Editorial overviews: Emerging Perspectives in Genome Architecture and Gene Regulation

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Abstract

This issue brings together a collection of studies delving into the complex architecture and dynamic regulation of 3D genome structure. The articles explore diverse aspects of chromatin organization, from the early establishment of topologically associating domains (TADs) during zygotic genome activation to the mechanics of chromatin in interphase nuclei. Highlighted topics include the the mechanisms and functions of loop extrusion, the key molecular players that fold the genome in 3D, the regulation of enhancer-promoter interactions, and novel insights into nuclear subcompartments driven by RNA and intrinsically disordered protein regions. Collectively, these manuscripts shed light on the interplay between genome structure and transcriptional regulation, offering new perspectives on how chromatin organization influences gene expression in both normal development and disease states.

While the DNA sequence of the genome is one-dimensional, it has become clear that to understand the function of the genome, it is necessary to understand the three-dimensional (3D) spatial structure of the genome. Traditional ensemble sequencing approaches have provided a foundational framework for understanding how the 3D structure of genomes influences transcription, replication, or recombination. Recent advances in several fronts,

including imaging, sequencing, structural biology, and gene editing, are now rapidly reshaping the field. Reviews in this issue integrate these methodologies to address long-standing questions about genome organization, gene regulation, and nuclear organization and mechanics, offering new perspectives that challenge classical models.

Understanding how chromatin behaves as a physical material is crucial to deciphering genome organization. The article of **Antoine Coulon** explores how chromatin responds to mechanical stimuli, showing that it is not merely a passive substrate but an active entity whose stiffness and tension influence genome folding and enhancer-promoter communication [1]. **Qi et al.** discuss how cohesin-mediated loop extrusion governs chromatin architecture, presenting a refined inchworm model that explains how ATP hydrolysis modulates chromatin loops and TAD formation [2]. **Rutkauskas and Kim** expand upon the above review focusing on cohesin by reviewing loop extrusion by SMC complexes in general, which include cohesin, condensin, SMC5/6, and MukBEF[3]. They compare and contrast loop extrusion mechanisms across the different complexes.

These insights emphasize that chromatin organization is not static but dynamically controlled by mechanical forces and protein complexes. The folding of the genome into loop domains and Topologically Associating Domains (TADs) is controlled by CTCF and cohesin, but CTCF also has other roles. **Corin et al.** discuss the other cohesin-independent roles of CTCF which include direct transcriptional factor function, DNA replication, DNA repair, and local nucleosome positioning [4]. This is further complemented by the review of **Do and Skok**, which discusses how cell-type specific DNA binding of CTCF is regulated. In addition, they focus on sequence motifs, chromatin accessibility, and co-factors that together regulate the binding of CTCF in health and disease [5]. **Amodeo** discuss the 3D genome determinants of cancer including aneuploidy, extra chromosomal DNA, translocations, copy-number alterations and other mechanisms and place these mechanisms in the context of the hallmarks of cancer [6].

Transcription is not constant, but known to occur in sporadic bursts. **Fountas and Lentra** discuss how the exchange dynamics of transcription factors and co-factors affect the dynamics of transcriptional bursting, with a focus on cooperativity and kinetics [7]. **Fillot and Mazza** add to this with a focus on how chromatin accessibility is regulated, the double-edged interplay with transcription factors which are both sensitive to accessibility and regulators of accessibility, as well as recent insights from single-molecule

tracking methods[8]. **Miao and Chong** further discuss transcription factors with a focus on their intrinsically disordered regions (IDR) in regulating protein interactions and transcription [9]. They discuss the importance of balance, and argue that optimal levels of multivalent IDR-IDR interactions are required for effective transcription.

Transcriptional control must integrate molecular events at enhancers with global gene expression patterns across developmental and tissue contexts. **Cardona et al.** provide a multiscale view of transcriptional regulation, employing polymer physics models to explain how chromatin structure influences transcriptional bursting and enhancer-promoter dynamics [10]. **Kittle and Levo** revisit the debate over whether physical proximity is required for transcriptional activation, arguing that enhancer-promoter contacts are transient and probabilistic rather than deterministic drivers of gene expression [11]. Moreover, **Bower and Kvon** discuss which protein factors are especially important for regulating medium ($50 - 400$kb) and long-range (> 400kb) enhancer-promoter interactions, with a focus on LIM-domain homeobox transcription factors [12]. Together, these perspectives describe complementary concepts that need to be considered to understand how transcriptional activity emerges from dynamic chromatin interactions.

Gene regulation extends beyond local promoter-enhancer interactions, requiring mechanisms that enable long-range communication within and between TADs. **Zunjarrao and Gambetta** describe how tethering elements, Polycomb loops, and enhancer hubs facilitate long-range gene regulation, revealing similarities between flies and mammals [13]. **Benjamin Prud'homme** examines how homologous chromosomes engage in transvection, a phenomenon in which alleles interact *in trans* to fine-tune gene expression [14]. These studies challenge the conventional view that regulatory interactions are limited by genomic distance, instead suggesting that nuclear organization creates functional hubs that coordinate gene expression over large genomic scales.

Beyond DNA-protein interactions, RNA molecules have emerged as key regulators of nuclear architecture, particularly through their roles in biomolecular condensates. **Muzzopappa and Erdel** highlight how RNA-driven phase separation organizes transcription factories and heterochromatin domains [15]. They propose that RNAs not only scaffold nuclear condensates but actively regulate their formation and dissolution, positioning RNA as an architect of genome organization rather than a passive byproduct of transcription.

The earliest stages of embryonic development require extensive reorga-

nization of the genome, including coordinated changes in transcription and translation. **Maillard et al.** explore this interplay during ZGA, highlighting how transcriptional bursting and translational control jointly ensure proper developmental progression [16]. Their review emphasizes the multiple regulatory layers that fine-tune gene expression in early embryos. **Bondarieva and Tachibana** review how loop extrusion and TAD formation contribute to zygotic genome activation (ZGA) in mammals, discussing whether chromatin topology is a prerequisite for transcriptional activation or a consequence of it [17]. Their synthesis highlights species-specific differences in genome folding and provides a framework for investigating how nuclear organization influences developmental trajectories. Next, **Tan et al.** discuss the fascinating case of singular olfactory receptor choice, where each mouse olfactory sensory neuron randomly chooses one and only one of the > 2000 possible olfactory receptor genes to express and how 3D genome structure reorganization is crucial for singular olfactory receptor choice[18].

Finally, machine learning models are playing an increasingly important role in predicting 3D genome folding from DNA sequence and epigomics, as well as for performing "computational experiments". **Smaruj et al.** discuss the latest developments in the field, practical considerations, as well as challenges and opportunities going forward [19].

Together, these contributions redefine our understanding of genome architecture, transcriptional regulation, and nuclear organization. They highlight how chromatin folding, mechanical forces, and long-range interactions orchestrate gene expression at multiple levels. By integrating perspectives from chromatin physics, molecular genetics, and developmental biology, this issue offers new directions for future research, bridging mechanistic insights with broader biological functions.

Declaration of Competing Interest

The authors declare no conflict of interest.

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