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Nuclear Location and the Control of Developmental Progression

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Abstract

It is now well established that the mammalian genome is highly organized. Chromosomes are structured as territories that only sporadically intermingle. Chromosome territories themselves are segregated into distinct environments, i.e. the transcriptionally inert/repressive (heterochromatic) and permissive (euchromatic) compartments. The transcriptionally permissive compartment is organized into domains (~0.5–3Mb) that consist of bundles of loops, are gene-rich and closely associated by activating epigenetic marks. During ontogeny and developmental progression chromatin states are highly dynamic. Recent studies have shown that loci and domains readily switch compartments. Switching nuclear neighborhoods is closely associated with changes in transcriptional activity and extensive chromatin reorganization. Here we discuss the implications of a dynamic genome and how it relates to the control of developmental progression.

Introduction

The unit of the chromatin fiber is the nucleosome. The nucleosome contains a 146 bp DNA stretch that is folded around an octamer of histones, named H2A, H2B, H3 and H4. The nucleosomes themselves are packaged as a 10 nm fiber. The 10 nm fiber, in the presence of histone H1, folds into the 30 nm fiber [1]. How the chromatin fiber is structurally organized beyond the 30 nm fiber remains largely unknown. Cytological approaches to study the organization of chromosomes have shown a confined geometry as demonstrated by the presence of chromosome arms and bands. These initial observations were followed by studies demonstrating distinct folding patterns that underpin chromosome topology. These studies suggested elaborate patterns of helical and radial configurations as well as rosette-like structures as units that underpin large-scale chromosome organization [2–5].

These very early studies suggested a highly organized chromatin structure and excluded the possibility that the genome can be described in terms of simple random walk statistics. Indeed, subsequent fluorescence hybridization studies combined with spatial distance measurements showed that spatial distances scale as a function of genomic separation with exponents that do not agree with those expected for free random walk behaviour [6–9]. Hence new models were developed to describe long-range chromatin topology. Prominent among these are the Random Walk/Giant Loop, the Multi-Loop-Subcompartment and the Random Loop Models. The Random Walk/Giant Loop model (RW/GL) implies that the genome undergoes free random walk behaviour but is confined by the presence of large

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loops (2–5Mbp) [8]. An alternative configuration for long-range chromatin topology involves the Multi-Loop-Subcompartment Model (MLS) [9]. The MLS model suggests that the chromatin fiber is comprised of ~1 Mbp compartments folded into rosettes that are connected by flexible linkers. Yet another topology, the Random-Loop (RL) model describes the folding principles of the genomes in terms of both large and small loops that dynamically associate and dissociate from loop attachment points [10].

Subsequently, experimentally derived spatial distance measurements were compared to simulated structures, leading to predictions as to how the genome might be folded in three-dimensional space. For example, spatial distances plotted as a function of genomic separation across the immunoglobulin heavy chain locus, agreed well with simulated measurements that assumed for the MLS but not the RW/GL topology [9,11]. 5C chromosome-capture studies have provided further support for a MLS topology [12]. Recent genome-wide studies have also indicated that transcriptionally active regions of the genome are organized into domains that are gene rich, are highly enriched for nascent transcripts and epigenetic marks consistent with that of a transcriptionally active environment, contain clusters of CTCF binding sites and are enriched for SINE elements [13–16]. The large majority of compartment size varies between 0.5 and 3 Mb, consistent with that experimentally observed for the immunoglobulin heavy chain locus and predicted by the MLS model [9,11,16,17]. Thus, overall these previous studies point to a genome in which the chromatin fiber is organized as alternating domains at Mb scales containing clusters of loops anchored, at least in part, by CTCF.

Compartmentalization of the genome

More than a century ago it was suggested that each chromosome folds into distinct nuclear terrains, named chromosome territories [18,19]. This proposal was initially abandoned but recently resurrected and verified [20,21]. Chromosome territories, in turn, are organized into distinct compartments that are comprised of transcriptionally permissive or inert/repressive environments, frequently referred to as euchromatic and heterochromatic chromatin. These compartments differ extensively from each other in terms of epigenetic marks deposited across histones, linker histones as well as non-histone proteins [22]. Specifically, the euchromatic compartment is characterized by deposition of H3K4me1, H3K4me2, H3K4me3, H3K36me3 as well as acetylated histones. In contrast, the heterochromatic compartment is closely associated with H3K9me3. Deposition of H3K9me3 occurs in nuclear bodies that also highly enriched for Heterochromatin protein 1 (HP-1) [23]. Heterochromatin enriched for both H3K9me3 and H3K27me3 associates with a network of interacting intermediate filaments and factors, commonly referred to as the nuclear lamina. Previous studies have provided insight as to how heterochromatic DNA associates with the nuclear lamina. Specifically, BAF (barrier to autointegration factor), has been shown to interact with histones and with lamin-interacting proteins including LAP2, Emerin and MAN1 [22]. HP-1 also interacts with the nuclear lamina by associating with the Lamin B receptor [24]. Two recent studies have demonstrated that methylation of H3K9 is critical to locate the heterochromatic compartment at the nuclear lamina [25,26].

Recent global studies have permitted the assignment of individual genes to either the euchromatic or heterochromatic neighborhoods. Most prominent among these are DNA methylation and formaldehyde cross-linking (Hi-C) approaches. The DamID approach has employed fusion proteins consisting of Lamin B or Emerin as the *E. coli* DNA adenine methyltransferase (Dam) to promote adenine methylation of DNA elements that are in close spatial proximity of the nuclear lamina. These studies revealed domains that are of similar size as that described for euchromatic domains [27]. Genome-wide formaldehyde cross-linking approaches have complemented these studies. Specifically, Hi-C analysis has

demonstrated that the genome of vertebrates is segregated into transcriptionally permissive and repressive compartments. Active domains were shown to interact with other active regions to form the euchromatic compartment whereas inactive domains primarily associate with other inactive regions to generate the heterochromatic neighbourhood. Within active compartments, genes cluster through promoter-promoter interactions and are actively transcribed in coordinate fashion to establish transcription factories that contain agglomerations of RNA polymerase II as well as other components of the transcriptional machinery. Largely these data are also compatible with transcription factories, resembling replication factories, in which genes are assembled into compartments that contain clusters of RNA polymerase II [15,28–30].

Switching Nuclear Neighborhoods

As described above the nucleus can be segregated into transcriptionally repressive (heterochromatin) and transcriptionally active (euchromatin) compartments. It is generally accepted that active transcription is primarily associated with the euchromatic and not with the heterochromatic compartment. The spatial redistribution of genes to specific nuclear structures has important consequences for the control of gene expression and numerous studies have indicated links between gene positioning and gene expression [31]. For example, β -globin gene expression is initiated at the nuclear membrane [32]. However, upon relocating to centrally localized regions of the nucleus, transcription rates are accelerated [32]. Immunoglobulin loci relocate during developmental progression. Upon maturation from progenitors into committed B cells, the *Igh* locus repositions away from the nuclear lamina [33–36]. Upon productive rearrangement the *Igh* locus repositions to the heterochromatic chromatin [37]. At the pre-B cell stage, the *Ig κ* alleles are segregated with one of the alleles located within the heterochromatic environment whereas the other allele is associated with the transcriptionally permissive environment to favor mono-allelic rearrangement [38]. These data have raised the question as to how widespread changes in nuclear location accompany developmental progression. Recent studies have provided insight into this question. During embryonic stem cell differentiation nuclear-lamina associating regions were shown to change nuclear neighborhoods [39]. Similarly, upon commitment to the B cell fate an ensemble of genes was identified that switched nuclear location [16]. Finally, during *C.elegans* ontogenesis genes that are developmentally regulated associate with the nuclear lamina in cell types where they are silenced but they dissociate in lineages where they are expressed [40].

Factors involved in chromatin topology and organization

What causes chromatin domains to organize and what mediates the interaction between chromatin domains at a global scale? To address these questions, high-coverage Hi-C data were compared to transcription factor occupancy. CTCF, which has been shown to act as insulator as well as architectural factor, was found to be localized at the boundaries and the interiors of chromatin domains [14,16,17,41]. When the endpoints of intra- and inter-domain genomic interactions were compared to CTCF and lineage-specific transcription factor occupancy, two distinct sets of genomic interactions were observed. CTCF occupancy was mostly enriched at the endpoints of intra-domain genomic interactions while lineage-specific transcription factors were enriched at the endpoints of both inter- and intra-domain genomic interactions [16]. These observations raise the possibility that CTCF and lineage-specific transcription factors are the central players to establish chromatin topology and organization. Further experimentation will be required to show how these factors influence the chromatin topology and organization at a global scale as well as at the single cell level.

Conclusion

How does relocating genes relate to patterns of gene expression? Conflicting results have been reported. Positioning of a reporter locus at the nuclear lamina showed significant silencing, whereas other studies using similar approaches did not observe significant changes in patterns of gene expression [42,43]. Global studies have provided mechanistic explanations for these apparent contradictions. Specifically, it was shown that genes that reposition from the repressive to permissive compartment either become transcriptionally active or continue to be silenced by deposition of H3K27me3 [16]. Thus, not the entire spectrum of genes that switch nuclear neighborhoods modulate patterns of gene expression (Figure 1).

Why do genes reposition within the nucleus? Recent global studies have provided insight into this question. Specifically, it was shown that the repositioning of genes is frequently associated with the activation or silencing of gene expression. Prominent among genes that switched nuclear location were key developmental regulators, such as *EBF1* for B cell differentiation and *Bcl11b* for T cell differentiation [16,44–46]. We are now faced with the question as to why genes, encoding for key regulators such as *Ebf1* and *Bcl11b*, are transcriptionally repressed in the transcriptionally inert compartment and not simply silenced by deposition of H3K27me3 in the transcriptionally permissive compartment? We propose that transcriptionally repressive compartments may not lead to the aberrant activation of gene expression since the entire neighborhood is silenced whereas silencing by H3K27me3 in the transcriptionally permissive compartment may readily lead to activation of gene expression by aberrant looping involving enhancers located in close spatial proximity. Efficient silencing might be relevant for genes encoding key regulators such as *Ebf1* and *Bcl11b* since inappropriate activation of such genes may readily lead to premature differentiation in multipotent progenitors. This might be particularly important for genes encoding for proteins with key regulatory responsibilities. Thus, premature stochastic activation of genes encoding critical regulators by active genes located within close spatial proximity may need to be avoided at all cost and we suggest that nuclear positioning in the heterochromatic compartment is a key mechanism to enforce multipotency.

An important question that will need to be addressed is whether the modulation of gene expression of key developmental regulators by nuclear location is a general principle. Are transcriptional regulators that modulate other developmental pathways also positioned in a repressive chromatin environment prior to specification and lineage commitment? Finally, the critical question is how the sequestration of developmental regulators is controlled. Intriguing studies have demonstrated that ThPok acts to recruit the *Igh* locus to the nuclear lamina [47]. Is ThPok also involved in sequestering *Ebf1* or *Bcl11b* to the nuclear lamina? Or perhaps are ncRNAs involved [48]? It seems likely that different loci will be positioned to distinct compartments by different tethers and it will be particularly important to identify the spectrum of tethers, how they act and how they are regulated.

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Figure 1.

Changes in the nuclear location of loci and genomic interactions within and between chromatin domains in developing B-lineage cells. Indicated are the changes in nuclear location of genes associated with the pre-pro-B to the pro-B cell transition. Specifically, at the multipotent cell stage, the *Ebf1* and *IgK* loci are located at the heterochromatic compartment and sequestered to the nuclear lamina. Upon B cell commitment, both loci dissociate away from the nuclear lamina and relocate to the transcriptionally permissive environment to associate with transcription factories. Such inter-domain interactions are mediated by lineage-specific transcription factors.