Chapter 10

Genome Organization inside the Nucleus

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Summary

Over the years, spatial organization of genetic material inside nucleus has been shown to be critical for genomic functions and its disruption has been linked to diseases. Although poorly understood, the recent advancement of technologies holds a promising future towards mapping the genome organization to a greater detail and understanding the underlying molecular mechanisms.

The mammalian cell nucleus is organized in a highly ordered manner. It is compartmentalized into chromosome territories along with many distinct nuclear bodies such as speckles, nucleoli, Cajal bodies among others [1-5]. Within nucleus, the genetic loci occupy preferential location. For instance, some gene loci are present at nuclear periphery; some other gene loci interact with nuclear bodies [6]. This preferential localization of gene loci varies depending on cell type or physiological conditions [7-8].

Increasing evidence suggests a role of spatial localization of genetic material in influencing its function. Several genes that change their nuclear location during cellular development also change their expression status [9-10]. For example, during lymphocyte development, immunoglobulin heavy chain (IgH) locus is located at the nuclear periphery when it is inactive. Whereas, when IgH gene is active, it is present in the nuclear interior [9]. There are also examples of gene loci changing their association with other nuclear bodies correlating with changes in transcription, such as heat shock genes associate with nuclear speckles upon activation by heat shock [11-12]. In addition, there are several descriptions where co-regulated genes cluster within the nuclear space, for instance co-expressed erythroid genes have been shown to cluster around nuclear speckles [13].

The molecular mechanism that governs the organization of genome is an active area of research. Some of the recent findings show that chromatin modifiers or epigenetic marks are responsible for the specific localization of a few genetic loci. For example, histone H3K9

di and tri-methylation by histone methyltransferase are required to localize some gene loci to nuclear periphery [14-17].

Disruption in the spatial organization of genome has been identified in multiple human diseases. Chromosomal translocations, which are common in various cancers, are proposed to preferentially occur between chromosomes occupying nearby space in the nucleus [18]. For example, chromosomes 12 and 16 that are frequently translocated in liposarcoma patients are also found in close proximity in differentiated adipocytes [19]. In a variety of diseases, there are examples where individual genes, larger genomic segments or whole chromosomes change their localization [20-21]. Additionally, several proteins involved in the higher order organization of the genome are also implicated in diseases [22-24]. The most prominent of these are laminopathies, which are a group of diseases caused by mutations in nuclear envelope (NE) proteins. For example, mutations in lamin A/C cause Emery-Dreifuss muscular dystrophy (EDMD) and premature aging disease Hutchison-Gilford progeria syndrome (HGPS) [25-27].

With the help of advanced approaches like Chromosome conformation capture techniques (also known as 3C based techniques), DNA adenine methyltransferase identification (DamID), and microscopy; nuclear organization of genome is mapped at a greater depth [28-33]. Mapping of the genome organization across different cell types, development stages, and various physiological conditions will help us to better understand the role genome organization in genome function. In depth knowledge of genome organization along with genome editing tools can help towards better diagnosis and treatment of diseases.

References

1. Misteli T. Beyond the sequence: Cellular organization of genome function. Cell. 2007; 128: 787-800

2. Cremer T, Cremer C. Chromosome territories, nuclear architecture and gene regulation in mammalian cells. Nat Rev Genet. 2001; 2: 292-301.

3. Sexton T, Schober H, Fraser P, Gasser SM. Gene regulation through nuclear organization. Nat Struct Mol Biol. 2007; 14: 1049-1055.

4. Meaburn KJ, Burman B, Misteli T. Spatial genome organization and disease. The Functional Nucleus. 2016; 1: 101-125.

5. Meaburn KJ. Spatial genome organization and its emerging role as a potential diagnosis tool. ECollection. 2016; 7: 134.

6. Bickmore WA, Van Steensel B. Genome architecture: Domain organization of interphase chromosomes. Cell. 2013; 152: 1270–1284.

7. Parada L, McQueen P, Misteli T. Tissue-specific spatial organization of genomes. Genome Biol. 2004; 7: R44.

8. Rao SS, Huntley MH, Durand NC, Stamenova EK, Bochkov ID, et al. A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping. Cell. 2014; 159: 1665–1680.

9. Kosak ST, Skok JA, Medina KL, Riblet R, Le-Beau MM, et al. (2002) Subnuclear compartmentalization of immunoglobulin loci during lymphocyte development. Science 296 (5565): 158–162.

10. Williams RR, Azuara V, Perry P, Sauer S, Dvorkina M, et al. Neural induction promotes large-scale chromatin reorganisation of the Mash-1 locus. J Cell Sci. 2006; 119: 132–140.

11. Hu Y, Kireev I, Plutz M, Ashourian N, Belmont AS. Large-scale chromatin structure of inducible genes: transcription on a condensed, linear template. J Cell Biol. 2009; 185: 87-100.

12. Khanna N, Hu Y, Belmont AS. HSP70 transgene directed motion to nuclear speckles facilitates heat shock activation. Curr Biol. 2014; 24: 1138–1144.

13. Brown JM, Green J, Das Neves RP, Wallace HA, Smith AJ, et al. Association between active genes occurs at nuclear speckles and is modulated by chromatin environment. J Cell Biol. 2008; 182: 1083–1097.

14. Zullo JM, Demarco IA, Pique-Regi R, Gaffney DJ, Epstein CB, et al. DNA sequence-dependent compartmentalization and silencing of chromatin at the nuclear lamina. Cell. 2012; 149: 1474–1487.

15. Kind J, Pagie L, Ortabozkoyun H, Boyle S, De Vries SS, et al. Single-cell dynamics of genome-nuclear lamina interactions. Cell. 2013; 153: 178–192.

16. Towbin BD, Gonzalez-Aguilera C, Sack R, Gaidatzis D, Kalck V, et al. Step-wise methylation of histone H3K9 positions heterochromatin at the nuclear periphery. Cell. 2012; 150: 934–947.

17. Bian Q, Khanna N, Alvikas J, Belmont AS. Beta-globin Cis-elements determine differential nuclear targeting through epigenetic modifications. J Cell Biol. 2013; 203: 767–783.

18. Bickmore WA, Teague P. Influences of chromosome size, gene density and nuclear position on the frequency of constitutional translocations in the human population. Chromosome Res. 2002; 10: 707–715.

19. Kuroda M, Tanabe H, Yoshida K, Oikawa K, Saito A, et al. Alteration of chromosome positioning during adipocyte differentiation. J Cell Sci. 2004; 117: 5897–5903.

20. Reddy KL, Andrew P. Feinberg higher order chromatin organization in cancer. Semin Cancer Biol. 2013; 23: 109-115.

21. Karen J, Meaburn D. Spatial genome organization and its emerging role as a potential diagnosis tool. Front Genet. 2016; 7:134.

22. Misteli T. Higher-order genome organization in human disease. Cold Spring Harb Perspect Biol. 2010; 2: a000794.

23. Woodcock CL. Chromatin architecture. Curr Opin Struct Biol. 2006; 16: 213–220.

24. Hock R, Furusawa T, Ueda T, Bustin M. HMG chromosomal proteins in development and disease. Trends Cell Biol. 2007; 17: 72–79.

25. Ellis JA, Shackleton S. Nuclear envelope disease and chromatin organization. Biochem Soc Trans. 2011; 39: 1683–1686.

26. Dittmer TA, Misteli T. The lamin protein family. Genome Biol. 2011; 12: 222.

27. Burke B, Stewart CL. The nuclear lamins: Flexibility in function. Nat Rev Mol Cell Biol. 2013; 14: 13–24.

28. Steensel VB, Dekker J. Genomics tools for unraveling chromosome architecture. Nat Biotechnol. 2010; 28: 1089–1095.

29. Guelen L, Pagie L, Brasset E, Meuleman W, Faza MB, et al. Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions. Nature. 2008; 453: 948–951.

30. Khanna N, Bian Q, Plutz M, Belmont AS. BAC manipulations for making BAC transgene arrays. Methods Mol Biol. 2013; 1042: 197–210.

31. Mattout A, Cabianca DS, Gasser SM. Chromatin states and nuclear organization in development: A view from the nuclear lamina. Genome Biology. 2015; 16: 174.

32. Belmont AS, Hu Y, Sinclair PB, Wu W, Bian Q, et al. Insights into interphase largescale chromatin structure from analysis of engineered chromosome regions. Cold Spring Harb Symp Quant Biol. 2010; 75: 453–460.

33. Ramani V, Shendure J, Duan Z. Understanding spatial genome organization: Methods and insights. Genomics Proteomics Bioinformatics. 2016; 14: 7–20.