



Editorial

## Chromatin Topology and Long-Range Genomic Interactions

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The ability to reprogram somatic cells to pluripotency provides both potential opportunities for regenerative medicine, as well as an intriguing model for studying cell reprogramming [1]. Although the generation of viable cloned mammals from adult cells is technically feasible, knowledge of such processes as chromatin reorganization, genome activation, and epigenetic modifications is necessary to gain a more thorough understanding of gene regulatory networks that govern nuclear programming. Chromatin architecture and genome wide interactions are not only altered during the transition from a somatic to a pluripotent state, but also play active, regulatory roles during differentiation and cell fate commitment [2,3].

The dynamics of chromatin reorganization during cellular differentiation and lineage specification is modulated by epigenetic factors, chromatin remodeling complexes and tissue-specific transcription factors (TFs) [4,5]. Histone modifications such as H3K4me3, H3K27ac and H3K36me3 maintain an open chromatin structure and facilitate transcription, while H3K9me3 and H3K27me3 histone marks are associated with a repressed chromatin state [4,5].

The ENCODE-generated data suggests that TFs preferentially bind to the consensus binding motif-enriched genomic regions suggesting that chromatin recognition is at least partly encrypted in the genome. However, the spatial topology of chromatin can have a profound impact on the TF binding preferences. According to the “permissive binding” model [6], TFs can discriminate an open chromatin structure lacking consensus motifs but marked by active histone modifications, whereas the genomic region without such marks does not allow permissive binding. Therefore, variability in the epigenetic landscape influences chromatin recognition by transcriptional regulatory complexes and can impact the expression of target genes in different cell types.

The presence of both active and repressive histone marks at promoters and enhancers of developmental genes helps to organize the bivalent chromatin conformation [4]. Bivalent chromatin contributes to genome-wide repression of developmental genes in pluripotent stem cells while keeping them poised for activation upon differentiation [4,5]. H3K4me1/K27me3 bivalency at histone 3 is an epigenetic signature of poised enhancers, whereas H3K4me1/H3K27ac is a hallmark feature of active enhancers [4]. The deposition

of bivalent marks is controlled by the enzymatic activities of Polycomb (PcG) and Trithorax (TrxG) group proteins [7].

A global increase of H3K27ac is accompanied by loss of H3K27me3 over the target genomic sites [4]. An epigenetic switch from methylation to acetylation at H3K27 catalyzed by p300 and CBP histone acetyltransferases correlates with the transcriptional activation of PcG-bound genes during mammalian embryonic stem cell (ESC) differentiation. The antagonistic activity of TrxG restricts the PRC2-mediated gene repression to keep a balance between ESC self-renewal and differentiation [4,5]. TrxG complex mediates H3K4me3 and H3K36me3 spreading across the transcriptionally active genomic regions. Ablation of either WDR5 or DPY-30, components of Trithorax complex, can lead to a significantly reduced expression of lineage-specific genes and decrease of H3K4me3 [4]. Thus, PcG and TrxG proteins are critical regulators of cellular homeostasis and embryonic development maintaining the expression of key tissue-specific genes in a spatiotemporal fashion.

Because PcG and TrxG play such a fundamental role in cell physiology, many different mechanisms have been evolving to anchor these regulatory complexes to discrete genomic loci. The recruitment of Polycomb to chromatin can be achieved via different molecular interactions.

- 1) JARID2, a member of Jumonji family, facilitates binding of PcG to chromatin to extend H3K27 trimethylation pattern [4,5].
- 2) CpG-islands support to establish and maintain the PcG-enriched chromatin domains [8]. A high density of unmethylated CpG dinucleotides is sufficient to initiate the PcG recruitment [9].
- 3) Short RNAs of approximately 50-200 nucleotides in length, transcribed from the 5' end of PRC2 target genes, can also mediate PcG binding [10].
- 4) Long non-coding RNAs could assist in actively recruiting PcG proteins by binding LSD1/Co-REST repressive complex or recognizing the GA-rich DNA segments [11,12].
- 5) Nucleosome density can also contribute to gene repression by PcG recruitment at polycomb response elements (PREs) [13].
- 6) The selective recognition of the *cis*-regulatory elements by TFs can mediate the recruitment of Polycomb complexes and ensure the repressed chromatin states across large genomic regions. For example, PcG binds to the YY1-enriched PREs that are largely devoid of nucleosomes [14]. REST/Snail complex can also facilitate the site-specific PcG binding [15,16].
- 7) Although polycomb-like protein PCL1 recognizes H3K36me3 modified nucleosomes, the co-occupancy mechanism is not well understood. However, it is established that PCL1 stabilizes PRC2 complex on bulk chromatin and mediates spreading of H3K27me3 across H3K36me3-enriched chromatin regions

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[17]. In mouse ESCs, co-occupancy of PLC1 with H3K36me3 and H3K27me3 leads to the repression of a subset of poised developmental genes.

- 8) Repetitive elements comprise over two-thirds of the human genome and recent studies revealed that REs play a central role in genome integrity, gene expression, and disease. Considerable evidence has been accumulated indicating that repetitive elements (REs) could contribute to the 3D chromatin organization associated with PcG binding [18].

Although PRC2 is the main Polycomb complex in mammalian cells, the other component of this group of proteins is PRC1 [7]. A prevalent model suggests that the PRC2-mediated H3K27 trimethylation targets PRC1 to chromatin. However, the PRC1 complex can interact with PREs through a PRC2-independent mechanism. For example, the recruitment of PRC1 to specific genomic locations can be achieved via interactions with Runx1 or KDM2b [19,20]. Histone demethylase KDM2b occupies unmethylated CpG islands and anchors a subset of PRC1 complexes to specific genomic loci in pluripotent stem cells [20].

Over the past few years there has been increased attention to the problem of establishing 3D nuclear architecture and the role of PcG proteins in long-range chromatin interactions mediated by chromosome folding. Given that the greatest portion of PRC2-mediated epigenetic modifications is located in genomic repeats, it was suggested that Polycomb proteins provide a structural scaffold for the 3D chromatin structure [18,21].

One of the main functions of PcG proteins is to maintain *Hox* genes in a repressed state. The spatial and temporal transcriptional control of *Hox* genes is essential for patterning the vertebrate anterior-posterior (A-P) body axis [22]. The sequential collinear activity of *Hox* genes along the A-P axis conserved throughout the animal kingdom is based on their relative position in the genome. Recent studies by Duboule and colleagues using mouse embryonic tissues revealed that spatial compartmentalization of *Hox* clusters may be key to the underlying molecular mechanisms of the collinear gene activation [23]. 3D re-organization of *Hox* genes is followed by dynamic changes in histone modifications [24]. While the transcriptionally inactive *Hox* cluster is organized into a single 3D conformation, activated *Hox* genes switch to a bimodal 3D organization where newly activated genes progressively cluster into a transcriptionally active compartment. Thus, this transition in spatial configuration coincides with the epigenetic switch from a negative to a positive transcription state.

In addition to the vertebrate A-P axis regulation, a late phase activation of *Hox* genes is crucial for the patterning and growth of distal structures across the A-P axis of a budding limb. Two levels of chromatin topology define the limb *HoxD* activity; a loss of H3K27me3 marks initiates the formation of an open genomic domain spanning the *HoxD* cluster in the distal posterior limb while the anterior part still retains a repressed chromatin state [25]. Epigenetic imbalance is accompanied by the change in 3D organization mediated by long-range chromatin interactions at the 5' *HoxD* genomic region specifically in the distal posterior limb. The formation of a chromatin loop between *HoxD* loci and the remote enhancer region is consistent with the time of distal limb bud development. Interestingly, a study by DeMare and colleagues [3] highlights the role of cohesin-associated interactions in the 3D organization during the limb development.

In summary, high-order chromatin organization plays a crucial role in the development of embryonic structures. Nuclear remodeling depends on long-range communications, which are mediated by a specific set of nuclear factors and structural protein complexes, and therefore set the stage for future research addressing fundamental questions of chromatin biology.

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#### References

- Cherry AB, Daley GQ (2013) Reprogrammed cells for disease modeling and regenerative medicine. *Annu Rev Med* 64: 277-290.
- Apostolou E, Ferrari F, Walsh RM, Bar-Nur O, Stadtfeld M, et al. (2013) Genome-wide Chromatin Interactions of the Nanog Locus in Pluripotency, Differentiation, and Reprogramming. *Cell Stem Cell* 12: 699-712.
- Demare LE, Leng J, Cotney J, Reilly SK, Yin J, et al. (2013) The genomic landscape of cohesin-associated chromatin interactions. *Genome Res*.
- Ong CT, Corces VG (2012) Enhancers: emerging roles in cell fate specification. *EMBO Rep* 13: 423-430.
- Li M, Liu GH, Izpisua Belmonte JC (2012) Navigating the epigenetic landscape of pluripotent stem cells. *Nat Rev Mol Cell Biol* 13: 524-535.
- Ernst J, Kellis M (2013) Interplay between chromatin state, regulator binding, and regulatory motifs in six human cell types. *Genome Res* 23: 1142-1154.
- Simon JA, Kingston RE (2013) Occupying chromatin: Polycomb mechanisms for getting to genomic targets, stopping transcriptional traffic, and staying put. *Mol Cell* 49: 808-824.
- Orlando DA, Guenther MG, Frampton GM, Young RA (2012) CpG island structure and trithorax/polycomb chromatin domains in human cells. *Genomics* 100: 320-326.
- Lynch MD, Smith AJ, De Gobbi M, Flenley M, Hughes JR, et al. (2011) An interspecies analysis reveals a key role for unmethylated CpG dinucleotides in vertebrate Polycomb complex recruitment. *EMBO J* 31: 317-329.
- Kanhere A, Viiri K, Araújo CC, Rasaiyaah J, Bouwman RD, et al. (2010) Short RNAs are transcribed from repressed polycomb target genes and interact with polycomb repressive complex-2. *Mol Cell* 38: 675-688.
- Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, et al. (2010) Long noncoding RNA as modular scaffold of histone modification complexes. *Science* 329: 689-693.
- Chu C, Qu K, Zhong FL, Artandi SE, Chang HY (2011) Genomic maps of long noncoding RNA occupancy reveal principles of RNA-chromatin interactions. *Mol Cell* 44: 667-678.
- Yuan W, Wu T, Fu H, Dai C, Wu H, et al. (2012) Dense chromatin activates Polycomb repressive complex 2 to regulate H3 lysine 27 methylation. *Science* 337: 971-975.
- Woo CJ, Kharchenko PV, Daheron L, Park PJ, Kingston RE (2010) A region of the human HOXD cluster that confers polycomb-group responsiveness. *Cell* 140: 99-110.
- Dietrich N, Lerdrup M, Landt E, Agrawal-Singh S, Bak M, et al. (2012) REST-mediated recruitment of polycomb repressor complexes in mammalian cells. *PLoS Genet* 8: e1002494.
- Arnold P, Scholer A, Pachkov M, Balwiercz P, Jorgensen H, et al. (2013) Modeling of epigenome dynamics identifies transcription factors that mediate Polycomb targeting. *Genome Res* 23: 60-73.
- Cai L, Rothbart SB, Lu R, Xu B, Chen WY, et al. (2013) An H3K36 methylation-engaging Tudor motif of polycomb-like proteins mediates PRC2 complex targeting. *Mol Cell* 49: 571-582.
- Casa V, Gabellini D (2012) A repetitive elements perspective in Polycomb epigenetics. *Front Genet* 3: 199.
- Yu M, Mazor T, Huang H, Huang HT, Kathrein KL, et al. (2012) Direct recruitment of polycomb repressive complex 1 to chromatin by core binding transcription factors. *Mol Cell* 45: 330-343.

20. Barrero MJ, Izpisua Belmonte JC (2013) Polycomb complex recruitment in pluripotent stem cells. *Nat Cell Biol* 15: 348-350.
21. Bantignies F, Cavalli G (2011) Polycomb group proteins: repression in 3D. *Trends Genet* 27: 454-464.
22. Gellon G, McGinnis W (1998) Shaping animal body plans in development and evolution by modulation of Hox expression patterns. *Bioessays* 20: 116-125.
23. Noordermeer D, Duboule D (2013) Chromatin architectures and Hox gene collinearity. *Curr Top Dev Biol* 104: 113-148
24. Noordermeer D, Leleu M, Splinter E, Rougemont J, De Laat W, et al. (2011) The dynamic architecture of Hox gene clusters. *Science* 334: 222-225.
25. Williamson I, Eskeland R, Lettice LA, Hill AE, Boyle S, et al. (2012) Anterior-posterior differences in HoxD chromatin topology in limb development. *Development* 139: 3157-3167.

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