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REVIEW

# NUCLEAR ARCHITECTURE AS AN EPIGENETIC REGULATOR OF NEURAL DEVELOPMENT AND FUNCTION

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**Abstract—The nervous system of higher organisms is characterized by an enormous diversity of cell types that function in concert to carry out a myriad of neuronal functions. Differences in connectivity, and subsequent physiology of the connected neurons, are a result of differences in transcriptional programs. The extraordinary complexity of the nervous system requires an equally complex regulatory system. It is well established that transcription factor combinations and the organization of cis-regulatory sequences control commitment to differentiation programs and preserve a nuclear plasticity required for neuronal functions. However, an additional level of regulation is provided by epigenetic controls. Among various epigenetic processes, nuclear organization and the control of genome architecture emerge as an efficient and powerful form of gene regulation that meets the unique needs of the post-mitotic neuron. Here, we present an outline of how nuclear architecture affects transcription and provide examples from the recent literature where these principles are used by the nervous system.**

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**Key words: nuclear architecture, epigenetics, nuclear envelope, DNA methylation, histone methylation, chromocenters.**

Contents



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*Abbreviations:* CTs, chromosome territories; FISH, fluorescence *in situ* hybridization; GFAP, glial fibrillary acidic protein; LADs, lamina-associated domains; LBR, lamin B receptor; Mb, megabases; OE, olfactory epithelium; ORs, olfactory receptors; OSN, olfactory sensory neurons; PML, promyelocytic leukemia protein; RNAP, RNA polymerase; TADs, topological-associated domains.

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## INTRODUCTION

The last decade has seen substantial growth in our understanding of mammalian genomes, both at the DNA sequence level and the regulatory mechanisms that modulate their function (Lander et al., 2001; Waterston et al., 2002; The ENCODE Project Consortium, 2012). Advances in genome biology have informed every discipline in biology, including neuroscience. Not only has our understanding of the development and evolution of the nervous system improved in response to the genomic revolution, but it has also reinforced the notion that genetic information governs neural processing and behavior. The recent striking demonstration that genes quantitatively affect distinct behavioral modules in the mouse (Xu et al., 2012), in a fashion similar to what was known for decades in invertebrates (Benzer, 1973), suggests that genetics play a major role in perception, cognition, and behavior of higher organisms. Appreciating the genetic underpinnings of neural processing, without a doubt, will modify our efforts to understand neurological and psychiatric disorders and will provide new approaches for the understanding of the brain.

Upon agreement that genes control behavior, an obvious next question is how the expression of these genes is regulated and coordinated for the generation of a functional nervous system. Seminal experiments performed over half a century revealed how combinations of transcription factors, utilizing the basic principles of synergy and cooperativity that were first described in the lambda phage (Ptashne, 1989), transform spatiotemporal cues to precise orchestration of gene expression and development of the nervous system (Albright et al., 2000). Although these regulatory mechanisms are, by and large, encoded by the genome itself, there are an increasing number of paradigms whereby information encoded in the DNA is overruled by so-called ‘‘epigenetic’’ factors. Although the term ‘‘epigenetic’’ in its original definition assumed heritability, in the case of post-mitotic neurons inheritance of epigenetic information is not applicable; therefore, for the needs of this review, the use of the term epigenetic refers to the Greek etymology of the word, which means ‘‘over the genetic

information''. Any time we use the term ''epigenetic'' in this essay, we simply refer to modifications of chromatin and its structure that do not result from changes to the underlying DNA sequence, regardless of heritability. DNA and post-translational histone modifications constitute the best-characterized epigenetic modifications, and their role in neural processes is described in detail in other reviews of this issue. Here, we will focus on a relatively novel axis of epigenetic regulation, which is not directly linked to the epigenetic marks of a genomic locus but instead to its nuclear coordinates. Experiments in various cell types and organisms suggest that the genetic material is a three-dimensional structure defined by topological constraints that may differ between cell types and differentiation states. Thus, the linear order depicted by the genomic coordinates is not necessarily retained in the 3-dimensional nuclear space. Therefore, a gene's nuclear neighborhood could potentially determine its transcriptional competence or activity, or coordinate the expression of many genes found on separate chromosomes by bringing them in close spatial proximity. Increasingly, evidence suggests nuclear organization does indeed have functional implications and is the subject of regulation. This suggests that the spatial organization of the nucleus, or nuclear architecture, is likely to play an important role in directing cellular differentiation, organismal development, and disease etiology. In this review, we discuss the current understanding of the role that nuclear architecture plays in the developing nervous system. We focus predominantly on the biology of mammalian organisms, but in some cases will include insights observed in other model organisms (e.g. *Drosophila melanogaster*). We will first provide a general survey of known features of 3-dimensional nuclear organization: higher-order organization of the chromatin fiber, spatial localization of chromosomes and distinct chromatin types, and organization of nuclear processes in nuclear bodies

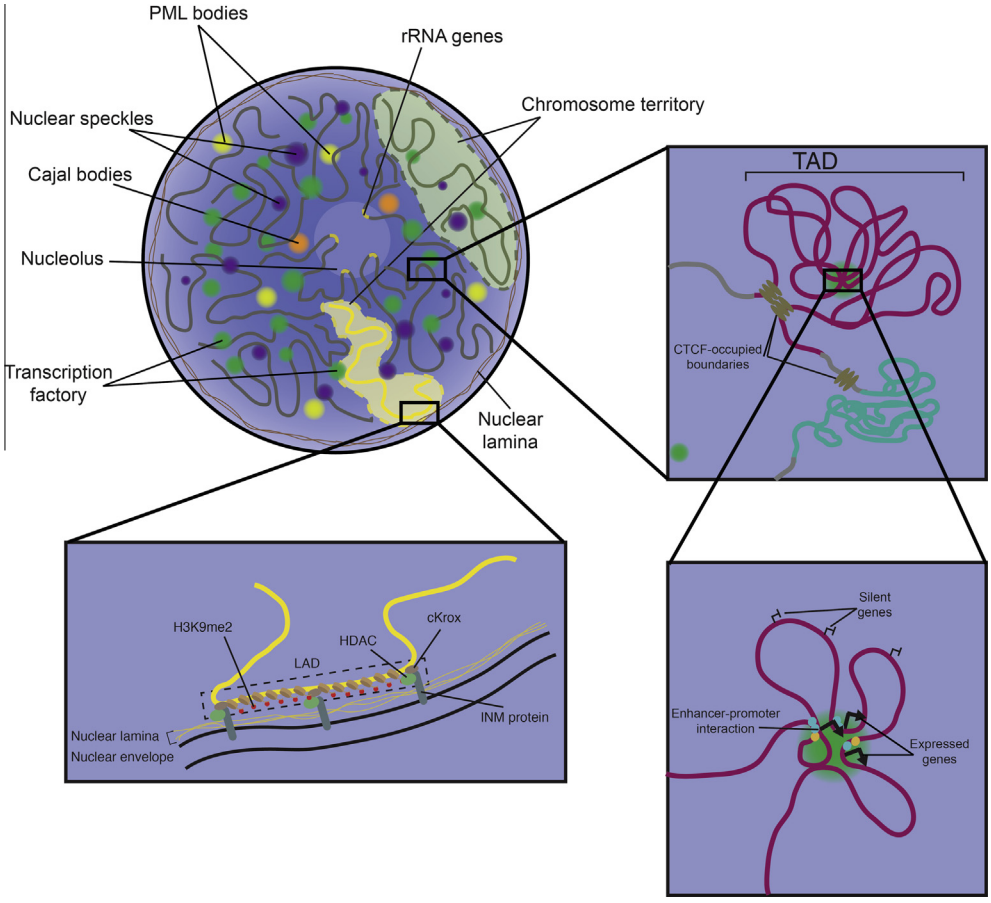


**Fig. 1.** Organization of chromatin in topological and lamina-associated domains. Cartoon model for the higher-order organization of chromatin. A mammalian nucleus shows chromosomes (dark gray lines) confined to distinct territories. rRNA genes are confined within the nucleolus. Cajal bodies are shown juxtaposed to the nucleolus. Nuclear speckles and transcription factories reflect high concentrations of the splicing and transcriptional machinery, respectively. These structures are depleted in nuclear compartments associated with repressed heterochromatin: the nuclear lamina and chromatin associated with the nucleolus. On right, a magnified view of the boxed region shows two topological-associated domains (TADs), colored red and green, separated by CTCF-bound boundary regions. Within each TAD are numerous chromosomal interactions; however, few interactions cross boundaries between TADs. On bottom right, further magnification of a transcription factory with a TAD demonstrates close associations between distal regulatory regions and expressed genes. Moreover, numerous expressed genes colocalize in this space and share similar sets of transcription factors (green and orange circles). Silent genes found in between these active genes in linear sequence loop away from the transcription factory and occupy a distinct region. On bottom left, a repressed chromatin domain is associated with the nuclear lamina, known as a lamina-associated domain (LADs). LADs have hallmarks that include high levels of repressive H3K9 methylation. Interactions between inner nuclear membrane proteins, such as emerin and Lap2β, with HDACs and cKrox are also essential for LAD establishment.