Journal of Stem Cell Research and Transplantation

Austin Publishing Group

Open Access Full Text Article

Editorial

High Resolution Mapping of 3D Chromatin Architecture in Embryonic Stem Cells

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Received: June 27, 2014; **Accepted:** June 02, 2014; **Published:** July 03, 2014

Keywords

3D chromatin; Genome; Long-range interactions; Embryonic stem cells

The Encyclopedia of DNA Elements (ENCODE) project hasgenerated a wealth of genomic information for identifying epigenetic modifications, transcription factor binding sites, non-coding RNA, and regulatory SNPs associated with diseases [1]. These discoveries were made possible due to the development of high-throughput DNA sequencing technologies and advanced computational tools for encrypting the complex eukaryotic genomes [2,3]. An increasing amount of evidence indicates that the genome organization is non-random and specific to cell type, developmental stage, or a disease status. Therefore, the chromosome folding principles and the mechanisms responsible for establishment, maintenance and alterations of the three dimensional (3D) chromatin, and the functional consequences of aberrant genome and nuclear topology have become areas of intense studies. New evidence indicates that the mammalian genome is composed of a hierarchy of long-distance genomic interactions, from chromatin loops that connect genes and enhancers to large-scale topology domains and chromosome compartments [3-7].

Topology activation domains (TADs) are large chromatin interaction compartments that contain the genomic regions constraining the spread of hetero chromatin [8]. Moreover, TAD sarestable across different cell types and highly conserved across species. The TAD boundaries are enriched for the insulator binding protein CTCF, housekeeping genes, transfer RNAs and short interspersed element (SINE) retrotransposons.

There are compelling data showing that remote chromatin interactions undergo dynamic reorganization at the sub-mega base scale during differentiation of embryonic stem cells (ESCs) [9]. The widespread enrichment of architectural proteins CTCF, Mediator, and Cohesinat the chromatin interaction sites is a common feature of chromosome looping. The CTCF-Cohesin complex anchors distant-acting constitutive interactions that form the topological basis for invariant chromatin domains. Conversely, Mediator-Cohesin complex defines short-range interactions within larger genomic regions. Collectively, studies by Phillips-Cremins et al. [9] revealed that cell-type-specific chromatin organization occurs at the sub-mega base scale and that architectural proteins shape the genome in a hierarchical fashion.Although the boundary sequences between TADs are enriched for CTCF and Cohesin binding sites, each complex contributes differentially to chromatin organization and gene regulation [10].

Jin et al. [11] have suggested that the 3D chromatin landscape defined by long-range contacts once established in a particular cell type is relatively stable and could influence the selection or activation of target genes by a ubiquitous transcription activator in a cell-specific manner. Another interesting observation is that distant-acting interactions aggregate into higher-order clusters, wherein proximal and distal genes are engaged through promoter-promoter contacts [12]. Most genes are transcribed cooperatively via promoter-promoter interactions, and a subset of the promoter interacting nodes could influence combinatorial complexity of transcriptional control. On the other hand, the same study suggested significant enrichment of enhancer-promoter interactions for cell-type-specific functions. Analysis of the complex regulatory repertoire revealed extensive co-localization among promoters and distal-acting enhancers [13]. If enhancer-promoter interactions exhibit high cell-type specificity, promoter-promoter interactions are common and mostly active among different cell types. In ESCs, master reprogramming factors are transcribed within the physical proximity to each other, implicating the importance of 3D chromatin architecture for co-regulation of developmental genes.

Analysis of the molecular basis of pluripotency indicates that Mediator and Cohesin are responsible for almost half of chromatin interactions in ESCs [14]. A study by Wei et al. [15] revealed that KLF4 participates in assembly of Cohesin rings to establish the stem cell-specific chromatin interactome. Upon reprogramming of induced pluripotent stem cells to the pluripotency state, Cohesin initiates chromosomal looping prior to transcriptional activation of *Oct4.* Depletion of KLF4 disrupts Cohesin subunits from the *Oct4* enhancer leading to chromatin interaction disturbance simplicating KLF4 in the integrity of the pluripotent-specific 3D chromatin topology [15]. Depletion of the Cohesin subunit SMC1 also affects the stemness by disrupting long-range interactions [16]. In developing mouse limbs, SMC1 orchestrates tissue-specific chromatin connectivity across promoters and distal enhancer regions [17]. Collectively, these observations highlight the fundamental contribution of architectural proteins and master transcription factors in the dynamic organization of the genome.

A large body of evidence suggests that different cell types are

Citation: Bayarsaihan D. High Resolution Mapping of 3D Chromatin Architecture in Embryonic Stem Cells. J Stem Cell Res Transplant. 2014;1(1): 1002.

defined by a specific set of transcription factors, distinct DNase I hyper sensitive sites; CpG islands and histone marks associated with active chromatin [18]. The genomic regions of co-regulated genes are enriched with a common set of transcription factors, chromatin remodeling complexes and epigenetic modifications [19]. In human ESCs, a wide range of master regulators, including ATF3, CTCF, GABPA, JUND, NANOG, RAD21 and YY1, facilitate large-scale interactions at the *OCT4* and *SOX2* loci [20]. Interestingly, the spatial intra- and inter-chromosomal 3D interactions mediated by these factors are less specific at transcriptionally repressed regions [21]. The recently proposed 'dog-on-a-lead' model predicts that chromosomes behave in a dominant manner across the genomic loci or regulatory domains indicating the overall genomic topology rather than genes or enhancers can specify for preferred interaction partners [22]. Therefore, the transcription factor clustering in ESCs could contribute to the robustness of the pluripotent state by facilitating the efficiency of transcription of nearby genes.

The fast development of high-through put sequencing methods has opened an exciting opportunity to interrogate spatial–temporal chromatin dynamics during embryonic development and correlate the 3D genome with tissue-specific gene expression. In recent years, limb development has become a promising model for investigating 3D genome [23]. During mouse limb development, genes within the *HoxD*-cluster transcribe in two phases: early on, when the arm and forearm are specified, and later, when digits are formed. A transition from the early to late phases is controlled by molecular switch mechanisms sponsored by opposite TADs. The centrally clustered *HoxD*-genes are regulated by the telomerictopology domain, which is subsequently replaced by the centromeric TAD [24]. The segregation between the two types of *HoxD*-expressing cells leads to the formation of the wrist, an intermediate cellular territory of low HOX protein content.

In conclusion, the architectural proteins form efficient and robust gene regulatory networks linking master transcription factors and chromatin remodeling enzymes with epigenetic modification that are essential for cell lineage specification. Further development of genome-wide sequencing techniques would reveal many new regulatory associations that mediate chromatin topology and gene expression. The answer to how a complex biological system can arise from a fertilized egg is encoded in the genome [25] and therefore, the 3D chromatin organization makes an important contribution to genome function by promoting the spatial and temporal interactions within chromosome territories that are critical for establishing high-level control modules to coordinate cell-type-specific gene expression.

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J Stem Cell Res Transplant - Volume 1 Issue 1 - 2014
ISSN : 2381-9065 | www.austinpublishinggroup.com

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