Genetic and epigenetic control of the spatial organization of the genome

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ABSTRACT Eukaryotic genomes are spatially organized within the nucleus by chromosome folding, interchromosomal contacts, and interaction with nuclear structures. This spatial organization is observed in diverse organisms and both reflects and contributes to gene expression and differentiation. This leads to the notion that the arrangement of the genome within the nucleus has been shaped and conserved through evolutionary processes and likely plays an adaptive function. Both DNA-binding proteins and changes in chromatin structure influence the positioning of genes and larger domains within the nucleus. This suggests that the spatial organization of the genome can be genetically encoded by binding sites for DNA-binding proteins and can also involve changes in chromatin structure, potentially through nongenetic mechanisms. Here I briefly discuss the results that support these ideas and their implications for how genomes encode spatial organization.

SPATIAL ORGANIZATION OF EUKARYOTIC GENOMES
Spatial organization, from organisms to molecules, is a defining feature of life. In multicellular organisms, cells are organized into tissues that are spatially segregated from each other. Cells serve to concentrate and organize biological activities, facilitating metabolism, growth, and division. In eukaryotic cells, membrane-bounded organelles compartmentalize biochemical reactions, permitting greater efficiency and control. Biochemical activities can also be concentrated and regulated through the formation of non-membrane-bounded, phase-separated liquid droplets such as P bodies, germ granules, nucleoli, and others (Courchaine et al., 2016).

Not only is the eukaryotic nucleus segregated from the cytoplasm, but it is also spatially organized within. It has long been appreciated that chromosomes are nonrandomly arranged (Rabl, 1885; Boveri, 1909). During mitosis, chromosome condensation and alignment are critical to facilitate proper segregation (Hirano, 1993; Gotta et al., 1993). The position of chromosomes with respect to nuclear landmarks such as the nuclear periphery reflects their interaction with stable subnuclear structures. Depending on the cell type, a varying but significant fraction of metazoan genomes is associated with the nuclear lamina. These lamina-associated-domains (LADs), up to 10 Mb in length, localize at the nuclear periphery (Figure 1A; Vogel et al., 2001; Taddei et al., 2001; Zimmer and Fabre, 2011). In differentiated cells, chromosomes tend to fold and occupy distinct, mostly nonoverlapping “territories” (Cremer et al., 2006; Cremer and Cremer, 2010). The position of chromosomes within the nucleus also correlates with cell type; gene-rich chromosomes that are more highly transcribed tend to be positioned toward the center of the nucleus, and gene-poor chromosomes tend to be positioned toward the nuclear periphery (Parada et al., 2004).

The arrangement of chromosomes with respect to nuclear landmarks such as the nuclear periphery reflects their interaction with stable subnuclear structures. Depending on the cell type, a varying but significant fraction of metazoan genomes is associated with the nuclear lamina. These lamina-associated-domains (LADs), up to 10 Mb in length, localize at the nuclear periphery (Figure 1A; Vogel et al., 2007; Guelen et al., 2008). Similarly, in budding yeast and fission yeast, telomeres and centromeres cluster together at opposite sides of the nucleus (Marshall et al., 1996; Heun et al., 2001; Taddei et al., 2010; Zimmer and Fabre, 2011). In differentiated cells, chromosomes tend to fold and occupy distinct, mostly nonoverlapping “territories” (Cremer et al., 2006; Cremer and Cremer, 2010). The position of chromosomes within the nucleus also correlates with cell type; gene-rich chromosomes that are more highly transcribed tend to be positioned toward the center of the nucleus, and gene-poor chromosomes tend to be positioned toward the nuclear periphery (Parada et al., 2004).

Individual genes are often nonrandomly positioned with respect to nuclear structures and with respect to each other and their position...
can change upon transcriptional activation or repression. Silenced loci within LADs localize at the nuclear periphery, but such loci are released from the lamina and move to a more internal site upon activation (Figure 1A; Kosak et al., 2002; Zink et al., 2004; Meister et al., 2010; Peric-Hupkes et al., 2010). Similarly, transcriptional induction can lead to a locus looping out from its chromosome territory (Figure 1B; Noordermeer et al., 2008). Heat shock genes reposition near stress granules upon induction (Khanna et al., 2014). Furthermore, in budding yeast, Drosophila, Caenorhabditis elegans, and mammalian cells, many active genes physically interact with nuclear pore proteins (Casolari et al., 2004, 2005; Brown et al., 2008; Capelson et al., 2010; Kalverda and Fornerod, 2010; Liang et al., 2013; Rohner et al., 2013). Whereas in yeast these interactions apparently occur exclusively at the nuclear periphery (with the nuclear pore complex [NPC]; Figure 1C), in flies and mammals, these interactions can occur either at the nuclear periphery or in the nucleoplasm (with soluble nuclear pore proteins; Capelson et al., 2010; Kalverda et al., 2010; Liang et al., 2013; Light et al., 2013). Interaction with the NPC leads to positioning at the nuclear periphery (Figure 1C). Thus changes in gene expression are frequently coupled to movement of loci with respect to nuclear landmarks.

Coregulated genes sometimes cluster together through interchromosomal interactions (Figure 1, B and D). Clustering has been observed between genes induced during erythropoiesis (Brown et al., 2006; Schoenfelder et al., 2010), genes induced by estrogen (Lin et al., 2009), and genes induced by infection (Apostolou and Thanos, 2008). In yeasts, both tRNA genes and genes that are targeted to the NPC undergo interchromosomal clustering (Figure 1D; chromosome territories (Cook and Marenduzzo, 2009; Heermann, 2011; Wang et al., 2015). Similarly, subnuclear structures are not stable landmarks but are built around the genes with which they colocalize. For example, nucleoli and histone locus bodies colocalize with the ribosomal DNA and histone genes, respectively. However, such bodies can be initiated to form at an ectopic locus by tethering nucleating factors to that site (Karpen et al., 1988; Kaiser et al., 2008; Mao et al., 2011; Shevtsov and Dundr, 2011). This type of spatial organization, although specific to particular genes and giving rise to a highly biased pattern, reflects an emergent property of certain genes rather than active positioning of genes near nuclear bodies. Distinguishing between nonrandom arrangements that are produced by active targeting mechanisms and those that are produced by emergent phenomena is critical to understanding nuclear architecture.

Here I focus on cases in which the nonrandom positioning of genes and chromosomal domains appears to be conferred by active targeting mechanisms. To define active mechanisms, I draw on the lessons from protein targeting to membrane-bound organelles. Active mechanisms that control subnuclear positioning ought to exhibit specificity and depend on information that is necessary and/or sufficient to promote targeting to stable sites.

**DNA-BINDING PROTEINS AND CHROMATIN MODIFICATIONS AFFECT THE SPATIAL ORGANIZATION OF THE GENOME**

If spatial organization of the genome is controlled by active mechanisms, then what is the source of the information? Is spatial organization encoded by the DNA sequence, chromatin changes
FIGURE 2: Transcription factors and chromatin function to control interactions with the nuclear periphery. (A) Targeting of genes to the nuclear lamina requires both transcription factors such as c-Krox and YY1 and methylation of histone H3 on lysine 9 (red circles). In C. elegans, this involves a nuclear envelope–localized protein called CEC-4 that binds to this mark. (B) Targeting to the NPC (or interaction with nuclear pore proteins in the nucleolus of Drosophila or mammals) requires transcription factors and, in some cases, chromatin changes. Several yeast transcription factors are both necessary and sufficient to cause targeting to the NPC. However, histone acetylation, H3K4 methylation (green circles), and H2A.Z incorporation (green nucleosomes) are also required in certain cases.

In budding yeast, transcription factor–binding sites have been functionally identified as both necessary and sufficient to target genes to the nuclear periphery (Ahmed et al., 2010; Light et al., 2010; Brickner et al., 2012, 2016; D’Urso et al., 2016; Randise-Hinchliff et al., 2016). Not every yeast transcription factor has this ability, suggesting that a subset of transcription factors affects gene positioning. Five transcription factors have been identified (Put3, Cbf1, Gcn4, Ste12, and Sfl1) that are both necessary for targeting endogenous loci to the periphery and whose binding sites function as “DNA zip codes” that are sufficient to target an ectopic site to the periphery (Figure 2B). In several of these cases (Gcn4, Ste12, and Sfl1), the transcription factors cause peripheral targeting when tethered to an ectopic site through a heterologous DNA-binding domain, confirming that they are indeed sufficient to confer positioning at the periphery (D’Urso et al., 2016; Randise-Hinchliff et al., 2016). This suggests that controlling gene positioning is an under-appreciated function of some transcription factors (Figure 2B).

Transcription factors and their binding sites also control interchromosomal clustering of coregulated genes. Before differentiation of T helper cells, the interferon γ gene clusters with a locus control region (LCR) on another chromosome, and this is regulated by the Drosophila–hypersensitive region of the LCR (Spilianakis et al., 2005). Clustering of the Interferon β gene with sites on other chromosomes in response to virus infection requires the NF-kB transcription factor (Apostolou and Thanos, 2008). Clustering of coregulated genes during erythropoiesis requires the Klf1 transcription factor (Schoenfelder et al., 2010), and clustering of bacterial artificial chromosomes carrying the HSP70 gene near nuclear speckles requires the HSF70 promoter (Hu et al., 2010). Similarly, clustering of tRNA genes in both budding yeast and fission yeast requires the sequence-specific transcription factor TFIIIC (Noma et al., 2006; Haeusler et al., 2008). In budding yeast, transcription factors that control positioning to the nuclear periphery are also necessary for specific interchromosomal clustering in association with the nuclear pore (Brickner et al., 2012, 2015; Randise-Hinchliff et al., 2016). Of
importance, insertion of their DNA-binding sites at an ectopic site in the genome can promote clustering with endogenous genes that possess the same binding site (Brickner et al., 2012, 2016; Randise-Hinchliff et al., 2016). This suggests that genomes encode both peripheral localization and interchromosomal clustering through cis-acting DNA elements such as transcription factor-binding sites.

Chromatin
Chromatin modifications often correlate with spatial position and, in some cases, are required for the normal spatial arrangement of the genome. Subtelomeric regions are silenced by the yeast histone deacetylase Sir2. Histone deacetylation recruits Sir4, which binds to both hypoacetylated histones and the nuclear envelope membrane protein Esc1, providing a physical link between chromatin state and a subnuclear structure (Taddei and Gasser, 2012). Lamina-associated domains tend to be transcriptionally repressed and methylated on histone H3 lysine 9 (Guelen et al., 2008; Wen et al., 2009; Yokochi et al., 2009; Kind et al., 2013). Loss of the H3K9 methyltransferase G9a leads to loss of peripheral H3K9me2 but does not obviously alter the peripheral localization of all genes (Yokochi et al., 2009). However, association of lamina-targeted BACs or endogenous LADs in human cells or lamina-associated repetitive arrays in C. elegans is dependent on H3K9 methylation (Towbin et al., 2012; Gonzalez-Sandoval et al., 2015). Thus, together with the transcription factors mentioned earlier, H3K9 methylation is required for the interaction with certain loci with the nuclear periphery (Figure 2A).

In C. elegans, H3K9 methylation may function alone in targeting to the lamina. The system in which this requirement was discovered used long arrays of transgenes (Meister et al., 2010). The H3K9 methylation of these arrays is apparently a nonspecific product of their repetitive nature. Targeting to the nuclear lamina and H3K9 methylation are mutually reinforcing events: H3K9 methylation is both promoted by targeting to the nuclear lamina and required for targeting to the lamina. A nuclear envelope–associated protein called CEC-4 binds to methylated H3K9 through a chromodomain to mediate localization of heterochromatin repetitive arrays to the nuclear lamina (Gonzalez-Sandoval et al., 2015). This suggests that H3K9 methylation alone can target such arrays to the nuclear lamina, independent of their sequence and presumably independent of DNA-binding proteins.

The intrachromosomal looping and clustering of Polycomb targets leads to formation of Polycomb bodies. This requires the Polycomb group protein PC (Lanzuolo et al., 2007). However, mutations that disrupt Polycomb response elements, which reduce recruitment of Polycomb group proteins, do not strongly affect either H3K27me3 or Polycomb body formation. This suggests that H3K27 methylation, rather than a DNA-binding protein, may facilitate the formation of Polycomb bodies.

Targeting of certain yeast genes to the NPC requires the SAGA histone acetyltransferase and is inhibited by the Rpd3(L) histone deacetylase (Cabal et al., 2006; Luthra et al., 2007; Randise-Hinchliff et al., 2016). Furthermore, targeting of yeast INO1 to the nuclear periphery after repression (a phenomenon called epigenetic transcriptional memory) requires both local incorporation of H2A.Z and dimethylation of H3K4 (Brickner et al., 2007; Light et al., 2010, 2013). Therefore chromatin modifications also play essential roles in targeting to the nuclear pore complex (Figure 2B).

In addition to active and poised genes, the NPC in budding yeast and Drosophila also interacts with persistent double-strand breaks, eroded telomeres, and collapsed replication forks, and this interaction facilitates DNA repair (Nagai et al., 2008; Kalocsay et al., 2009; Ryu et al., 2015). Relocalization of DSBs to the NPC requires both H2A.Z and SUMOylation of either chromatin or repair factors, leading to a physical interaction with the SUMO-dependent ubiquitin ligase Siks/Siks8, which interacts with the NPC component Nup84 (Nagai et al., 2008; Kalocsay et al., 2009; Churikov et al., 2016; Hongome et al., 2016). Thus positioning of DNA damage, which is unlikely to be dependent on DNA sequence, is mediated by changes in chromatin and associated proteins.

Coordinating the function of DNA-binding proteins and chromatin
Because transcription factors and chromatin changes influence each other and can have indirect effects, in most cases, it remains to be determined whether either of these mechanisms alone is sufficient to confer spatial positioning. Furthermore, the function of transcription factors themselves might be regulated by posttranslational modifications such as acetylation and SUMOylation (Texari et al., 2013). In cases in which both DNA-binding proteins and chromatin modifications play essential roles in controlling the spatial organization of the genome (i.e., neither is sufficient), they might function in the same linear pathway or by a combinatorial mechanism.

The requirement for histone acetylation or methylation in targeting genes to the NPC (Figure 2B) may represent either a direct role for chromatin in mediating targeting to the NPC or a role for chromatin in regulating transcription factor binding/function. In support of this idea, Rpd3(L) regulates Pu3 DNA binding, and SAGA is required for targeting of certain genes to the periphery because histone acetylation promotes binding of transcription factors. In support of this idea, SAGA is required for peripheral targeting of genes whose subnuclear localization is regulated by transcription factor occupancy but is not required for peripheral targeting of genes whose subnuclear localization is regulated downstream of transcription factor occupancy (Randise-Hinchliff et al., 2016). This suggests that histone acetylation (or other functions of SAGA) may regulate transcription factor occupancy by regulating either DNA binding or transcription factor abundance.

The histone modifications associated with transcriptional memory are necessary but not sufficient to confer targeting to the nuclear periphery. Mutants lacking H2A.Z or unable to methylate H3K4 fail to target genes to the NPC during memory (Brickner et al., 2007; Light et al., 2010, 2013). However, neither H2A.Z nor H3K4me2 is sufficient to cause targeting to the NPC (Light et al., 2010; D’Urso et al., 2016). This suggests that targeting to the NPC requires both a transcription factor and the correct chromatin state and that they may function together (Figure 2B). Future work will distinguish a direct role for chromatin in affecting gene positioning in this system from a regulatory role.

CONCLUSION

Nuclear cell biology is an important and challenging area. Future work will seek to develop a more complete understanding of the molecular and evolutionary mechanisms that control the spatial organization of the genome. To make progress, we must first address two important issues. First, we must distinguish spatial organization that is a product of emergent properties of nuclear biology from spatial organization that is the product of active mechanisms. Both types of phenomena contribute to the spatial organization of the genome, and they need to be integrated to understand the whole. Second, we must carefully define the relationship between DNA-binding proteins and chromatin changes in determining spatial organization. Subnuclear positioning of genes and domains is controlled by DNA-binding proteins, chromatin structure, and, in some cases, both. This suggests that both DNA sequence–dependent
and DNA sequence–independent mechanisms affect the spatial organization of the genome. Understanding the evolutionary processes that can select for such mechanisms poses an exciting and important problem for future work.

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