Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Cell Biology

The nucleus and gene expression: the center of the cyclone

Editorial overview

Asifa Akhtar and Karla Neugebauer

Current Opinion in Cell Biology 2012, **24**:293–295

Available online 30th April 2012

0955-0674/$ – see front matter

DOI http://dx.doi.org/10.1016/j.ceb.2012.04.001

Asifa Akhtar

Max Planck Institute of Immunobiology and Epigenetics, Stübeweg 51, 79108 Freiburg im Breisgau, Germany
e-mail: akhtar@ie-freiburg.mpg.de

Asifa Akhtar is a Max Planck Investigator at the Max Planck Institute of Immunobiology and Epigenetics, Freiburg, Germany. Her research focuses on X chromosomal regulation as a paradigm to study the role of chromatin, epigenetic regulators as well as noncoding RNAs in gene expression control combining biochemistry, genetics, and genomics approaches.

Karla Neugebauer

Max Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauerstrasse 108, 01307 Dresden, Germany
e-mail: neugebau@mpi-cbg.de

Karla Neugebauer is a senior group leader at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany. Her research focuses on the relationship between transcription, chromatin, and RNA processing in living cells, using budding yeast, mammalian cells, and zebrafish embryos as model systems.

As the origin of the word 'nucleus' suggest, this cellular compartment is central to cellular function. It contains the blueprint for cell metabolism, morphology and identity, and it integrates signals from the environment alongside that internal set of instructions. Nuclear function reflects the coordinated deployment of several sophisticated molecular machines that work in concert at various levels inside and outside of the nucleus. This issue covers a broad range of topics encompassing gene expression, molecular function and cellular identity, giving a nice flavor of the recent advances in various fields. Many of this year's hottest breakthroughs follow on the dogged pursuit of classical paradigms of nuclear function, such as DNA repair; others follow from research areas with a shorter history, such as the role of noncoding RNA and nuclear reprogramming. The topics can be broadly divided into: transcription and post-transcriptional control, chromatin and epigenetic regulation, and DNA replication and genome stability.

Transcription and post-transcriptional events

Owen-Hughes and Gkikopoulos provide a brief overview of the RNA Polymerase II (Pol II) transcription cycle starting from the nucleosomal template, initiation and elongation. This review discusses the tight coupling of histone and other post-translational modifications in the transcription cycle, which has become increasingly complex over the last couple of decades. Multiple multiprotein complexes act at the chromatin and DNA level to ensure efficient passage of Pol II through the genes. For example, large coactivator complexes integrate regulatory signals from a variety of ubiquitous or tissue-specific transcription factors to activate or repress gene transcription. In addition to the multisubunit Pol II machinery, the mediator coactivator complex is required for transcription of most, if not all, protein-coding genes. Larivière and colleagues take the question of transcription regulation a step further and provide a global overview of mediator complex structures. The size and flexibility of different mediator modules have made it difficult to obtain high-resolution structures of this essential complex. However, individual pieces are being structurally analyzed. It is therefore imminent that the combination of different high-resolution techniques available to structural biologists will build a comprehensive atomic puzzle of this crucial transcription coactivator complex.

A classic mode of post-transcriptional control is RNA processing. Minasaki and Eckmann explore the remarkably complex world of 3′ end nontemplated nucleotide addition by a whole host of nucleotidyltransferases. These enzymes add various numbers of As and Us to 3′ ends in different cellular compartments to modulate RNA stability and translation. Meanwhile, alternative splicing — discussed by Irimia and Blencowe — introduces variability into the bodies of most mRNAs. Here, the challenge for the field is to sort out the myriad of mRNA species expressed in cells and

determine which of these are actually translated into proteins, on the one hand, and how broadly protein functions differ due to changes in amino acid sequence introduced by alternative splicing. Aalto and Pasquinelli remind us that not all transcripts are coding, and among non-coding RNAs, the smallest ones regulate gene expression. This timely review helps us to make sense of the plethora of tiny RNAs reported recently, urges caution in naming small RNAs, and further predicts that the gene expression output of a given cell may be a function of that cell's small RNA repertoire. The nuclear envelope constitutes the major gateway between the nucleus and cytoplasm, through which the trafficking of RNAs and proteins occur. In recent years, the nuclear periphery has been shown also to play an important role in regulation of gene activity by helping to compartmentalize active or repressed genes. Burns and Wente discuss the interplay between the nuclear pore complex and the inner nuclear membrane proteins (INM) in trafficking cargoes.

The review by Hebenstreit and colleagues returns to the basics of transcriptional regulation, taking stochasticity and the expression of the genome as a series of interacting networks into account. This cutting edge perspective forces us to reconsider what is noise and what has evolved to be highly precise. Noise — influenced by transcriptional circuits and epigenetic regulation — may play an important role in the attainment of cellular fate.

Epigenetic regulation imposing memorable cell fate decisions

Any consideration of chromatin begins with the concept of higher order chromosome structure. As discussed by Bian and Belmont, the dogma of the 30 nm fiber has been challenged in recent years and requires redefinition. The widespread application of 3C and related techniques inform not only on long-distance interactions across the nucleus, but also on chromatin folding. The emerging view suggests multiple kinds of 30 nm fibers serve as the substrate for epigenetic regulation. DNA methylation is the classical epigenetic mark, which plays an important role in differential gene regulation. DNA methylation is not only important in higher eukaryotes but there is recent evidence pointing to its role in insects, such as honeybees. Interestingly, queen and worker bees show differential patterns of DNA methylation, suggesting that epigenetic regulation may underlie phenotypic plasticity in these insects. Patalano and colleagues provide an interesting and provocative comparison between cell differentiation systems and insect societies. They provide a conceptual model for how loss and regain of phenotypic plasticity might be conserved for individual specialization in both cells and societies.

Vastenhouw and Schier provide a comprehensive survey of histone modifications, and discuss the hotly debated topic of the inheritance of a particular chromatin state from parent to offspring. The jury is still out, but it is possible that further analysis of noncoding RNAs or sequence-specific transcription factors and histone modifications may help answer how chromatin states are re-established or inherited after fertilization. Gill and colleagues elaborate on the topic of totipotency involving extensive epigenetic reprogramming of the germline state into an embryonic state. They summarize changes in chromatin states during mammalian gametogenesis and examine the evidence that early mammalian embryogenesis may be affected by inheritance of epigenetic information from the parental generation. Clearly, future work will be instrumental in revealing how chromatin and epigenetics states in mature germ cells are specified.

Gribnau and Grootegoed discuss a prime example of epigenetic phenomena, X inactivation. It appears that the evolution of heterologous sex chromosomes in mammals involved the co-evolution of two layers of gene dosage compensation: X chromosome inactivation in female cells as well as a twofold upregulation of dose sensitive X-linked genes in males and females. Over the last two decades, tremendous advances have been made in understanding the regulation of the inactive X chromosome by identification of regulatory RNA and protein factors implicated in this process. Much less is known about how the active X chromosome is regulated. Future studies are eagerly awaited to provide additional insights into the mechanisms at play in balancing the genome.

Delest and colleagues discuss another set of highly studied epigenetic regulators, the polycomb proteins. Polycomb (repressors) and trithorax (activators) group of proteins are major regulators for generation of correct body plan; their loss leads to dramatic homeotic transformations. Polycomb group (PcG) protein-mediated repression constitutes one of the early examples of epigenetic regulatory mechanisms identified, conferring stable silencing of Hox genes long after the disappearance of the transcription factors that set up their initial expression patterns during embryogenesis. Recent genome-wide binding analyses of these factors in various model organisms have revealed that polycomb protein targets are evolutionarily conserved, and many target genes are involved in the control of cell fate decisions. Interestingly, chromosome capture of individual loci as well as global analysis had recently revealed that polycomb-mediated organization is not restricted to the linear epigenomic scale but also involves higher order chromatin organization through chromatin looping. The rich resource of genome-wide linear maps combined with upcoming chromatin interactions maps makes the polycomb system an ideal example of epigenetic regulation and chromosome architecture. Interestingly, PcG bodies have been the subject of recent controversy. As Dundr's review points out, nuclear bodies are often the site of

either function or macromolecular assembly. The PcG bodies, assumed to be sites of repression, appear to consist of coalesced chromatin marked by PcG.

Faithful duplication of the genome is essential for life. Minichromosome Maintenance 2–7 (Mcm2–7) proteins are important players in DNA replication. Boos and colleagues discuss how loading, unloading and unwinding activities of these helicases are intricately regulated to achieve precise regulation in each cell cycle. Similarly, pre-mRNA splicing is also a high fidelity nuclear activity that relies on families of helicases, discussed by Cordin and colleagues. DEAH-box, DEAD-box and Ski2-like helicases control conformational rearrangements within the spliceosome. Although helicase substrates are elusive, the suggestion that helicases act mechanically as switches to create a 'domino effect' during splicing, by which a new conformation provides the substrate for the next helicase in line. Finally, the role of histone ubiquitin ligases are highlighted by Luijsterburg and van Attikum, who elaborate on the importance of chromatin remodeling in the execution of the DNA damage response.

This collection of remarkable pieces places the nucleus and gene expression at the center of the cyclone, an inner space that knows no limits.