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Editorial overview: Genome architecture and expression

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This issue of *Current Opinion in Genetics and Development* is centered on Genome Architecture and Expression, with a focus on epigenetic regulation. The packaging of eukaryotic genomes into higher-order chromatin structures is thought to impact gene expression. The discoveries that chromosomal structural proteins are necessary for normal expression and that chromosomes are organized into territories in which high frequency contacts between distant portions of the chromosome are conserved highlight that there is underlying organization of eukaryotic DNA. This issue explores developments in understanding the mechanisms and molecular players involved in this genome organization, an understanding that is essential to fully elucidate the fundamental relationship between nuclear organization and genome function.

A major model for understanding the interplay between chromatin structure, genome organization, and gene expression in mammals is X chromosome inactivation. X chromosome silencing is a developmentally regulated process that centers on the long non-coding RNA, Xist RNA, which coats the X chromosome to recruit chromatin modifiers associated with silencing. The discoverer of X chromosome inactivation, Mary Lyon, passed away in January 2015. In the 50+ years since Dr. Lyon reported the first evidence of this epigenetic phenomenon much progress has been made, and Galupa and Heard provide a concise overview of recent findings in the field, focusing on regulation of Xist during development, and examining the role of chromosome conformation in regulating the dynamics of this locus. This review also shows that many interesting questions remain about how long non-coding RNAs impact chromosome organization, answers to which are likely to inform our understanding of the many long non-coding RNAs that are emerging as regulators of gene expression.

While mammals silence one X chromosome in females to equalize X-linked gene dosage between the sexes, the roundworm *Caenorhabditis elegans* down regulates gene expression from both X chromosomes by half in XX hermaphrodites. This down regulation requires that the dosage compensation complex, which includes chromosomal structural proteins,

assembles on both X chromosomes. Lau and Csankovszki describe how dosage compensation complex activity results in compaction of the X chromosomes and changes in histone post-translational modifications, that ultimately limit RNA Polymerase II loading to decrease expression chromosome-wide. *C elegans* dosage compensation provides an example of how an altered epigenetic state is achieved by the combination of chromosomal structural proteins and chromatin modifiers. It seems likely that using this combination will be a recurring theme in regulation of gene expression in metazoans.

Flies have found yet another way to achieve dosage compensation, by up regulating expression from the single X chromosome in males two-fold. This process requires the Male Specific Lethal complex, which contains non-coding RNAs and chromatin modifiers. This complex is necessary for X chromosome-wide gene regulation in flies, but also regulates single genes in both flies and mammals. Thus, Male Specific Lethal complex epitomizes how evolution has likely allowed an activity that functions locally to be repurposed to regulate gene expression chromosome-wide. Keller and Akhtar highlight recent advances in biochemical and structural analysis of the components of Male Specific Lethal complex modules, which provide insight into their function in fly X chromosome regulation. A better understanding of how this complex regulates gene expression on a chromosome-wide and gene-by-gene basis will provide insight into the mechanisms used to target epigenetic regulators to particular regions of the genome, an important aspect of epigenetic gene regulation that is not fully understood.

In contrast to dosage compensation, which has been studied relatively extensively, eukaryotic repetitive elements are not well characterized. A substantial portion of the human genome, estimates range from 50–70%, consists of repetitive elements, and remarkably little is known about the regulation and molecular composition of these elements. Because many of these repetitive elements are mobile, they have shaped and have the potential to continue altering our genome. Understanding the content and origins of this ‘dark matter’ of the genome represents an important step toward completely deciphering the organization and function of the human genome sequence. Padeken et al. summarize recent studies characterizing different classes of repetitive elements, their organization, and the mechanisms that keep the repetitive regions of our genomes silent and stable.

One region of the chromosome that can contain a large number of repetitive sequences is the centromeric region. In most eukaryotes centromeres are packaged in a unique histone, cenH3, and are embedded in highly repetitive pericentric satellite DNA. However there is considerable evolutionary diversity among species: some have lost cenH3 and others distribute centromeric function along the whole chromosome rather than restricting it to one point. In addition, loss of a centromere can trigger formation of a new centromere, indicating that this crucial regulator of chromosome integrity can be epigenetically defined. Steiner and Henikoff provide a synopsis of recent findings in centromere biology, summarizing structural studies of cenH3 and describing molecular analysis of pericentric heterochromatin. The studies comparing and contrasting the many different ways different organisms have solved the problem of chromosome segregation highlight the evolutionary flexibility of the systems that organize *cis*-regulatory elements and mediate their association with other types of cellular machinery.

Our understanding of nuclear organization is largely derived from two broad classes of experimental methods: microscopy, which interrogates single cells, but provides limited nucleotide-level resolution of interactions, and chromatin conformation capture based experiments, which provide high resolution information about the most highly populated states in a large population of cells. However, biological processes are highly dynamic, and understanding the dynamics of nuclear organization will be undoubtedly be important in dissecting how genome architecture regulates gene expression. Fraser et al. summarize recent progress toward bridging this gap, bringing nucleotide-resolution of three-dimensional genomic interactions to single cells. These types of cutting edge methods have the potential to inform us whether nuclear organization regulates or reflects genome function.

Epigenetic regulation is particularly important in pluripotent stem cells, which are a widely used *ex vivo* model for studying events occurring during mammalian development. Gene-environment interactions, such as response to developmental signaling molecules or other environmental factors, impact chromatin organization. Indeed the epigenome of pluripotent stem cells is sensitive to medium composition, and this sensitivity has significant implications when considering how best to culture these cells for regenerative medicine. Imprinted genes, which are expressed in a parent-of-origin dependent manner, provide a particularly sensitive readout to epigenetic alterations. Greenberg and Bourc'his review recent literature showing imprint and other epigenetic abnormalities in mouse and human pluripotent stem cells, which may have implications for their use in cell-based therapies.

Germ cells are a specialized class of pluripotent cells — upon fertilization they give rise to all cell types in the adult organism. Dramatic alterations in chromatin structure accompany the transition from diploidy to haploidy and the specialization of the sperm and oocyte. Additional epigenetic alterations occur after fertilization, as the two genomes mix. Despite these changes, some epigenetic marks appear to be inherited across generations. Feng and Chen discuss recent insights into epigenetic regulation of germ cell differentiation and transgenerational inheritance in different metazoan species. Determining the molecular mechanisms that allow information to be perpetuated across this period otherwise marked by dynamic alterations in the epigenome will be important for understanding this most enigmatic aspect of epigenetic inheritance.

Biographies

Barbara Panning is a Professor in the Department of Biochemistry and Biophysics at University of California, San Francisco. Her group studies mammalian stem cell epigenetics and X chromosome inactivation. Their goal is to understand how chromatin regulatory proteins, post-translational modifications, and non-coding RNAs are used to regulate gene expression.

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