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Editorial overview

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Moshe Yaniv is an Emeritus Professor of Molecular Biology at the Pasteur Institute in Paris. He has been active in the field of gene expression, chromatin structure and DNA tumour viruses. During recent years his laboratory has been working on chromatin remodeling complexes and their function in development and growth control in the mouse.

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Sarah CR Elgin is a Professor of Biology, of Genetics, and of Education at Washington University in St. Louis. She has been active in the field of chromatin structure and its role in regulation of gene expression. During the last few years she has focused on the question of formation and maintenance of heterochromatin, using *Drosophila melanogaster* as the model system. She serves on the Scientific Advisory Board of the EU Epigenome network and is a member of the NIH modENCODE group.

Differential gene expression is the central feature of normal development in a multi-cellular organism, or of the life cycle of a unicellular eukaryote. Our appreciation of both the complexity of eukaryotic genomes and of the chromatin packaging that they utilize has continued to grow in recent years. While at one point pioneering studies focused on transcription from DNA templates, now the intricate features of the chromatin template hold our attention. Histones are no longer considered mere 'cellophane wrapping' (they are there, but you can see right through them), as famously claimed at a past Keystone meeting, but are acknowledged as a critical part of the regulatory system.

Several technical developments have framed much of the progress made during the past year. For example, genome sequencing, ChIP on chip and other high-throughput techniques have allowed us to examine not just a few genes, but the whole genome in looking at chromatin characteristics such as particular histone modifications. It is gratifying that many of the inferences made by study of a few genes have been verified by study of the genome; even better, new patterns have emerged. An examination of these developments is provided by the reviews by Mendenhall and Bernstein, and by Mellor and colleagues, looking in particular at events in early mouse or human cell differentiation. Progress in describing the role of specific transcription factors in inducing pluripotency and re-directing cell fate is reported in the review by Boyer and colleagues. This work has shown that many genes, not just the handful recognized earlier by Lis and co-workers [1,2] are poised for transcription, a theme developed in the review by Wade and Struhl on the critical transition from initiation to elongation. Both initiation and elongation depend upon nucleosome remodeling, and Racki and Narlikar have provided us with an update on the mechanisms used to achieve this. An interesting question is to what extent the chromatin environment of transcription may impact subsequent splicing of transcripts, and Muchardt and colleagues develop this topic.

As we learn more about the biochemistry of chromatin, the complexity and utility of post-translational protein modifications never ceases to amaze us. This year progress has been made in particular in understanding lysine methylation and demethylation. The review by Huang and Berger emphasizes the fact that not only histones, but also the non-histone chromosomal proteins are targets of such modifications. While in the first instance methylation was thought to be a fairly stable modification (particularly in comparison to acetylation or phosphorylation), work of the past few years has identified several histone demethylases, as described by Helin and his colleagues, emphasizing that this modification is dynamic as well. Many

non-histone chromosomal proteins appear to function by reading the histone modification marks; one of the best-studied examples is the interaction of Heterochromatin Protein 1 (HP1) with histone H3 methylated at lysine 9, an interaction prominently associated with gene silencing. However, we need to be alert to the fact that many proteins play diverse roles, and Fanti and Pimpinelli report here on the additional roles of HP1 in telomere stability and in positive regulation of gene expression, the latter perhaps via a role in transcript elongation.

A salient characteristic of eukaryotic genomes is that genes are not only regulated by gene-specific transcription factors, they are also regulated by the larger chromatin state, with large domains (for example, the X chromosome) subject to distinct regulatory influences, presumably via chromatin packaging. A basic premise is that the underlying information for this organization must be found in the DNA, in the organization of the genome, and Straub and Becker explore the emerging evidence supporting this concept. Tremendous progress have been made in the last few years in recognizing the on-going challenge in regulating the repetitious elements in our genomes, and the report by Siomi and Siomi on the recent findings in Drosophila, particularly examining the piRNA system. The mosaic of genes and repeats which are observed has generated opportunities to co-opt some of the invading sequences to control genes, creating opportunities for epigenetic regulation, as discussed by Weil and Martienssen and by Cuzin and colleagues, emphasizing work in plants and mammals, respectively. Such regulation can involve several different RNAi pathways, and Pontes and Pikaard report on new findings on the contrast between plants and animals in processing small RNAs. The repetitious sequences in the genome also present significant challenges to maintaining genome stability, a topic developed by Peng and Karpen looking at heterochromatic and rDNA sequences. Rog and Cooper discuss the challenge of maintaining telomeres, in particular the interplay between the DNA damage response machinery and the DNA replication machinery. Finally, as our appreciation of epigenetic regulatory mechanisms grows, we need to explore the question of epigenetic variation in populations, and how that variation might be a substrate for evolution, a new aspect of chromatin work presented in the review by Richards.

All in all, the last few years have been busy and exciting. The complexity of the genome as a mosaic of repetitious elements and genes presents many puzzles, and more riddles will need to be solved before we will appreciate how this complex assembly works as a whole. We note that repetitive elements and their vestiges evolve much more rapidly than unique sequences, and may play an important role in speciation. There is no longer any doubt that the packaging of DNA by histones provides a critical component of gene regulation, with intricate modification patterns used to regulate unpackaging for transcription, duplication or repair, followed by equally important repackaging to maintain transcription fidelity and genome integrity, as well as epigenetic memory. Not only is the modification pattern read and used by additional chromatin proteins, functional protein complexes may be targeted by mechanisms using the small RNA systems. It all adds up to a very complex and highly interactive system, which perhaps should be no surprise, given the complexity of the organisms that emerge! We look forward to many more years of effort, each bringing new insights and new surprises, as we continue to explore chromosomes and expression mechanisms.

References

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