediately after the 3′ splice site emerges from the polymerase exit channel. They further observed accumulation of RNA Pol II over these exons, suggesting a splicing-dependent slow-down of transcription elongation rate. Although much of pre-mRNA splicing events occur co-transcriptionally on active genes, when the intra-nuclear localization of splicing factors is examined, nuclear bodies termed nuclear speckles light up as hubs of these factors. The exact significance of these structures, and their physical and functional relationship with site of active genes are still debated. Andrew Belmont (University of Illinois at Urbana-Champaign, USA) reviewed his group’s recently pub-
lished and unpublished work showing long-range, apparently active movement of Hsp70 transgenes to nuclear speckles and the strong enhancement of heat-shock induced transcriptional activation seen after contact of Hsp70 transgenes with nuclear speckles. The Hsp70 DNA locus was detected using the lacO-LacI system, the HSP70 mRNA by MS2 tagging, and the nuclear speckles using a GFP-fusion protein marker, thereby allowing the detection of active and non-active Hsp70 in living cells. To determine how prevalent nuclear speckle association is for endogenous genes, they developed a new genomic method, termed TSA-Seq, for mapping cytological proximity to nuclear compartments. The genome-wide results obtained show that a large fraction of highly expressed active genes localized close to nuclear speckles. Future applications of the TSA-Seq method should allow probing of the relationship between transcriptional activation and gene movement to different nuclear compartments. While DNA tagging in living mammalian cells has been typically achieved by the lacO-LacI DNA tagging system via the stable genomic integration of these sequences, it has not been straightforward to use this approach for the tagging of specific genomic sequences. Recent developments in the rapidly evolving genome editing field indicate that such sequence-specific approaches are now feasible. Thoru Pederson (UMass Medical School, USA) described a multi-color CRISPR (clustered regularly interspaced short palindromic repeats) method to measure inter- and intra-chromosomal 3-D configurations of genomic loci in live cells. He also introduced a method, termed CARDS (for CRISPR Arrayed Repeat Detection System) in which dCas9-GFP and a designed sgRNA can be applied to fixed cells in a simple 30 min procedure. This protocol could have diagnostic potential for Amyotrophic Lateral Sclerosis (ALS) and other repeat expansion-based diseases. Pederson focused the remainder of his talk on a new system in which the dynamics of Cas9 and a sgRNA can be tracked in live cells based on dual colors, offering insights that may aid the deployment of CRISPR for gene regulation and editing.

The three-dimensional organization of a genome plays a critical role in regulating gene expression, yet little is known about the machinery and mechanisms that determine higher-order chromosome structure. The structural maintenance of chromo-
somes (SMC) protein complexes, namely, cohesin, condensin and the Smc5/6 complex are essential for genome stability and influence replication, segregation, transcription and repair. Barbara Meyer (UC-Berkeley, USA) presented the results of a collabora-
tion with Job Dekker’s laboratory (UMass Medical School, USA), in which they used X-chromosome dosage compensation as a model to explore the role of higher-order chromosome struc-
ture in regulating gene expression. The C. elegans dosage compen-
sation complex (DCC), a condensin complex, binds to both X-chromosomes of hermaphrodites via sequence-specific recruitment sites (rex sites) to reduce chromosome-wide gene expression by half. They showed that the DCC actively remodels X-chromosomes of hermaphrodites into a unique, sex-specific spatial con-
formation, distinct from that of autosomes, using its highest-affinity rex sites to facilitate long-range interactions across the X-chromosome. Without DCC binding, the structure of the X-chromosome resembles that of autosomes. The changes in higher-order X-chromosome structure achieved by the DCC then influence gene expression over long distances. Studying the condensin complexes in the yeast Saccharomyces cerevisiae, Camilla Sjögren (Karolinska Institute, Sweden) presented her group’s analysis of the Smc5/6 complex, the least understood
complex in the family. Their analysis suggests that the chromosomal association of Smc5/6 indicates the presence of sister chromatid entanglements, and that these structures accumulate as a consequence of replication-induced DNA supercoiling. New observations also suggest that Smc5/6 binds chromosomes in response to high levels of transcriptionally induced superhelical stress, indicating that the processes of replication and transcription modulate chromosome segregation by triggering the formation of sister chromatid entanglements.

In the nuclei of fission yeast cells the 3 chromosomes are anchored to the nuclear membrane via telomeres and centro-meres in a bouquet–like arrangement. Karl Ekwall’s group (Karolinska Institute, Sweden) has mapped interactions with inner membrane proteins by DNA adenine methyltransferase identification (Dam-ID) and found additional repressed chromosomal domains to be in close association with the inner membrane. A role for chromatin remodelling in nuclear organization was recently revealed by functional characterization of the chromatin remodelling factor Fft3. Fft3 binds to several chromosomal boundary elements consisting of tRNA genes and long terminal repeat (LTR) elements where it affects nucleosome occupancy and maintains boundary activity. In the absence of Fft3 the genes in subtelomeric domains are derepressed and move away from the nuclear envelope. The LTR barrier at subtelomere 2L correlates with a topologically associating domain boundary defined by others using Hi-C analysis. Interestingly, high-resolution nucleosome turnover measurements indicate that nucleosomes at this subtelomeric LTR barrier show high turnover and that this is likely a crucial aspect of boundary activity involving Fft3.

A series of talks discussed the topic of non-coding RNAs (ncRNAs). Joan Steitz (Yale University, USA) spoke about a novel transcript type derived from mammalian protein-coding genes. These RNAs, which are termed DoGs for downstream of gene containing transcripts, possess long non-coding regions (often >45 kb in length) and remain chromatin bound. DoGs are inducible by osmotic stress through an IP3 receptor signalling-dependent pathway, indicating active regulation. DoGs are generated by decreased termination of the upstream transcript, a previously undescribed mechanism for rapid transcript induction. Relative depletion of poly-A signals in DoG regions correlates with increased levels of DoGs after osmotic stress. Steitz’s laboratory detected DoG transcription in several human cell lines, and they have identified thousands of DoGs genome-wide. Altogether they suggest that DoGs may function to maintain nuclear integrity after stress. Marc Bühler (Friedrich Meischer Institute for Biomedical Research, Switzerland) talked about recent work from his laboratory that solves a long-standing problem in the field of RNAi-mediated heterochromatin formation and highlights fundamental roles for the transcription and RNAi machineries in building epigenetic memory. Although endogenous small RNAs play critical roles in chromatin-mediated processes across kingdoms, efforts to initiate chromatin modifications in trans by using siRNAs have been inherently difficult to achieve in eukaryotic cells. Using fission yeast, his group discovered that the RNA polymerase-associated factor 1 complex (PaflC) impedes small RNA-directed formation of heterochromatin and epigenetic gene silencing. Upon inhibition of PaflC, they were able to induce silencing of genes that lasts up to 5 generations, even in the absence of the siRNA that initiated the repression. Investigations of this novel activity of PaflC in other organisms are ongoing in the Bühler laboratory. Finally, Eric Meyer (Institut de Biologie de l’Ecole Normale Superieure, France) spoke about small RNA-mediated trans-nuclear crosstalk in the ciliate Paramecium tetraurelia. Ciliates are unicellular eukaryotes with 2 distinct kinds of nuclei, the germline micronuclei and the somatic macronuclei, in the same cytoplasm. The non-Mendelian inheritance of mating types in P. tetraurelia is one of the oldest problems in epigenetics. Early studies showed that the new somatic macronucleus, which in ciliates develops from the germline micronucleus after fertilization, becomes determined for type O (Odd) or type E (Even) under the control of the parental macronucleus, still present in the cytoplasm, resulting in a maternal pattern of inheritance at conjugation. Recent identification of the genes involved showed that type E is determined by expression of the ciliary transmembrane protein mtA, and that type O is determined by developmental excision of the mtA promoter. Excision was shown to be regulated by scnRNAs, a meiosis-specific class of small RNAs initially produced from the entire germline genome. scnRNAs first scan the maternal macronucleus to identify missing sequences, and then allow the zygotic macronucleus to reproduce the same deletions. Although this mechanism likely evolved as a genome-defense mechanism targeting the elimination of transposable elements in the developing macronucleus, this genome-wide, trans-nuclear crosstalk between germline and somatic genomes can thus be co-opted to regulate cellular genes, allowing transgenerational epigenetic inheritance of alternative phenotypes in the absence of germline genetic polymorphisms.

Taken together, the studies presented at the Wenner-Gren international symposium put the spotlight on the intricate connections between genomie organization of the eukaryotic cell nucleus and nuclear dynamics, emphasizing their importance in transcriptional regulation, genome maintenance, and cellular function. Furthermore, the ground-breaking research highlighted the often dynamic nature of the interplay between structural elements such as nuclear lamina, nuclear actin, and cohesins, with protein complexes such as the transcription and splicing machineries involved in gene regulation processes. The recent findings have already stimulated further research into this growing field, and we are sure to witness the unraveling of more nuclear secrets in the years to come.

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No potential conflicts of interest were disclosed.

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