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Editorial overview: Genome architecture and expression: Connecting genome composition and nuclear architecture with function

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Incorporation of the eukaryotic genome into a nucleus provides regulatory mechanisms that are not available to prokaryotes. This volume contains review articles that describe recent advances in our understanding of eukaryotic genome structure and nuclear organization. Together, the developing picture is one of a dynamic nucleus that builds upon DNA sequence and composition to promote formation of nuclear organization that is optimized for gene expression.

Packaging of eukaryotic genomes requires histones. These small basic proteins form nucleosomes that assemble DNA into an 11 nm fiber. How higher-order genome organization is built from nucleosomes remains unclear. To date, neither microscopy-based nor modeling approaches have provided a unifying view of interphase chromatin structure. Nevertheless, new technologies that enhance *in vivo* observations of fluorescently labeled chromatin are challenging the idea of the hierarchical organization of the 30 nm fiber, as reviewed by Maeshima *et al.* These new data suggest that cellular chromatin consists of an irregularly folded 10 nm fiber that has a dynamic liquid-like structure, which plays important roles in genomic functions such as transcription, replication and repair.

A nearly ubiquitous feature of eukaryotic chromosomes is the presence of highly compacted chromatin domains, called heterochromatin. Spatially, heterochromatin is found in three major nuclear compartments, the nuclear periphery, the perinucleolar region, and pericentromeric bodies. Politz *et al.* review mechanisms involved in the structure and function of these transcriptionally repressive compartments, emphasizing that formation of heterochromatin associated domains depends both upon the biophysical properties of component proteins that promote self-association and their tethering properties for their domain stabilization. Maintenance of the function of heterochromatic domains is linked to correct nuclear positioning. As highlighted by the review of Gonzalo and Eissenberg, telomeres are heterochromatic domains that preferentially position near the nuclear envelope or perinucleolar regions in animal cells. Interestingly, such localization depends on interactions of telomeres with lamins, a prominent family of structural proteins that builds a protein network critical for maintaining nuclear architecture. Mutations in lamins are associated with telomere damage, evidenced by changes in telomeric chromatin modifications and transcription, implying that compartmentalization helps maintain genome stability. Indeed, the repair of DNA damage depends upon nuclear positioning as well. Emerging evidence suggests that double strand breaks

relocate to the nuclear periphery or to the nucleolus to achieve optimal recruitment of DNA repair machinery and ensure genome stability (Kalousi and Soutoglou). In addition to roles in establishing chromosome architecture and genome stability, lamins build protein assemblies that associate with cytoskeletal components in the cytoplasm. Mechanical coupling of the nucleus with the cytoskeleton plays a critical role in physiological processes, such as nuclear positioning during cell migration and provides a protein network capable of transferring environmental signals to the nucleus to activate new transcriptional programs (Bohnekamp *et al.*)

Recent data have clarified mechanisms involved in chromosome positioning within the nucleus. One review summarizes data that reveals how origins of DNA replication impact nuclear organization, suggesting that the sequence of the genome itself provides information that guides establishment of chromatin domains (Marks *et al.*). Evidence of the extent to which DNA sequence influences chromosome positioning is seen in Dipteran insects, such as Drosophila, where homologous chromosomes align end-to-end in somatic tissues. However, this degree of pairing of homologous chromosomes is extreme. As reviewed in Joyce *et al.*, most organisms including mammals, distinguish between homologous maternal and paternal chromosomes, placing these chromosomes in distinct nuclear territories. Emerging evidence indicates that the degree of homologue association may be regulated, reflecting on a balance between factors that antagonize or promote pairing. As such, factors that antagonize pairing appear to prevail in mammals. As the degree of interactions between homologues establishes constraints for chromosome positioning, homologue associations may provide heritable information critical for establishing genome organization at the scale of chromosomes. The relative position of homologues within the nucleus likely impacts chromosome-wide transcriptional regulation. For example, interactions between chromosomes contributes to mechanisms of dosage compensation, a process that equalizes gene dosage imbalances. As reviewed by Sharma and Meister, studies in worms, flies and mammals reveal that *X* chromosome dosage compensation involves targeting and spreading of specialized dosage compensation complexes along the *X* chromosome. Once associated, these complexes change the chromatin composition and the nuclear position of targeted chromosomes, establishing a specialized nuclear compartment, called the *X* domain.

In spite of advances in our understanding of chromosome positioning, factors that impart regional variation within chromosomes remain largely unknown. Organization of the genome into interspersed active and inactive chromatin domains requires the definition of boundaries that constrain interactions between neighboring domains. Much evidence suggests that domain boundaries are established by binding of architectural proteins that define long-range interactions. One review discusses the role of CTCF in establishing domain boundaries (Ali *et al.*). In mammals, the boundary function of CTCF depends upon recruitment of cohesin, a protein complex comprised of structural maintenance proteins (SMCs), implying that this complex has critical interphase functions, in addition to roles in mitosis. The importance of cohesins in gene transcription is illustrated by the consequences of their deregulation for disease (Watrin *et al.*). Unexpected links between diseases and another basic component of chromatin have been discovered in recent years. In addition to canonical histones, several families of histones variants exist. In this issue, Zinc and Hake review the link between alteration in expression of specific histone variants and disease, outlining medical consequence of essential specialization of the roles of histone variants and their potential link with the impact of histone variants on genome organization. Other mechanisms that might govern chromatin changes at the scale of individual loci include the action of pioneer transcription factors, a class of transcription factors that are distinguished by their ability to bind their DNA recognition sites with a compacted chromatin context. During cell fate changes, pioneer factors modify chromatin accessibility and as a consequence reconfigure transcriptional networks (Zaret and Mango).

Technological advances in next generation deep sequencing have improved our understanding of genome composition and its relationship to gene expression. These studies have provided a clearer view of transposon families within genomes. Two reviews examine the impact of retroelements on genome function, a class of genetic elements that transpose using an RNA intermediate. The review by Molaro and Malik describes host mechanisms involved in silencing retroelements. In germline cells, the massive reprogramming of silent chromatin promotes retroelements mobilization, creating chromatin discontinuities within chromosomes that require multiple strategies for repair to ensure maintenance of genome integrity. The second review by Mita and Boeke emphasizes how transposon mobility expands and rewires gene regulatory networks on an evolutionary time scale, suggesting that developmental windows of transposon reactivation might provide opportunities for evolution and adaptation of new functions. An implication of this view is that retrotransposons active in human disease might represent failed attempts towards evolutionary adaptation.

Genome-wide transcriptional analyses demonstrate that eukaryotic genomes are extensively transcribed. Indeed, genome-wide transcription generates large amounts of repeat RNAs. As reviewed by Hall and Lawrence, repeat-rich RNAs appear to have a fundamental role in chromosome architecture and regulation. Recent findings

suggest that one class of abundant RNAs, the repeat rich 'Cot-1 RNA', represents an abundant stable component of euchromatic chromosome territories. Further, emerging evidence indicates that Cot-1 RNAs scaffold both active and repressive chromatin states. A second class of abundant RNAs are long noncoding RNAs (lncRNAs), RNA transcripts longer than 200 bp that lack a protein coding capacity. Although discovered several decades ago, our understanding of the biological roles of this class of RNAs remains limited. Building from systematic, unbiased genomic screens for lncRNAs in *Saccharomyces cerevisiae*, Alcid and Tsukiyama propose two features of lncRNAs that can distinguish those RNAs with biological function. These include lncRNAs that are produced from dedicated preinitation complexes and lncRNAs that display highly regulated transcription. Improved identification of functional lncRNAs will expand our understanding of the roles of this RNA class in transcription and chromatin dynamics.

The development of novel computational tools has made it possible to integrate biologically relevant networks with three-dimensional genome architecture (He and Tan). Although early technologies based on chromosome conformation capture were performed on populations of cells, novel chemistry has been developed that enables the use of smaller amounts of starting material, allowing analysis of chromosome structure in single cells (Martinez-Jimenez and Odom). As a result, it is becoming clear that the chromatin landscape is dynamic, varying in cells of different fates and in different phases of the cell cycle. Hence, data obtained from earlier studies represent an ensemble of possible chromatin profiles adopted by a particular cell type.

In summary, reviews in this volume provide information about the current view of the connections between nuclear organization and gene expression. One emerging theme is that the genome sequence itself plays a fundamental role in shaping the epigenetic landscape of the nucleus. These articles foreshadow the future, as they highlight outstanding questions whose resolution will provide a deeper understanding of the dynamic nucleus. We thank all authors for their review articles and hope that you enjoy reading them.