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Spatial organization of genome architecture in neuronal development and disease

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ABSTRACT

Although mammalian genomes encode genetic information in their linear sequences, their fundamental function with regard to gene expression depends on the higher-order structure of chromosomes. Current techniques for the evaluation of chromosomal structure have revealed that genomes are arranged at several hierarchical levels in three-dimensional space. The spatial organization of genomes involves the formation of chromatin loops that bypass a wide range of genomic distances, providing a connection between enhancers and chromosomal domains. Furthermore, they form chromatin domains that are arranged into chromosome territories in the three-dimensional space of the cell nucleus. Recent studies have shown that the spatial organization of the genome is essential for normal brain development and function. Activity-dependent alterations in the spatial organization of the genome can regulate transcriptional activity related to neuronal plasticity. Disruptions in the higher-order chromatin architecture have been implicated in neuropsychiatric disorders, such as cognitive dysfunction and anxiety. Here, we discuss the growing interest in the role of genome organization in brain development and neurological disorders.

Contents

Abbreviations: 3C, chromosome conformation capture; CTCF, CCCTC-binding factor; SMC, structural maintenance of chromosomes; CdLS, Cornelia de Lange syndrome; FISH, fluorescent in situ hybridization; Hi-C, high-throughput chromosome conformation capture; TAD, topologically associated domain; ES, embryonic stem; iPSC, induced pluripotent stem cells; Ldb1, LIM domain-binding protein 1; P, postnatal day; LTP, long-term potentiation; NMDA, *N*-methyl-D-aspartic acid; NGF, nerve growth factor; GABA, gamma-aminobutyric acid; TF, transcription factor; SINE, short interspersed nuclear element; eRNA, enhancer RNA; NELF, negative elongation factor; BDNF, brain-derived neurotrophic factor; ATRX, alpha-thalassemia X-linked gene; MeCP2, methyl-CpG-binding protein 2; Dlk1, delta-like homologue 1; Meg3, maternally expressed 3; Igf2, insulin-like growth factor 2; Dlx, distal-less homeobox; NIPBL, nipped-B-like protein.

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1. Introduction

Numerous studies have demonstrated that epigenetic modifications, such as DNA methylation, histone acetylation, and histone methylation, are crucial for neuronal circuit formation and function (Day and Sweatt, 2011; Puckett and Lubin, 2011; Sweatt, 2013; Zovkic et al., 2013). For example, increase of histone methylation and phosphorylation in the hippocampus regulates memory formation (Gupta et al., 2010). Besides these modifications to the linear genome, recent studies have shown that appropriate gene expression also requires chromosomes to fold into three-dimensional (3D) structures. Technological innovations, e.g., improved microscopic approaches and chromosome conformation capture (3C), reveal the precise genome topology. Genomes are organized at spatially hierarchical levels, from chromatin loops that allow associations between enhancers and genes over a short- and long-range of the linear genome to the formation of chromosome domains and chromosome territories. These higher-order architectures permit the genomic loci to interact with each other to form intra- and inter-chromosomal connections in the 3D space of the nucleus (Miele and Dekker, 2008; Misteli, 2008; van Steensel and Dekker, 2010). Each cell has a unique pattern of spatial genome organization, and there are no genomic loci connections that are exactly the same among different cell populations (Croft et al., 1999; Orlova et al., 2012; Parada et al., 2003; Strickfaden et al., 2010). These observations support the importance of the spatial organization of chromosomes in the regulation of gene expression and genome maintenance, and the relevance of genome organization to neuronal function has recently begun to be unraveled. Increasing evidence has shown that activity-induced changes in chromosome architecture contribute to neuronal plasticity. In this review, we discuss the hierarchical view of genome structure, and how disturbances in the 3D structure of chromosomes induce behavioral abnormalities. Since the role of epigenetic modifications to the linear genome, such as histone modifications and DNA methylation, in neural processes have been well characterized and discussed in many reviews, here we focus on the spatial configuration of the chromosome during development and disease in the brain.

2. Hierarchical view of genome organization

The sequencing of the human genome in 2001 (Lander et al., 2001; Venter et al., 2001) provided an overview of the genome at the linear sequence level, and produced a further question about how gene expression is regulated and organized for cellular function. High-resolution mapping of epigenetic modifications, such as DNA methylation and histone modifications, provided insight into this question from the viewpoint of linear genome structure (two dimensions). However, another hierarchical level of epigenetic regulation exists at the higher-order level of chromosome organization and the territorial organization of chromosomes in the 3D space of the cell nucleus (Bickmore and van Steensel, 2013; Cavalli and Misteli, 2013; Gibcus and Dekker, 2013; Lanctot et al., 2007). This hierarchy of chromosomal structure is similar to aspects of protein structure, starting with the folding of the amino acid sequence (primary structure) into a secondary structure, such as an alpha-helix and beta-helix, culminating in their aggregation into a functional protein conformation (Fig. 1) (Sexton and Cavalli, 2015). In this section, we present recent insights into the hierarchical structures of the chromosome; epigenetic modifications to the linear genome (primary structure), chromatin loops and topologically associated domains (secondary structure), and 3D genomic locations in the nucleus (tertiary structure).

2.1. Chromatin loops

The proteins associated with chromosome scaffolding have a crucial role in the regulation of chromatin loops, in particular the cohesin complex, insulator protein CCCTC-binding factor (CTCF), the general co-activating mediator complex, and the accessory proteins, which load or release the cohesin complex onto chromosomes (Hadjur et al., 2009; Kagey et al., 2010; Splinter et al., 2006; Wendt et al., 2008).

In humans, the cohesin complex forms a ring-like structure that is comprised of four core subunits: the evolutionarily conserved structural maintenance of chromosomes (SMC) protein heterodimer, SMC1α or SMC1β and SMC3, the doublestrand-break repair protein, RAD21, and the stromal antigen homologue, SA1 or SA2

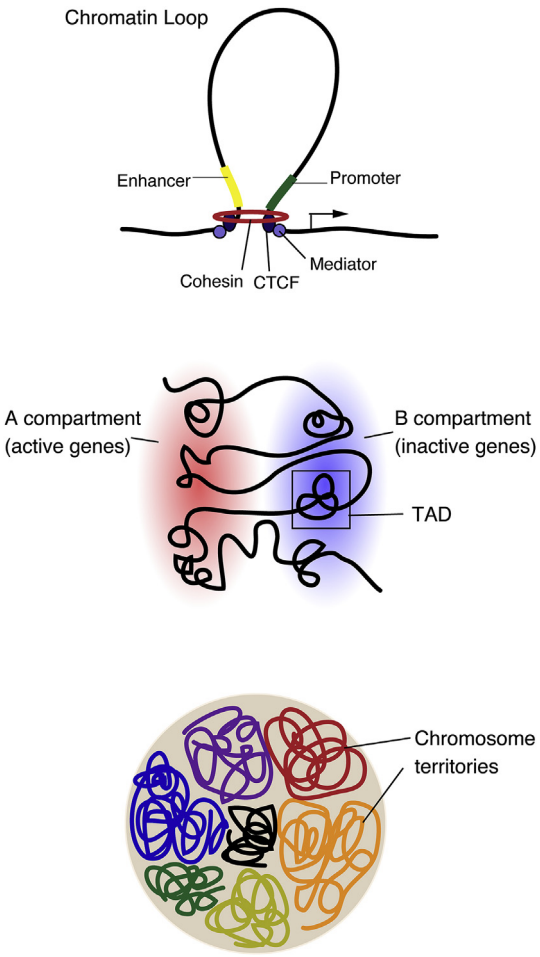

Fig. 1. Hierarchical organization of the genome in the three-dimensional space of the nucleus.

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