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Impact of nuclear organization and dynamics on epigenetic regulation in the central nervous system: implications for neurological disease states

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Abstract

Epigenetic mechanisms that are highly responsive to interoceptive and environmental stimuli mediate the proper execution of complex genomic programs such as cell type-specific gene transcription and post-transcriptional RNA processing and are increasingly thought to be important for modulating the development, homeostasis, and plasticity of the central nervous system (CNS). These epigenetic processes include DNA methylation, histone modifications, and chromatin remodeling, all of which play roles in neural cellular diversity, connectivity, and plasticity. Further, large-scale transcriptomic analyses have revealed that the eukaryotic genome is pervasively transcribed, forming interleaved protein-coding RNAs and regulatory non-protein-coding RNAs (ncRNAs), which act through a broad array of molecular mechanisms. Most of these ncRNAs are transcribed in a cell type- and developmental stage-specific manner in the CNS. A broad array of post-transcriptional processes, such as RNA editing and transport, can modulate the functions of both protein-coding RNAs and ncRNAs. Additional studies implicate nuclear organization and dynamics in mediating epigenetic regulation. The compartmentalization of DNA sequences and other molecular machinery into functional nuclear domains, such as transcription factories, Cajal bodies, promyelocytic leukemia nuclear bodies, nuclear speckles, and paraspeckles, some of which are found prominently in neural cells, is associated with regulation of transcriptional activity and post-transcriptional RNA processing. These observations suggest that genomic architecture and RNA biology in the CNS are much more complex and nuanced than previously appreciated. Increasing evidence now suggests that most, if not all, human CNS diseases are associated with either primary or secondary perturbations in one or more aspects of the epigenome. In this review, we provide an update of our emerging understanding of genomic

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architecture, RNA biology, and nuclear organization and highlight the interconnected roles that deregulation of these factors may play in diverse CNS disorders.

Keywords

epigenetics; non-coding RNAs; genomic architecture; nuclear organization; RNA editing; RNA trafficking; post-transcriptional processing; epigenetic memory; laminopathies, cohesinopathies; spinal muscular atrophy; nuclear ataxias

Introduction

Many studies have focused on characterizing the roles played by classical epigenetic mechanisms—DNA methylation, histone post-translational modifications, nucleosome remodeling and higher-order chromatin regulation—in mediating normal and pathological processes through the modulation of genomic function [1–6]. In the central nervous system (CNS), these mechanisms are responsible for regulating developmental, cell type-specific, and activity-dependent changes in gene expression and function, in large part because they are highly responsive to interoceptive and environmental stimuli [1]. These classical epigenetic processes are, thus, critical for promoting neural cellular diversity and neural network connectivity and plasticity. Not surprisingly, perturbations in these critical aspects of the epigenome are increasingly being linked to the molecular pathophysiology of a broad array of CNS diseases [1].

The epigenome broadly defined, however, refers to the sum total of cellular mechanisms that are responsible for mediating the proper execution of genomic programs. These mechanisms include gene transcription, post-transcriptional RNA processing and translation, as well as higher-order processes, such as DNA replication, repair and recombination; X chromosome inactivation, genomic imprinting, and gene dosage effects; and centromere and telomere maintenance and the protection of genomic integrity [1–9]. Further studies enabled by the advancement of next-generation sequencing technologies and high resolution imaging techniques have, therefore, focused on describing the roles played by additional interrelated epigenetic regulatory mechanisms, such as non-coding RNA (ncRNA)-driven processes and nuclear organization and dynamics, in mediating this diverse array of genomic programs [1,10–15]. These have lead to important scientific discoveries that have revolutionized our understanding of genomic structure, function, regulation, and evolution.

Indeed, the eukaryotic genome is pervasively transcribed from modular transcriptional units that are responsible for generating multiple interleaved and overlapping protein-coding transcripts and ncRNAs in both sense and antisense orientations [16–18]. There are an increasing number of distinct ncRNAs classes that have been described, including both short and long ncRNAs, which serve as flexible, high-fidelity information-encoding and functional molecules with a spectrum of structural, regulatory, and catalytic roles [19]. In fact, a broad array of molecular and cellular processes is transacted by ncRNAs, through dynamic interactions with DNA, protein-coding RNAs and other ncRNAs, and proteins [10]. These functions are facilitated by the unique features of RNA molecules, which include their relatively low bioenergetic cost to the cell; their conduciveness to post-transcriptional processing (e.g., alternative polyadenylation, capping, alternative splicing, and editing), translational control, and intracellular and intercellular transport; and their ability to engage in conformational (analog) and sequence-specific (digital) interactions that are exquisitely sensitive to interoceptive and environmental stimuli [20,21].

An increasing number of studies have begun to focus on characterizing the dynamic interplay that occurs between nuclear organization and genomic processes in diverse cellular contexts [1,10–15]. These studies suggest that the nucleus itself plays a vital role in the execution of genomic programs, such as gene transcription and silencing, in response to developmental, homeostatic, stress and other signals. Indeed, nuclear architecture promotes the temporal and spatial segregation and association of myriad DNA sequences, RNAs, proteins, and other factors through the localization of specific genomic sequences and the establishment of functional nuclear domains, such as transcription factories, Cajal bodies (CBs), promyelocytic leukemia nuclear bodies (PML-NBs), nuclear speckles, and paraspeckles. These organizational features are, to some degree, responsible for mediating nuclear and cytoplasmic processes including DNA replication, DNA repair, transcription, post-transcriptional RNA processing, and RNA nuclear-cytoplasmic transport [1,10–15].

Considering these observations, it is not surprising that perturbations in these aspects of the epigenome are also being recognized as the primary mechanisms responsible for causing a number of CNS diseases or as secondary effects resulting from primary pathological processes. Therefore, in this review, we provide an overview of our emerging understanding of genomic architecture, ncRNA biology, and nuclear organization, highlighting the roles these factors play in the CNS. Moreover, we call attention to diverse CNS disorders whose pathobiology may partly be related to aberrations in nuclear organization and dynamics, aspects of the epigenome that are the least well understood, including laminopathies, cohesinopathies, and various neurodegenerative diseases [22–35].

Genomic architecture

Large-scale genomic analyses, such as the ENCODE project [18] and FANTOM consortiums [16,17], have provided incontrovertible evidence that our views of genomic structure, function, regulation, and even evolution need to be refined. Canonical definitions of genes and traditional views of gene regulation are now being replaced with an increasingly sophisticated view of the distribution and molecular function of transcriptional and regulatory genomic elements [36]. The eukaryotic genome is pervasively transcribed into RNAs, including both protein-coding RNAs and ncRNAs, and these are not organized in a linear fashion. Rather, the genome is surprisingly modular with each base pair having the potential to serve as a multifunctional transcriptional unit. Multiple overlapping, bidirectional, and often independently regulated and processed sense and antisense transcripts can be transcribed from these transcriptional units [16–18]. In addition, some precursor transcripts are subject to post-transcriptional processing and cleavage events that may lead to the generation of many distinct protein-coding RNAs and ncRNAs. The identification of mechanisms that give rise to chimeric transcripts has also blurred lines, which have conventionally demarcated individual genes [37]. For example, trans-splicing events may occur in between different transcripts, and gene fusion may lead to the joining of separate genes through transcription or other processes.

These observations imply that a complex network of regulatory controls modulates genomic function and, further, that these processes are highly cell- and tissue-specific. A broad array of molecular factors is responsible for modulating transcription and post-transcriptional processing, including those that act *in cis* (e.g., DNA elements and ncRNAs) and *in trans* (e.g., proteins and ncRNAs). Transcription and post-transcriptional processing are coordinated by complementary epigenetic mechanisms including but not limited to DNA methylation, histone modifications and higher-order chromatin regulation, ncRNAs as well as nuclear organization and dynamics [1–15].

A variety of DNA elements participate in short- and long-range interconnected transcriptional regulation. These include promoters, enhancers, repressors/silencers, insulators, complex locus control regions (LCRs), and imprinting control regions (ICRs) [38–43]. These elements may be located upstream, downstream, or within the introns and exons of genes they modulate. Genome-wide characterization of promoter regions has revealed that most genes have multiple promoters with a number of possible transcription start sites. In ENCODE regions, for example, 81.5% of the genes tested had additional transcription start sites that were either 5' distal or internal to the annotated gene boundary [39]. Many promoters initiate transcription in both directions; some bidirectional gene pairs exhibit co-expression while others show more divergent expression profiles. Like promoters, enhancer and repressor/silencer elements also regulate genes by recruiting factors that bind to DNA in a sequence-specific manner or indirectly through protein-protein interactions leading to activation or repression of transcription. These elements function by promoting the looping of DNA, modifying chromatin structure and interacting with components of the transcriptional machinery. Enhancers usually operate *in cis* to their gene targets and are typically clustered 100 kb upstream, downstream or even within a gene; however, regulation *in trans* has also been observed for paired sister chromosomes [40]. Through transvection, enhancers associated with one allele may activate the promoter of a second allele that is located on a homologous chromosome. Insulators are DNA elements that limit the effects of promiscuous regulatory elements, and they are often located in between the promoter region and enhancer or silencer elements of adjacent genes and gene clusters [44]. LCRs have been found in association with various complex gene loci (i.e., the *Hbb* gene cluster) and play a role in controlling the expression of genes at these loci in a developmentally regulated and cell type-specific manner through long-range allelic and non-allelic interactions between chromosomes [41]. Similarly, ICRs control the epigenetic silencing of imprinted genes through CCCTC-binding factor (CTCF)- and/or ncRNA-dependent mechanisms that include DNA methylation and histone modifications. ICRs have also been shown to control non-allelic imprinting at the *Igf2/H19* and the *Wsb1/Nf1* gene loci. CTCF, a chromatin insulator, plays a critical role in arbitrating long-range chromatin interactions, directing DNA regions into transcription factories (see below) and facilitating interactions with other genomic regions [42,43]. CTCF is involved in various aspects of epigenetic regulation, such as genomic imprinting, X-chromosome inactivation, ncRNA transcription, and establishment of local chromatin structure at repetitive elements [42,43].

Chromatin is not simply a passive structure that packages DNA within the nucleus, but rather it serves key functions in nuclear processes such as the regulation of gene expression. Nuclear structural and functional dynamics are shaped by nucleosome remodeling, modification of histone tails, and replacement of canonical histones with histone variants [4–8,13,45–47]. The loosely packaged euchromatin is readily accessible to the transcriptional machinery, while the more densely packaged heterochromatin is less transcriptionally active. Heterochromatin has a reduced recombination frequency, is often localization to the nuclear periphery, and replicates late in the cell cycle. Heterochromatic domains contain transposable elements and other repetitive sequences, are associated with centromeres and telomeres, and are linked to particular histone modifications. These domains play an important role in the organization of chromosomes in the nucleus. Formation of facultative heterochromatin is often localized to promoter regions and may be developmentally or environmentally regulated. The establishment of these chromatin domains is important for epigenetic gene silencing in a cell type- or tissue specific- manner. Furthermore, heterochromatin domain formation is an important mechanism for developmental programming and cell fate decisions. For example, progressive nuclear and epigenetic remodeling of the *MHC-Oct3/4* gene locus marks the developmental phases of embryonic stem (ES) cell differentiation [48]. Cellular stress mechanisms, such as senescence, may also promote the formation of specific chromatin states.

Histone- and chromatin-modifying enzymes and associated macromolecular complexes play a key role in epigenetic regulation of transcription. Studies of the corepressor complexes recruited by repressor element 1 silencing transcription factor (REST) and CoREST have helped to characterize some of these enzymes complexes and their functions in neural cells [11,49,50]. REST binds and recruits various corepressor complexes that may cause either short-term transcriptional repression or long-term gene silencing. Recruitment of REST and CoREST complexes is cell type- and developmental stage-specific and is an important mechanism for integrating a diverse array of maturational cues and for programming of neural cell fate.

Recent studies on the factors driving the evolution of the human genome and the sources promoting inter- and intra-individual genetic variation suggest that our understanding of these processes also needs to be refined [51,52]. For example, a significant percentage of the human genome is comprised of mobile genetic elements, including various subclasses of short interspersed nuclear elements (SINEs) and long interspersed nuclear element elements (LINEs) [52]. Some of these subclasses continue to generate new retrotransposon insertions both in the germ line and in somatic cells, thus influencing chromosomal integrity, gene expression and, no doubt, disease. Interestingly, LINE-1 (L1) elements comprise approximately 17% of the human genome and seem to be active in neuronal cells where they may contribute to neuronal cellular diversity and activity-dependent plasticity [53–55]. The mechanisms responsible for regulating mobile genetic element activity include DNA editing enzymes (see below), DNA methylation status, and ncRNAs. Small ncRNAs, such as piwiRNAs (piRNAs) and short interfering RNAs (siRNAs), target retrotransposons and are thought to constrain the propagation of these elements within the germ line [56]. It is less well known what specific restrictions against retrotransposon activity are at work in somatic cells [57] such as neurons, though it is intriguing to hypothesize that these ncRNAs have roles in mediating CNS development, homeostasis, and plasticity, in part, through their effects on retroelements.

RNA biology

Non-coding RNAs

The eukaryotic genome is transcribed into a broad array of ncRNAs. These include subclasses that are well characterized (e.g., ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs)) as well as many whose functions are still emerging (e.g., microRNAs (miRNAs), long ncRNAs (lncRNAs), siRNAs, piRNAs, small nucleolar RNAs (snoRNAs), promoter-associated small RNAs (PASRs) and transcription initiation RNAs (tiRNAs)) [19]. These novel subclasses of ncRNAs participate in complex, multilayered epigenetic regulatory processes.

MiRNAs are the most well characterized ncRNA subclass. They are approximately 22 nucleotide transcripts that modulate the expression of target mRNA transcripts through sequence-specific interactions predominantly with 3’ untranslated regions (3’UTRs) of these mRNAs [58]. A single miRNA can target hundreds of mRNAs, repressing their translation and sequestering them for storage or degradation. These factors are expressed in a cell type- and maturational stage-specific manner, where they are implicated in highly environmentally responsive regulation of gene expression programs. In the CNS, miRNAs have diverse roles in promoting neural development, homeostasis, and plasticity [58].

LncRNAs are another emerging ncRNA subclass defined as ncRNA transcripts longer than 200 nucleotides. These factors have a number of functions including regulating transcription by recruiting transcription factors and histone-modifying enzymes to gene regulatory elements and modulating chromatin structure by recruiting chromatin-remodeling factors

(e.g., Polycomb repressor complex 2 (PRC2) and CoREST) to specific genomic sites [59,60]. While these mechanisms underlying ncRNA-mediated local and long-distance epigenetic regulation are currently the focus of intense scrutiny, an integrated understanding of these complex mechanisms has not yet emerged. However, like miRNAs, most lncRNAs seem to be expressed in a cell type- and developmental stage-specific manner, particularly within in the CNS, [1,61–66]. The biological roles played by lncRNAs have not been fully characterized, though lncRNAs unequivocally participate in regulating cell fate decisions in the CNS and in other tissues. For example, many lncRNAs are differentially expressed in the developing and adult mouse brain and during oligodendrocyte (OL) lineage specification, maturation and myelination. These lncRNAs are implicated in modulating the expression and function of protein-coding RNAs, which are themselves differentially regulated and associated with important roles in brain development and adult function [66]. Furthermore, lncRNAs are integrated within the transcriptional networks underlying pluripotency, and the over expression or knock down of specific lncRNAs modulate ES cell lineage potential through effects on mRNA levels of the Oct4 and Nanog pluripotency-associated transcription factors [67,68]. These diverse ncRNA subclasses can, in turn, be further modulated though additional post-transcriptional processing, such as RNA editing and transport.

RNA editing

RNA and DNA editing are closely linked mechanisms that significantly diversify the transcriptome and allow for the environmentally responsive recoding of RNA and DNA [21]. For example, editing of adenosine to inosine (A to I) is catalyzed by adenosine deaminases that act on RNA (ADARs), and editing of (deoxy)cytidine to (deoxy)uridine ([d]C to [d]U) is catalyzed by the apolipoprotein B (ApoB) editing catalytic subunit (APOBEC) family of cytidine deaminases that act on RNA and DNA. The expression of these families of enzymes is spatiotemporally regulated in the brain [65]. Recent analyses have shown that RNA editing occurs not only in mRNAs associated with synaptic function, as was initially believed, but also in many ncRNAs, including miRNAs [69].

Interestingly, the amount of RNA editing in humans is significantly greater than in non-human primates. This RNA editing takes place largely in transcripts derived from Alu sequences, the most abundant SINE retroelements in the human genome. Editable human-specific Alu sequences are significantly enriched in genes related to neuronal functions and neurological diseases [70]. Members of the APOBEC3 protein family are found in human neuronal cells and are also implicated in the regulation of retroelements [71,72], further suggesting a link between retroelements, RNA and DNA editing, and CNS function in humans. These observations are consistent with findings of deregulated ADAR and APOBEC activities in a spectrum of neurodevelopmental, neurodegenerative, and neuropsychiatric diseases as well as brain cancers [65].

Intracellular transport of RNAs

Trafficking of proteins and RNAs is essential for cellular function, particularly in the nervous system. RNAs are packaged into ribonucleoprotein particles (RNPs) and transported along the neuronal cytoskeleton from the nucleus to distal sites where local protein synthesis is activated by synaptic activity and neurotransmitter signaling [73]. Activity-dependent dendritic protein synthesis results in modulation of neuronal and synaptic structure and function and is implicated in a variety of processes including, but not limited to, regulation of the cytoskeleton, receptor trafficking, modulation of the extracellular matrix, and stable forms of long-term potentiation (LTP) and long-term depression (LTD). For example, the immediate early gene *Arc* (*Arg3.1*) is translated synaptically in the dentate gyrus and is implicated in LTP consolidation [74]. On the other hand, this activity-dependent modulation

of gene expression through sequestration, repression and activation of various RNAs can also take place through bidirectional axodendritic transport: from nucleus to dendrite as well as from dendrite to nucleus. During trafficking, mRNAs within the RNP are bound to sequence-specific RNA-binding proteins (RBPs) and miRNAs that repress translation. At the dendrite, synaptic activity and neurotransmitter signaling locally de-repress translation.

Cytoplasmic mRNAs are packaged into discrete RNP-containing RNA granules during intracellular transport. RNA granules orchestrate site-specific gene expression by modulating the deployment of specific ncRNAs and the translation of certain proteins. Subsequently, the byproducts of mRNA metabolism can self-assemble into dynamic, functional RNA-containing cytoplasmic structures, such as stress granules (SGs) and processing bodies (PBs). These structures may share substrate mRNAs, ncRNAs, proteins and other components but they also contain unique factors and perform different functions [75–77]. SG and PB assembly involves factors related to splicing, transcription, adhesion, signaling and development. Recent evidence demonstrates that mRNAs silenced by miRNAs are localized to PBs for storage or degradation. Moreover, RNP remodeling induced by the RNA-induced silencing complex (RISC) or RNA helicase activity may lead to alterations of the 5' translation initiation complex of mRNAs within PBs. PBs may also facilitate access of the de-capping complex promoting degradation of some mRNAs while other mRNAs stored in PBs can be released for translation. These cytoplasmic RNA-containing structures control mRNA turnover and translational repression and also participate in trafficking RNAs to axons and dendrites. The RNAs participate in regulating growth cone dynamics and axonal pathfinding and remodeling, as well as activity-dependent synaptic plasticity and homeostasis.

Transcription and translation are not directly coupled. Post-transcriptional processing and transport of RNA serve as opportunities for temporal and spatial regulation of gene expression through specialized “RNA operons” and “RNA regulons”. RNA operons refer to complexes of functionally related RNAs and trans-acting factors including RBPs, other RNA interactors such as argonaute proteins, ncRNAs and related factors. These associate together, thereby acting as hubs for co-regulation of RNAs within RNP modules subserving splicing, nuclear export, stability, localization and translation [78]. Furthermore, RNA regulons represent epigenetic mechanisms that coordinate higher-order dynamics of groups of RNAs and RNA operons in a combinatorial fashion modulating their molecular composition and contributing to complex and emergent functional properties [79].

Intercellular transport of RNAs

In plants, long distance systemic transport pathways for specific RNAs, including mRNAs and miRNAs, play a key role in processes including virus defense, gene silencing, regulation of development, and nutrient allocation. Emerging evidence in eukaryotes also suggests that both mRNAs and ncRNAs can participate in local and more distant intercellular transfer where they may act as dynamic regulatory and signaling molecules [80]. For example, studies of exogenous siRNA introduction into *C. elegans* result in systemic distribution and subsequent systemic gene expression knockdown. These experiments have implicated Sid1, a transmembrane protein that serves as receptor for dsRNA, as a vehicle for passive transport of siRNAs into cells and as a key mechanism for systemic RNA interference [81].

Another mechanism of intercellular RNA transport is through exosomes. These RNA-containing microvesicles are secreted by cells such as B cells and macrophages and participate in antigen delivery and presentation [82]. They are also secreted by neurons [83]. Secretory exosomes contain a variety of mRNAs and ncRNAs and express cell recognition molecules on their surface for selective targeting and uptake into recipient cells. In the CNS, activity-dependent changes in exosome processing may regulate neural network connectivity

by differential activation and processing of mRNAs and regulatory ncRNAs supplementing the known mechanisms of anterograde and retrograde signaling across synapses [84]. In fact, some authors have suggested that exosomes bud from the postsynaptic membrane when stimulated transferring post-synaptic RNAs and newly synthesized proteins back to the presynaptic terminal, thereby contributing to retrograde signaling-mediated synaptic plasticity. Further, in CNS disease states such as glioblastoma multiforme, a particularly virulent form of primary brain cancer, tumor cells can deliver mRNAs, miRNAs and proteins to normal cells via secretory exosomes, and these may play roles in supporting and/or propagating the tumor [85,86].

Informational content of RNA molecules

Understanding RNA-based networks and their mechanism of action requires an appreciation for the inherent properties of RNA molecules. Specifically, the ability of RNA to store, transform and transmit both “digital” and “analog” information is a key feature of RNA-based systems [20]. Watson and Crick base pairing represents digital information whereby canonical nucleotide hybridization rules are determined by the most energetically favored conformations of these molecules. The digital information encoded by an mRNA is not used completely in polypeptides derived from the mRNA because of codon degeneracy. Analog information is, however, captured by more continuous secondary and tertiary RNA structures that are determined by ionic charges and hydrophobic properties [87]. This structural analog information may also be modified based on the specific thermodynamic conditions within the cellular microenvironment, such as temperature and ion concentrations and gradients, resulting in flexible structure and charge characteristics of RNA molecules.

Dynamic interactions between RNA, DNA and protein networks are necessary to carry out normal cellular activities, and this digital and analog information carrying capacity allows RNA to assimilate with both the digital language of DNA and the analog world of protein structure. Because of these attributes, RNA is able to serve as both a high fidelity informational molecule as well as a functional complex that can sense changes in the cellular environment and adapt its structure and function accordingly. In addition, RNA allows efficient coupling of cellular energy requirements with information storage and processing compared with DNA or protein because it is information dense and can be rapidly activated, modified, transported and degraded. Significant differences in profiles of evolutionary conservation, particularly when comparing ncRNA primary sequence organization and higher order structural features, suggest that RNA contains sophisticated forms of embedded genomic information that contribute to enhancing molecular diversity and functional versatility within the mammalian nervous system [88]. Moreover, RNA conformational plasticity and highly interactive and constantly evolving RNA regulatory circuitry may have been instrumental in allowing these nucleic acids to participate in accelerated evolution because they are not constrained by the intricate and interdependent intracellular signaling networks associated with protein species. This may represent a more general mechanism by which RNA signaling networks have established their preeminence in mediating the explosive innovations in brain form and function that have occurred during higher eukaryotic evolution.

RNA as a biosensor

The detection of catalytic RNAs, or ribozymes, in the 1980s and the recent identification of many other classes of biologically relevant RNAs have spurred interest in further characterizing the plethora of functions mediated by these RNAs. Many studies suggest that one of these tasks is to sense and regulate cellular metabolism in concert with protein-based networks [89–95]. Numerous metabolic enzymes have been shown to bind RNA directly or associate indirectly with RNA in complexes. Most of these enzymes are conserved

throughout evolution, distributed widely, and participate in indispensable cellular pathways. These complexes seem to behave as sensors for particular cellular conditions and through various mechanisms regulate metabolic activity. For example, the metabolic enzyme aconitase is also an iron-responsive RNA-binding regulatory element (IRE-BP) that binds to RNAs containing iron-responsive elements (IREs) [96]. RNAs with IREs can sense when intracellular iron concentrations are above a certain threshold through conformational changes and form RNA-protein complexes that are not metabolically active. When cells are iron depleted, the RNA-protein complex dissociates, and the protein functions as an active aconitase. Interestingly, these pathways are associated with protection from neural oxidative damage and, when disrupted, with neurodegeneration [96,97].

Stereoisomers

The genome also contains sequence elements that have the potential to form left-handed Z-DNA structures that have been observed specifically in regions of active transcription where they may provide relief of torsional strain, modulate chromatin structure, and bind RNA editing enzymes [98]. Further, these may be relevant in the pathophysiology of neurological disorders, such as Alzheimer disease [30]. Although active transcription is not required for the formation of Z-DNA, it has been associated with expansion of Z-DNA regions and serves as an important mechanism for modulating gene expression and chromatin structure. For example, activation of colony-stimulating factor 1 (CSF1) by BRG1, a chromatin-remodeling enzyme, results in Z-DNA formation within its promoter and disruption of nucleosomal structure, and both BRG1 and Z-DNA formation are necessary for this chromatin remodeling process [99]. In addition, Z-RNA formed during transcription can also preferentially bind to RNA editing enzymes, such as ADAR1, which can then modify the new RNA transcript [100].

Nuclear organization and dynamics

Nuclear organization and dynamics refer to the shifting spatial arrangements of chromosomes, chromatin, and specific gene loci within the nucleus; the formation and movement of functional nuclear domains; and the interplay that occurs between these factors during the execution of genomic programs (e.g., gene transcription and post-transcriptional processing) [1,10–15]. The genome can undergo controlled local and long-range movements, more global reorganization, as well as other shifts (e.g., chromatin states) that have functional consequences for nuclear processes. Further, the nucleus contains a number of specialized sub-organelles comprised of particular proteins and RNA species, including some whose roles have been characterized and others that are less well understood. These heterogeneous nuclear domains can dynamically assemble and disassemble, associate with specific genomic loci, interact with chromatin, move, and undergo other changes. These three-dimensional features of nuclear structure and function do not arise randomly. Rather, they are associated with particular physiological cues and cellular processes, such as cell-cycle progression and differentiation. Although the regulation and function of many nuclear features has not yet been elucidated, recent advances have highlighted the interconnected nature of nuclear organization and dynamics with epigenetic regulation.

General structure of the nucleus

The genome and nucleoplasm are surrounded by the nuclear envelope and associated nuclear pore complexes and the nuclear lamina. These structures are not only mechanical components of the nucleus but they also play key functional roles, including modulating chromatin organization, gene expression and epigenetic regulation and various signaling pathways. The nuclear envelope is a double-layered membrane that separates the cytoplasmic and nuclear compartments [101]. It is contiguous with the endoplasmic

reticulum, though it is characterized by enrichment of specific proteins within its inner and outer membranes. The nuclear and cytoplasmic compartments communicate through several openings in the nuclear envelope called nuclear pores, which are formed by the nucleoporin family of proteins [102]. Nuclear pore complexes form channels that promote the bidirectional exchange of proteins, RNAs, and RNPs. The nuclear envelope rests on the nuclear lamina [35,103]. It is a meshwork of intermediate filament proteins found within the inner nuclear membrane that is comprised of lamins and lamin-associated proteins. These factors are responsible for reinforcing the nucleoskeleton, interlinking the nucleoskeleton and cytoskeleton, anchoring nuclear pore complexes, and tethering chromatin to the nuclear envelope as well as for organizing chromatin and regulating signaling and transcription. The integrity of the nuclear lamina is critical for most nuclear activities and leads to a broad range of disorders when compromised (see below).

Spatial arrangement of chromosomes and genes within the nucleus

Chromosome territories represent a basic feature of nuclear architecture [104]. Transcription, transcriptional regulation, and other activities at specific genomic loci correlate with chromosomal positioning in the nucleus. For example, a recent study constructed spatial proximity maps of the human genome employing Hi-C, a technique that couples proximity-based ligation with massively parallel sequencing. These observations suggested the presence of two distinct genomic compartments [105]. One compartment was largely comprised of transcriptionally active, gene-rich chromosomal regions with open chromatin domains, whereas the other compartment was gene-poor with closed chromatin domains. This study further implied that molecular interactions are more likely to occur between chromosomal regions within each compartment.

Complementary studies have shown that the specific localization of genes in distinct nuclear regions has the potential to promote their transcriptional activation or repression [106,107]. For example, radial nuclear compartmentalization appears to play a key role in gene expression, with transcriptional activity being more prevalent in the interior of the nucleus and transcriptional repression being more common in the periphery. Peripheral localization is also associated with the suppression of transcription in heterochromatic regions, such as centromeres and telomeres, which may be tethered to the nuclear envelope. Moreover, repositioning of a gene from the periphery to the interior and vice versa can be associated with gene activation and repression, respectively.

For example, *Mash1* is a neural gene, which is highly expressed during neural lineage commitment of ES cells, and *Mash1* expression is accompanied by repositioning of the gene locus within the nucleus. The *Mash1* locus is preferentially located at the nuclear periphery in ES cells, where it is associated with repressive histone modifications. With neural lineage commitment, the locus specifically migrates towards the interior of the nucleus, where it is associated with increased levels of H3K9 acetylation and lower levels of H3K27 trimethylation concomitant with active transcription of *Mash1* [108]. By contrast, during progressive stages of OL lineage maturation, the myelin gene, *PLP*, remains at the nuclear periphery, despite being up regulated [109]. This is consistent with other observations demonstrating that the nuclear periphery can be permissive for the transcription of certain genes. For example, during T helper cell differentiation, the *IFN*-γ locus remains at the periphery during transcriptional activity and inactivity [110]. Further, genes in the periphery that are localized near the nuclear pore complex may be associated with transcriptional activity, suggesting that these genes are recruited to the nuclear periphery in order to promote mRNA export into the cytoplasm [111].

Chromatin states for a particular gene may confer epigenetic cellular memory of previous transcriptional activation, enabling a cell and its progeny to adapt rapidly to transcriptional

cues [112]. In fact, the non-canonical histone variant H2A.Z is incorporated into the promoters of recently repressed genes and is required to maintain them at the nuclear periphery [45]. For example, the rate of *GAL1* transcriptional induction is regulated by epigenetic memory that is inherited by daughter cells. The *GAL1–10* locus repositions from a more central nucleoplasmic to a peripheral localization when activated but subsequently remains at the nuclear periphery for seven generations despite repression [45]. This rapid reactivation of *GAL1* requires H2A.Z [45] and the SWI/SNF ATP-dependent chromatin remodeling enzyme complex [113].

Looping of actively transcribed genes is another mechanism that has been linked to more short-term transcriptional memory [114,115]. Looping is a phenomenon that refers to the juxtaposition of promoter and terminator regions of genes. It is thought to be a product of transcription, and gene loops that are maintained after transcription has been repressed have been designated as memory gene loops (MGLs). These MGLs can persist for one to four hours and promote rapid reactivation of the repressed gene. Intriguingly, looping has been observed in all transcriptionally active genes, including those in humans, analyzed by chromosome conformation capture (3C), a sensitive method for detecting physical genomic interactions. However, not all loops are MGLs nor do MGLs alone mediate transcriptional memory. Mlp1 (TPR in mammalian cells), a nuclear pore complex associated protein, is required for maintaining MGLs, and both Mlp1 and SWI/SNF are required for transcriptional memory.

Functional nuclear domains

The nucleus is compartmentalized into structural and functional sub-organelles (i.e., nuclear domains, bodies, or compartments), such as transcription factories, nucleoli, CBs, PML-NBs, nuclear speckles, and paraspeckles that serve as transcriptional and post-transcriptional control mechanisms [116].

The molecular machinery involved in the process of transcription can preassemble into a number of distinct and spatially restricted nuclear foci called *transcription factories* that are responsible for the coordinated, rapid, and efficient activation of gene expression. For example, immediate early genes commonly reposition into these existing transcription factories during transcriptional activation by looping out of their chromosomal territories [117]. Similarly, actively transcribed globin genes associate with hundreds of other transcribed genes from various intra- and inter-chromosomal regions and with the transcription factor, Klf1 in transcription factories that are found in the nuclei of mouse erythroid cells [118]. Intriguingly, a recent study in neurons suggested that transcription factories may be responsible for the activity-dependent transcriptional regulation of cytochrome C oxidase (COX), a multisubunit bigenomically encoded enzyme [119]. 3C analysis revealed that 10 genomic loci encoding the nuclear subunits of COX and three loci encoding mitochondrial transcription factors critical for the transcription of mitochondria-encoded COX subunits all occupy the same nuclear sites [119]. Further, transcription factories can either be "poised" or "active" depending on the phosphorylation state of RNA polymerase II (Pol-II), implying that functionally related genes associated with poised transcription factories can very quickly be induced in response to specific stimuli [120].

The *nucleolus* is a nuclear compartment that represents a very large transcription factory involved in ribosomal biogenesis [121]. Mammalian nuclei usually contain a single nucleolus that is established by clusters of ribosomal DNA (rDNA) repeats called nucleolus organizer regions (NORs). The structure of the nucleolus is dynamic and can react to external stimuli [122,123]. rRNAs are transcribed by Pol-I, and their expression is regulated by specific epigenetic factors [124]. Inactive NORs exist in a heterochromatic state mediated by the repressive NoRC chromatin remodeling complex and by regulatory ncRNAs

transcribed from the intergenic spacer (IGS) that separates rRNA genes [124,125]. In contrast, active NORs exist in euchromatic states mediated by activating Cockayne syndrome protein B (CSB), the histone methyltransferase, G9a, and the DNA methylation-related proteins, MBD3 and Gadd45a [124]. The *perinucleolar compartment* (PNC) is a nuclear body closely associated with the nucleolus, whose specific function remains known. However, components of the PNC include ncRNAs transcribed by Pol-III, such as those derived from Alu elements, and various RBPs including PTB, which is important for CNS-specific alternative splicing [126].

Cajal bodies (or coiled bodies; CBs) are characterized by the presence of the signature CB protein, p-80/coilin, and a heterogeneous group of other factors that dynamically co-localize with coilin [127,128]. These factors include but are not limited to NPAT, a histone transcription factor; fibrillarin and NOPP140, which are also components of the nucleolus; and survival of motor neuron (SMN), which is mutated in the neuromuscular disease, spinal muscular atrophy (SMA). This structure was initially described by Santiago Ramon y Cajal in neurons, where it is prominent, but is also present in other cell types. The number and size of CBs in a cell vary during specific cellular states (i.e., cell-cycle phase) and are responsive to the overall levels of gene transcription. Further, CBs are also responsive to cell stress (i.e., viral infection and DNA damage), and CBs can be associated with PML-NBs (see below), suggesting that these nuclear domains may co-regulate certain nuclear events. In some cell lines and fetal tissues, the Gemini of CBs or “gems” represent SMN-containing nuclear bodies found adjacent to CBs, whose functions remain unknown [128].

CBs are implicated primarily in mediating small nuclear ribonucleoprotein (snRNP) metabolism. They contain a high concentration of snRNPs and other RNA processing factors and play key roles in the biogenesis of several classes of snRNP. snRNPs re-entering the nucleus are targeted to the CB, where snRNAs are modified (methylation and pseudouridylation). These modifications are mediated by small CB-specific RNAs (scaRNAs), a subclass of small nucleolar RNAs (snoRNAs). In addition, CBs may also play roles in histone mRNA processing, through close associations with histone locus bodies, and also possibly in telomere maintenance [128]. Further, CBs have been implicated as sites of siRNA and miRNA biogenesis in plants [129].

Promyelocytic leukemia nuclear bodies (PML-NBs) are dynamic and heterogeneous macromolecular protein complexes formed generally, but not always, by multimers of SUMOylated promyelocytic leukemia (PML), a promiscuous scaffolding protein, and its various direct and indirect partners, which include eIF4E and Sp100 [130]. The PML protein was initially identified as a part of the fusion proteins resulting from the reciprocal chromosomal translocation of chromosomes 15 and 17 that is found in patients with acute promyelocytic leukemia (APL). As such, the best-known biological functions of PML and PML-NBs are roles in cellular proliferation and apoptosis discovered, in part, through studies of APL and several different types of cancers [131]. These roles may be mediated through interactions with key factors including, for example, the tumor suppressors, p53 and pRb; the oncoprotein, Mdm2; the DNA repair factor, RAD51; the signaling molecules, mTOR and Akt; and the pro-apoptotic factors, c-jun and Daxx. Further studies seeking to elucidate the composition and function of PML-NBs have revealed an interactome of 166 protein partners for PML, of which, the vast majority are involved in regulating transcription [132]. These results are consistent with previous studies suggesting that PML-NBs are associated with nuclear regions of high transcriptional activity. These factors are also implicated in cell cycle regulation, post-translational modifications, virus-host interactions, DNA damage/repair responses, and apoptosis/stress responses [132]. Intriguingly, a subclass of PML-NBs, termed ALT-associated PML bodies (APBs), associates with telomeres and

mediates a process referred to as alternative lengthening of telomeres (ALT) that allows telomere maintenance independently of telomerase activity in cancer cells [133].

PML-NBs are also implicated in epigenetic processes through interactions with chromatin and associations with various epigenetic regulatory factors, such as HP1 as well as various histone methyltransferases, histone deacetylases and DNA methyltransferases. For example, PML interacts with the genome-organizing factor, SATB1, to promote the organization of the major histocompatibility complex (MHC) class I locus into distinct higher-order chromatin-loop structures, linking PML with higher-order chromatin organization and gene regulation [134]. Moreover, the PML-NB associated factor, Daxx, is also involved in the deposition of the histone variant H3.3 that has been implicated in the epigenetic memory of cellular state in neural progenitor cells (NPCs) [47,135].

One recent study of the developing CNS serves as an example that has expanded our understanding of PML and PML-NB function during normal development [136]. PML is expressed selectively in NPCs in the ventricular zone of the developing mouse neocortex [136]. *Pml*$^{-/-}$ mice exhibit increases in the overall number of proliferating NPCs; alterations in the ratio of radial glial cells and basal progenitors, two major NPC subtypes; and defects in cortical development. These effects of PML are mediated by its interactions with pRb and PP1α in PML-NBs. These observations highlight the roles of PML and PML-NBs in modulating cell fate in the CNS and are consistent with evidence implicating the loss of the PML protein in the development and progression of primary CNS malignancies (i.e., oligodendroglial tumors and medulloblastomas) [131]. These findings are also congruent with the roles of PML and PML-NBs in modulating hematopoietic stem cell maintenance [137] and progenitor cell fate in the mammary gland [138].

Nuclear speckles are dynamic nuclear compartments that contain snRNPs and a number of post-transcriptional pre-mRNA metabolism factors. Proteomic analysis has identified 178 speckle proteins with roles in pre-mRNA processing, mRNA binding/packaging, and mRNA transport roles [139]. In fact, speckles are thought to act as the main sites for storage, assembly, and recycling of spliceosomal machinery. Some of these factors have an arginine/serine-rich domain, which targets them to speckles. Similarly, histidine repeats seem to target genes associated with nervous system development to speckles [140]. Some genes, including heat-shock genes and erythroid and muscle cell differentiation genes, are associated with and even cluster around speckles when transcribed [141]. These observations suggest that these gene-speckle associations promote the maturation of such RNAs. Notably, in OLs, active transcription of the *PLP* gene induces the formation of adjacent speckles, suggesting that speckles are important for myelin formation [109]. Also, NeuN/Fox-3, a marker for post-mitotic neurons, is reliably found in nuclear speckles, further highlighting the importance of these structures in the CNS [142].

Nuclear paraspeckles are more recently characterized nuclear domains that are implicated in the regulation of mRNA nuclear export [143–146]. A mammalian lncRNA, *NEAT1/VINC/MEN*ε/β, is the primary component responsible for the formation and maintenance of paraspeckles, and paraspeckles are often associated closely with the *NEAT1* gene locus [143–146]. To form paraspeckles, *NEAT1* associates with a relatively small number of proteins including, most prominently, members of the *Drosophila* Behavior Human Splicing (DBHS) family of proteins—PSPC1, SFPQ and P54NRB. These proteins bind to single- and double-stranded DNA and RNA and are involved in various aspects of RNA transcription (i.e., transcription initiation and termination) and post-transcriptional processing (i.e., splicing). However, the key function of paraspeckles seems to be promoting the retention of hyper-edited mRNAs in the nucleus [147].

For example, the expression of the mouse-specific RNA, *Ctn*, is regulated by nuclear retention within paraspeckles [148]. *Ctn* is transcribed from the same gene locus as *mCAT2* but utilizes an alternative promoter and distal polyA site. Compared with canonical *mCAT2*, *Ctn* has a much longer 3'UTR containing repeat elements subject to A-to-I RNA editing. The cleavage of this long 3'UTR promotes nuclear export and results in increased levels of mCAT2 protein. Intriguingly, a number of factors with important roles in the CNS have relatively long 3'UTRs [149] and are subject to high levels of RNA editing [70]. These observations suggest that paraspeckles and the associated RNA nuclear retention mechanism are particularly important in mediating key CNS functions.

The roles of paraspeckles have already been linked to neurobiological processes, including neural differentiation and circadian rhythm maintenance. Notably, *NEAT1* is not expressed in human ES cells but is expressed during differentiation [150], including in neuronal and OL lineages [66]. Further, Sox9, a key OL developmental transcription factor, may be a paraspeckle component [151]. Also, P54NRB is required for circadian rhythm maintenance through effects on the circadian rhythm maintenance factor, PER1 [152].

Similarly, the lncRNA, *Gomafu* has also been detected in differentiating NPCs and post-mitotic neurons in regions of the nucleus that do not co-localize with known nuclear domains [153]. These observations suggest that *Gomafu* is localized in a novel nuclear domain and possibly that lncRNAs, more generally, constitute cell-type-specific components of the nuclear matrix.

The functional roles of additional nuclear bodies, including but not limited to stress bodies [154], cleavage bodies [155], polycomb bodies [156], matrix-associated deacetylase bodies [157], clastosomes [158], DDX1 bodies [159], and FBXO25-associated nuclear domains [160] are still emerging.

Neurological diseases

Abnormalities in nuclear organization and dynamics have been associated with a variety of CNS disease states. These impairments represent primary pathogenic mechanisms for a subset of these disorders and have been linked to epigenetic deregulation. The functional significance of nuclear lesions such as aberrant nuclear domains or inclusions, which are found in disorders including some common neurodegenerative diseases, is largely unknown.

Laminopathies or envelopathies

Lamins and lamin-associated proteins are important for the structural and functional integrity of the nucleus. Disorders of these factors cause a range of diseases called laminopathies or envelopathies [35]. The A-type lamins, lamin A and lamin C, are alternatively spliced variants encoded by the *LMNA* gene. *LMNA* mutations typically present with muscle, peripheral nerve, and adipose symptoms (e.g., lipodystrophies) or progeria. These neurological diseases include neuromuscular disorders, autosominal dominant (and rarely recessive) Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy type 1B, and congenital muscular dystrophy; peripheral neuropathy, Charcot-Marie-Tooth disease type 2B1 [23]; and progeria phenotypes, Hutchinson-Gilford progeria syndrome, atypical Werner Syndrome, variant progeroid disorders, and mandibuloacral dysplasia [161]. By contrast, other genes, including *LMNB1*, which is mutated in adult-onset autosomal dominant leukodystrophy, encode B-type lamins [25]. Mutations in lamin-associated proteins also cause neurological diseases. EMD is responsible for X-linked forms of Emery-Dreifuss muscular dystrophy [162]. SYNE1 is responsible for a form of autosomal recessive cerebellar ataxia [163]. TOR1A/DYT1 is responsible for an early-onset form of torsion dystonia [164]. A variety of studies show that the molecular pathophysiology of these

laminopathies is related to defects in the normal profiles of gene-specific and genome-wide chromatin rearrangements [27,165,166]. In addition, other interesting observations suggest that the pathology of disorders not traditionally thought to be laminopathies, such as fragile X tremor ataxia syndrome may, in fact, be due to dysregulation of lamin A/C function [24]. Similarly, irregularities in the nuclear envelope (i.e., fragmentation, prominent nuclear pore aggregation, and a close association with paired helical filaments) have been noted as features of Alzheimer's disease [26].

Cohesinopathies

Mutations in cohesin and related proteins lead to diseases termed cohesinopathies [29]. Cornelia de Lange syndrome (CdLS) and Roberts syndrome (RBS) are the best characterized and are associated with clinical findings including growth and mental retardation, limb deformities, and craniofacial anomalies as well as a spectrum of neuropathological lesions [167]. Because cohesin is a multi-subunit complex that is known to be responsible for facilitating cohesion between sister chromatids and enabling proper chromosome segregation during cell division and post-replicative DNA repair, it might be expected that defects in these processes underlie the pathogenesis of cohesinopathies. However, this is not the case [32]. Interestingly, transcriptional dysregulation is one of the hallmarks of these diseases, suggesting that cohesin may subserve alternative non-canonical roles. In fact, the cohesin pathway is now being linked to a range of additional functions related to genome organization and dynamics [32]. These potentially include mediating local gene regulation, long-distance intergenomic interactions, and nuclear positioning of genomic sequences. Cohesin co-localizes with and is perhaps recruited by CTCF to specific genomic sites [168]. Studies have shown that cohesin can mediate transcriptional activation, transcriptional repression, and transcription termination at these sites. Further, disruption of cohesin-mediated gene regulation is categorically linked to aberrations in neuronal development [32]. In addition, cohesin facilitates enhancer-promoter interactions, which suggests that it may promote formation or stabilize of chromatin loops. Cohesin can modulate the *IFN*-γ, imprinted *Igf2/H19*, *Hbb*, and *apolipoprotein* gene loci [32]. It has also been observed that cohesin may regulate *GAL2* transcription and recruitment to the nuclear periphery [169] and facilitate the nuclear positioning of telomeres [32]. Together, these observations suggest that cohesinopathies may result from deregulation of chromatin organization within the nucleus.

Disorders linked to functional nuclear domains

Nuclear domains are thought to play roles in cellular processes, such as cell stress, DNA damage and apoptosis, which are associated with the pathophysiology of diverse CNS disorders. Factors that are deregulated in these diseases may be functional components of these domains. For example, reductions in the CB-associated SMN protein result in SMA, a neuromuscular disorder characterized by degeneration of the anterior horn cells of the spinal cord [170]. It remains unclear why mutations or deletions of the *SMN1* gene, a ubiquitously expressed factor, give rise to cell type-specific pathology. However, this pattern is also observed in other neurodegenerative diseases. One hypothesis is that neurons, in general, and motor neurons, in particular, are selectively vulnerable to the deregulation of RNA metabolism that is the result of SMN depletion [171]. SMN is part of a complex that mediates the biogenesis of spliceosomal snRNPs [172]. Specifically, it is involved as a chaperone in the assembly of spliceosomal snRNPs in the cytoplasm and their delivery to the CB [172]. CUG-BP1 plays a role in the pathogenesis of myotonic dystrophy and is enriched in PNCs [173]. Similarly, CDKL5, a protein that is localized to nuclear speckles and involved in regulating their function, is linked to a variant of Rett syndrome, an autistic spectrum disorder. CDKL5 over expression promotes speckle disassembly and down regulation affects nuclear speckles, suggesting deregulation of splicing may underlie the

neurodevelopmental deficits characteristic of this CDKL5-related disorder [174]. TDP-43, a protein linked to frontotemporal lobar degeneration and amyotrophic lateral sclerosis, is found in speckles [175]. Notably, a factor that plays a major role in familial forms of Alzheimer's disease, APP, localizes to nuclear bodies called AFT complexes that are associated with, but are distinct from, nuclear speckles, CBs and PML-NBs [33].

Nuclear domains may not only be associated with factors implicated in neurological diseases, but these domains may also exhibit abnormalities in these disorders (reviewed in detail in [31]). For example, reorganization of nuclear speckles and CBs is a prominent feature found in so-called Purkinje cell degeneration mutant mice. These mice exhibit selective and progressive degeneration of specific neuronal populations [28]. Also, immunodeficiency, centromere instability and facial anomalies (ICF) syndrome results from defects in DNA methylation, chromatin remodeling and transcriptional regulation, and HP1 proteins accumulate in one giant PML-NB [176]. PML has also been found in the nuclear inclusions associated with various neurodegenerative disorders [31].

Disorders linked to miscellaneous nuclear defects

Dysfunction of transcriptional regulation, DNA repair, and other nuclear processes has been implicated as a key factor in the pathogenesis of various CNS disorders including forms of hereditary ataxia [34]. Transcriptional deregulation is involved in the pathogenesis of the dominantly inherited ataxias—spinocerebellar ataxia types 1 and 17 (SCA1 and SCA17). SCA1 is caused by an expanded repeat in the *ATXN1* gene that may influence transcriptional regulation and splicing [177]. In fact, ATXN1 interacts with various regulators of transcription (e.g., CIC and RORα/Tip60), RNA species, as well as RNA-processing proteins (e.g., RBM17) [34]. Similarly, SCA17 is caused by an expanded repeat in the *TBP* gene encoding a TATA-binding transcription factor (TBP/TFIID) essential for the function of all three nuclear RNA polymerases [178]. Abnormalities in single-strand break and double-strand break DNA repair pathways are also involved in the pathogenesis of inherited ataxias. Ataxia telangiectasia (AT) arises from defects due to *ATM* gene mutations [179]. Ataxia with ocular apraxia type 1 (AOA1) and spinocerebellar ataxia and neuropathy 1 (SCAN1) are caused by mutations in the *APTX* and *TDP1* genes, respectively [180,181]. Why mutations in these factors result in neuronal cell-type specific pathology and “nuclear ataxias” remains unknown. However, one hypothesis is that the specific epigenetic state of neuronal DNA makes it either more or less accessible to DNA-binding proteins and thus confers selectively vulnerability on these cells [34].

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References

1. Mehler MF. Epigenetic principles and mechanisms underlying nervous system functions in health and disease. Prog Neurobiol. 2008; 86:305–341. [PubMed: 18940229]
2. Robertson KD. DNA methylation and human disease. Nat Rev Genet. 2005; 6:597–610. [PubMed: 16136652]
3. Jenuwein T, Allis CD. Translating the histone code. Science. 2001; 293:1074–1080. [PubMed: 11498575]
4. Kouzarides T. Chromatin modifications and their function. Cell. 2007; 128:693–705. [PubMed: 17320507]
5. Szyf M. Epigenetics, DNA methylation, and chromatin modifying drugs. Annu Rev Pharmacol Toxicol. 2009; 49:243–263. [PubMed: 18851683]

6. Cairns BR. The logic of chromatin architecture and remodelling at promoters. Nature. 2009; 461:193–198. [PubMed: 19741699]
7. Schoeftner S, Blasco MA. A 'higher order' of telomere regulation: telomere heterochromatin and telomeric RNAs. EMBO J. 2009; 28:2323–2336. [PubMed: 19629032]
8. Peng JC, Karpen GH. Epigenetic regulation of heterochromatic DNA stability. Curr Opin Genet Dev. 2008; 18:204–211. [PubMed: 18372168]
9. Payer B, Lee JT. X chromosome dosage compensation: how mammals keep the balance. Annu Rev Genet. 2008; 42:733–772. [PubMed: 18729722]
10. Mattick JS, et al. RNA regulation of epigenetic processes. Bioessays. 2009; 31:51–59. [PubMed: 19154003]
11. Qureshi IA, Mehler MF. Regulation of non-coding RNA networks in the nervous system--what's the REST of the story? Neurosci Lett. 2009; 466:73–80. [PubMed: 19679163]
12. Nunez E, Fu XD, Rosenfeld MG. Nuclear organization in the 3D space of the nucleus - cause or consequence? Curr Opin Genet Dev. 2009; 19:424–436. [PubMed: 19846290]
13. Zhao R, Bodnar MS, Spector DL. Nuclear neighborhoods and gene expression. Curr Opin Genet Dev. 2009; 19:172–179. [PubMed: 19339170]
14. Lanctot C, et al. Dynamic genome architecture in the nuclear space: regulation of gene expression in three dimensions. Nat Rev Genet. 2007; 8:104–115. [PubMed: 17230197]
15. Joffe B, Leonhardt H, Solovei I. Differentiation and large scale spatial organization of the genome. Curr Opin Genet Dev. 2010
16. Carninci P, et al. The transcriptional landscape of the mammalian genome. Science. 2005; 309:1559–1563. [PubMed: 16141072]
17. Katayama S, et al. Antisense transcription in the mammalian transcriptome. Science. 2005; 309:1564–1566. [PubMed: 16141073]
18. Birney E, et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature. 2007; 447:799–816. [PubMed: 17571346]
19. Taft RJ, et al. Non-coding RNAs: regulators of disease. J Pathol. 2010
20. St Laurent G 3rd, Wahlestedt C. Noncoding RNAs: couplers of analog and digital information in nervous system function? Trends Neurosci. 2007; 30:612–621. [PubMed: 17996312]
21. Farajollahi S, Maas S. Molecular diversity through RNA editing: a balancing act. Trends Genet. 2010; 26:221–230. [PubMed: 20395010]
22. Cohen M, et al. Transcriptional repression, apoptosis, human disease and the functional evolution of the nuclear lamina. Trends Biochem Sci. 2001; 26:41–47. [PubMed: 11165516]
23. De Sandre-Giovannoli A, et al. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot-Marie-Tooth disorder type 2) and mouse. Am J Hum Genet. 2002; 70:726–736. [PubMed: 11799477]
24. Arocena DG, et al. Induction of inclusion formation and disruption of lamin A/C structure by premutation CGG-repeat RNA in human cultured neural cells. Hum Mol Genet. 2005; 14:3661–3671. [PubMed: 16239243]
25. Padiath QS, et al. Lamin B1 duplications cause autosomal dominant leukodystrophy. Nat Genet. 2006; 38:1114–1123. [PubMed: 16951681]
26. Sheffield LG, et al. Nuclear pore complex proteins in Alzheimer disease. J Neuropathol Exp Neurol. 2006; 65:45–54. [PubMed: 16410748]
27. Shumaker DK, et al. Mutant nuclear lamin A leads to progressive alterations of epigenetic control in premature aging. Proc Natl Acad Sci U S A. 2006; 103:8703–8708. [PubMed: 16738054]
28. Valero J, et al. Pre-neurodegeneration of mitral cells in the pcd mutant mouse is associated with DNA damage, transcriptional repression, and reorganization of nuclear speckles and Cajal bodies. Mol Cell Neurosci. 2006; 33:283–295. [PubMed: 16978877]
29. Liu J, Krantz ID. Cohesin and human disease. Annu Rev Genomics Hum Genet. 2008; 9:303–320. [PubMed: 18767966]
30. Vasudevaraju P, et al. Role of DNA dynamics in Alzheimer's disease. Brain Res Rev. 2008; 58:136–148. [PubMed: 18342372]

31. Woulfe J. Nuclear bodies in neurodegenerative disease. Biochim Biophys Acta. 2008; 1783:2195–2206. [PubMed: 18539152]
32. Bose T, Gerton JL. Cohesinopathies, gene expression, and chromatin organization. J Cell Biol. 2010; 189:201–210. [PubMed: 20404106]
33. Konietzko U, et al. Co-localization of the amyloid precursor protein and Notch intracellular domains in nuclear transcription factories. Neurobiol Aging. 2010; 31:58–73. [PubMed: 18403052]
34. Orr HT. Nuclear ataxias. Cold Spring Harb Perspect Biol. 2010; 2 a000786.
35. Worman HJ, Ostlund C, Wang Y. Diseases of the nuclear envelope. Cold Spring Harb Perspect Biol. 2010; 2 a000760.
36. Pheasant M, Mattick JS. Raising the estimate of functional human sequences. Genome Res. 2007; 17:1245–1253. [PubMed: 17690206]
37. Gingeras TR. Implications of chimaeric non-co-linear transcripts. Nature. 2009; 461:206–211. [PubMed: 19741701]
38. Jeziorska DM, Jordan KW, Vance KW. A systems biology approach to understanding cis-regulatory module function. Semin Cell Dev Biol. 2009; 20:856–862. [PubMed: 19660565]
39. Denoeud F, et al. Prominent use of distal 5' transcription start sites and discovery of a large number of additional exons in ENCODE regions. Genome Res. 2007; 17:746–759. [PubMed: 17567994]
40. Bulger M, Groudine M. Enhancers: the abundance and function of regulatory sequences beyond promoters. Dev Biol. 2010; 339:250–257. [PubMed: 20025863]
41. Theo Sijtse Palstra RJ. Close encounters of the 3C kind: long-range chromatin interactions and transcriptional regulation. Brief Funct Genomic Proteomic. 2009; 8:297–309. [PubMed: 19535505]
42. Wallace JA, Felsenfeld G. We gather together: insulators and genome organization. Curr Opin Genet Dev. 2007; 17:400–407. [PubMed: 17913488]
43. Ohlsson R, Lobanenkov V, Klenova E. Does CTCF mediate between nuclear organization and gene expression? Bioessays. 2010; 32:37–50. [PubMed: 20020479]
44. Raab JR, Kamakaka RT. Insulators and promoters: closer than we think. Nat Rev Genet. 2010; 11:439–446. [PubMed: 20442713]
45. Brickner DG, et al. H2A.Z-mediated localization of genes at the nuclear periphery confers epigenetic memory of previous transcriptional state. PLoS Biol. 2007; 5:e81. [PubMed: 17373856]
46. Chow CM, et al. Variant histone H3.3 marks promoters of transcriptionally active genes during mammalian cell division. EMBO Rep. 2005; 6:354–360. [PubMed: 15776021]
47. Goldberg AD, et al. Distinct factors control histone variant H3.3 localization at specific genomic regions. Cell. 2010; 140:678–691. [PubMed: 20211137]
48. Aoto T, et al. Nuclear and chromatin reorganization in the MHC-Oct3/4 locus at developmental phases of embryonic stem cell differentiation. Dev Biol. 2006; 298:354–367. [PubMed: 16950240]
49. Abrajano JJ, et al. REST and CoREST modulate neuronal subtype specification, maturation and maintenance. PLoS One. 2009; 4:e7936. [PubMed: 19997604]
50. Abrajano JJ, et al. Differential deployment of REST and CoREST promotes glial subtype specification and oligodendrocyte lineage maturation. PLoS One. 2009; 4:e7665. [PubMed: 19888342]
51. Mattick JS. Deconstructing the dogma: a new view of the evolution and genetic programming of complex organisms. Ann N Y Acad Sci. 2009; 1178:29–46. [PubMed: 19845626]
52. Rebollo R, et al. Jumping genes and epigenetics: Towards new species. Gene. 2010; 454:1–7. [PubMed: 20102733]
53. Coufal NG, et al. L1 retrotransposition in human neural progenitor cells. Nature. 2009; 460:1127–1131. [PubMed: 19657334]
54. Faulkner GJ, et al. The regulated retrotransposon transcriptome of mammalian cells. Nat Genet. 2009; 41:563–571. [PubMed: 19377475]
55. Chang S, et al. Small regulatory RNAs in neurodevelopmental disorders. Hum Mol Genet. 2009; 18:R18–R26. [PubMed: 19297398]

56. Thomson T, Lin H. The biogenesis and function of PIWI proteins and piRNAs: progress and prospect. Annu Rev Cell Dev Biol. 2009; 25:355–376. [PubMed: 19575643]
57. Li C, et al. Collapse of germline piRNAs in the absence of Argonaute3 reveals somatic piRNAs in flies. Cell. 2009; 137:509–521. [PubMed: 19395009]
58. Schratt G. Fine-tuning neural gene expression with microRNAs. Curr Opin Neurobiol. 2009; 19:213–219. [PubMed: 19539460]
59. Qureshi IA, Mattick JS, Mehler MF. Long non-coding RNAs in nervous system function and disease. Brain Res. 2010
60. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. Nat Rev Genet. 2009; 10:155–159. [PubMed: 19188922]
61. Mercer TR, et al. Specific expression of long noncoding RNAs in the mouse brain. Proc Natl Acad Sci U S A. 2008; 105:716–721. [PubMed: 18184812]
62. Ponjavic J, et al. Genomic and transcriptional co-localization of protein-coding and long non-coding RNA pairs in the developing brain. PLoS Genet. 2009; 5:e1000617. [PubMed: 19696892]
63. Fineberg SK, Kosik KS, Davidson BL. MicroRNAs potentiate neural development. Neuron. 2009; 64:303–309. [PubMed: 19914179]
64. Royo H, Cavaille J. Non-coding RNAs in imprinted gene clusters. Biol Cell. 2008; 100:149–166. [PubMed: 18271756]
65. Mehler MF, Mattick JS. Noncoding RNAs and RNA editing in brain development, functional diversification, and neurological disease. Physiol Rev. 2007; 87:799–823. [PubMed: 17615389]
66. Mercer TR, et al. Long noncoding RNAs in neuronal-glial fate specification and oligodendrocyte lineage maturation. BMC Neurosci. 2010; 11:14. [PubMed: 20137068]
67. Dinger ME, et al. Long noncoding RNAs in mouse embryonic stem cell pluripotency and differentiation. Genome Res. 2008; 18:1433–1445. [PubMed: 18562676]
68. Sheik Mohamed J, et al. Conserved long noncoding RNAs transcriptionally regulated by Oct4 and Nanog modulate pluripotency in mouse embryonic stem cells. RNA. 2009
69. Nishikura K. Functions and Regulation of RNA Editing by ADAR Deaminases. Annu Rev Biochem. 2009
70. Paz-Yaacov N, et al. Adenosine-to-inosine RNA editing shapes transcriptome diversity in primates. Proc Natl Acad Sci U S A. 2010
71. Zhou L, et al. Activation of toll-like receptor-3 induces interferon-lambda expression in human neuronal cells. Neuroscience. 2009; 159:629–637. [PubMed: 19166911]
72. Schumann GG. APOBEC3 proteins: major players in intracellular defence against LINE-1-mediated retrotransposition. Biochem Soc Trans. 2007; 35:637–642. [PubMed: 17511669]
73. Vuppalanchi D, Willis DE, Twiss JL. Regulation of mRNA transport and translation in axons. Results Probl Cell Differ. 2009; 48:193–224. [PubMed: 19582411]
74. Chotiner JK, et al. Assessment of the role of MAP kinase in mediating activity-dependent transcriptional activation of the immediate early gene Arc/Arg3.1 in the dentate gyrus in vivo. Learn Mem. 2010; 17:117–129. [PubMed: 20154358]
75. Buchan JR, Parker R. Eukaryotic stress granules: the ins and outs of translation. Mol Cell. 2009; 36:932–941. [PubMed: 20064460]
76. Anderson P, Kedersha N. RNA granules: post-transcriptional and epigenetic modulators of gene expression. Nat Rev Mol Cell Biol. 2009; 10:430–436. [PubMed: 19461665]
77. Kulkarni M, Ozgur S, Stoecklin G. On track with P-bodies. Biochem Soc Trans. 2010; 38:242–251. [PubMed: 20074068]
78. Mansfield KD, Keene JD. The ribonome: a dominant force in co-ordinating gene expression. Biol Cell. 2009; 101:169–181. [PubMed: 19152504]
79. Culjkovic B, et al. eIF4E is a central node of an RNA regulon that governs cellular proliferation. J Cell Biol. 2006; 175:415–426. [PubMed: 17074885]
80. Dinger ME, Mercer TR, Mattick JS. RNAs as extracellular signaling molecules. J Mol Endocrinol. 2008; 40:151–159. [PubMed: 18372404]
81. Feinberg EH, Hunter CP. Transport of dsRNA into cells by the transmembrane protein SID-1. Science. 2003; 301:1545–1547. [PubMed: 12970568]

82. McLellan AD. Exosome release by primary B cells. Crit Rev Immunol. 2009; 29:203–217. [PubMed: 19538135]
83. Smalheiser NR. Do Neural Cells Communicate with Endothelial Cells via Secretory Exosomes and Microvesicles? Cardiovasc Psychiatry Neurol. 2009:383086. [PubMed: 20029619]
84. Mercer TR, et al. Noncoding RNAs in Long-Term Memory Formation. Neuroscientist. 2008; 14:434–445. [PubMed: 18997122]
85. Chen C, et al. Microfluidic isolation and transcriptome analysis of serum microvesicles. Lab Chip. 2010; 10:505–511. [PubMed: 20126692]
86. Skog J, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. Nat Cell Biol. 2008; 10:1470–1476. [PubMed: 19011622]
87. Holbrook SR. Structural principles from large RNAs. Annu Rev Biophys. 2008; 37:445–464. [PubMed: 18573090]
88. Pang KC, Frith MC, Mattick JS. Rapid evolution of noncoding RNAs: lack of conservation does not mean lack of function. Trends Genet. 2006; 22:1–5. [PubMed: 16290135]
89. Andre G, et al. S-box and T-box riboswitches and antisense RNA control a sulfur metabolic operon of Clostridium acetobutylicum. Nucleic Acids Res. 2008; 36:5955–5969. [PubMed: 18812398]
90. Wang JX, Breaker RR. Riboswitches that sense S-adenosylmethionine and S-adenosylhomocysteine. Biochem Cell Biol. 2008; 86:157–168. [PubMed: 18443629]
91. Regulski EE, Breaker RR. In-line probing analysis of riboswitches. Methods Mol Biol. 2008; 419:53–67. [PubMed: 18369975]
92. Barrick JE, Breaker RR. The distributions, mechanisms, and structures of metabolite-binding riboswitches. Genome Biol. 2007; 8:R239. [PubMed: 17997835]
93. Strobel SA, Cochrane JC. RNA catalysis: ribozymes, ribosomes, and riboswitches. Curr Opin Chem Biol. 2007; 11:636–643. [PubMed: 17981494]
94. Coppins RL, Hall KB, Groisman EA. The intricate world of riboswitches. Curr Opin Microbiol. 2007; 10:176–181. [PubMed: 17383225]
95. Henkin TM, Grundy FJ. Sensing metabolic signals with nascent RNA transcripts: the T box and S box riboswitches as paradigms. Cold Spring Harb Symp Quant Biol. 2006; 71:231–237. [PubMed: 17381302]
96. Rouault TA. The role of iron regulatory proteins in mammalian iron homeostasis and disease. Nat Chem Biol. 2006; 2:406–414. [PubMed: 16850017]
97. Rogers JT, et al. Iron and the translation of the amyloid precursor protein (APP) and ferritin mRNAs: riboregulation against neural oxidative damage in Alzheimer's disease. Biochem Soc Trans. 2008; 36:1282–1287. [PubMed: 19021541]
98. Wang G, Vasquez KM. Z-DNA, an active element in the genome. Front Biosci. 2007; 12:4424–4438. [PubMed: 17485386]
99. Liu H, et al. Cooperative activity of BRG1 and Z-DNA formation in chromatin remodeling. Mol Cell Biol. 2006; 26:2550–2559. [PubMed: 16537901]
100. Placido D, et al. A left-handed RNA double helix bound by the Z alpha domain of the RNA-editing enzyme ADAR1. Structure. 2007; 15:395–404. [PubMed: 17437712]
101. Hetzer MW. The nuclear envelope. Cold Spring Harb Perspect Biol. 2010; 2 a000539.
102. Strambio-De-Castillia C, Niepel M, Rout MP. The nuclear pore complex: bridging nuclear transport and gene regulation. Nat Rev Mol Cell Biol. 2010; 11:490–501. [PubMed: 20571586]
103. Wilson KL, Foisner R. Lamin-binding Proteins. Cold Spring Harb Perspect Biol. 2010; 2 a000554.
104. Cremer T, Cremer C. Chromosome territories, nuclear architecture and gene regulation in mammalian cells. Nat Rev Genet. 2001; 2:292–301. [PubMed: 11283701]
105. Lieberman-Aiden E, et al. Comprehensive mapping of long-range interactions reveals folding principles of the human genome. Science. 2009; 326:289–293. [PubMed: 19815776]
106. Pickersgill H, et al. Characterization of the Drosophila melanogaster genome at the nuclear lamina. Nat Genet. 2006; 38:1005–1014. [PubMed: 16878134]
107. Kumaran RI, Spector DL. A genetic locus targeted to the nuclear periphery in living cells maintains its transcriptional competence. J Cell Biol. 2008; 180:51–65. [PubMed: 18195101]

108. Williams RR, et al. Neural induction promotes large-scale chromatin reorganisation of the Mash1 locus. J Cell Sci. 2006; 119:132–140. [PubMed: 16371653]
109. Nielsen JA, Hudson LD, Armstrong RC. Nuclear organization in differentiating oligodendrocytes. J Cell Sci. 2002; 115:4071–4079. [PubMed: 12356912]
110. Hewitt SL, et al. Nuclear repositioning marks the selective exclusion of lineage-inappropriate transcription factor loci during T helper cell differentiation. Eur J Immunol. 2004; 34:3604–3613. [PubMed: 15484194]
111. Ahmed S, Brickner JH. Regulation and epigenetic control of transcription at the nuclear periphery. Trends Genet. 2007; 23:396–402. [PubMed: 17566592]
112. Brickner JH. Transcriptional memory at the nuclear periphery. Curr Opin Cell Biol. 2009; 21:127–133. [PubMed: 19181512]
113. Kundu S, Horn PJ, Peterson CL. SWI/SNF is required for transcriptional memory at the yeast GAL gene cluster. Genes Dev. 2007; 21:997–1004. [PubMed: 17438002]
114. Tan-Wong SM, Wijayatilake HD, Proudfoot NJ. Gene loops function to maintain transcriptional memory through interaction with the nuclear pore complex. Genes Dev. 2009; 23:2610–2624. [PubMed: 19933151]
115. Laine JP, et al. A physiological role for gene loops in yeast. Genes Dev. 2009; 23:2604–2609. [PubMed: 19933150]
116. Lamond AI, Sleeman JE. Nuclear substructure and dynamics. Curr Biol. 2003; 13:R825–R828. [PubMed: 14588256]
117. Osborne CS, et al. Myc dynamically and preferentially relocates to a transcription factory occupied by Igh. PLoS Biol. 2007; 5:e192. [PubMed: 17622196]
118. Schoenfelder S, et al. Preferential associations between co-regulated genes reveal a transcriptional interactome in erythroid cells. Nat Genet. 2010; 42:53–61. [PubMed: 20010836]
119. Dhar SS, Ongwijitwat S, Wong-Riley MT. Chromosome conformation capture of all 13 genomic Loci in the transcriptional regulation of the multisubunit bigenomic cytochrome C oxidase in neurons. J Biol Chem. 2009; 284:18644–18650. [PubMed: 19439416]
120. Ferrai C, et al. Poised transcription factories prime silent uPA gene prior to activation. PLoS Biol. 2010; 8 e1000270.
121. Cook PR. The organization of replication and transcription. Science. 1999; 284:1790–1795. [PubMed: 10364545]
122. Louvet E, et al. Dynamics and compartmentation of the nucleolar processing machinery. Exp Cell Res. 2005; 304:457–470. [PubMed: 15748891]
123. Shav-Tal Y, et al. Dynamic sorting of nuclear components into distinct nucleolar caps during transcriptional inhibition. Mol Biol Cell. 2005; 16:2395–2413. [PubMed: 15758027]
124. McStay B, Grummt I. The epigenetics of rRNA genes: from molecular to chromosome biology. Annu Rev Cell Dev Biol. 2008; 24:131–157. [PubMed: 18616426]
125. Mayer C, et al. Intergenic transcripts regulate the epigenetic state of rRNA genes. Mol Cell. 2006; 22:351–361. [PubMed: 16678107]
126. Makeyev EV, et al. The MicroRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing. Mol Cell. 2007; 27:435–448. [PubMed: 17679093]
127. Klevecz RR, Murray DB. Genome wide oscillations in expression. Wavelet analysis of time series data from yeast expression arrays uncovers the dynamic architecture of phenotype. Mol Biol Rep. 2001; 28:73–82. [PubMed: 11931391]
128. Nizami Z, Deryusheva S, Gall JG. The Cajal Body and Histone Locus Body. Cold Spring Harb Perspect Biol. 2010
129. Pontes O, Pikaard CS. siRNA and miRNA processing: new functions for Cajal bodies. Curr Opin Genet Dev. 2008; 18:197–203. [PubMed: 18337083]
130. Borden KL. Pondering the puzzle of PML (promyelocytic leukemia) nuclear bodies: can we fit the pieces together using an RNA regulon? Biochim Biophys Acta. 2008; 1783:2145–2154. [PubMed: 18616965]
131. Gurrieri C, et al. Loss of the tumor suppressor PML in human cancers of multiple histologic origins. J Natl Cancer Inst. 2004; 96:269–279. [PubMed: 14970276]

132. Van Damme E, et al. A manually curated network of the PML nuclear body interactome reveals an important role for PML-NBs in SUMOylation dynamics. Int J Biol Sci. 2010; 6:51–67. [PubMed: 20087442]
133. Yeager TR, et al. Telomerase-negative immortalized human cells contain a novel type of promyelocytic leukemia (PML) body. Cancer Res. 1999; 59:4175–4179. [PubMed: 10485449]
134. Kumar PP, et al. Functional interaction between PML and SATB1 regulates chromatin-loop architecture and transcription of the MHC class I locus. Nat Cell Biol. 2007; 9:45–56. [PubMed: 17173041]
135. Drane P, et al. The death-associated protein DAXX is a novel histone chaperone involved in the replication-independent deposition of H3.3. Genes Dev. 2010; 24:1253–1265. [PubMed: 20504901]
136. Regad T, et al. The tumor suppressor Pml regulates cell fate in the developing neocortex. Nat Neurosci. 2009; 12:132–140. [PubMed: 19136970]
137. Ito K, et al. PML targeting eradicates quiescent leukaemia-initiating cells. Nature. 2008; 453:1072–1078. [PubMed: 18469801]
138. Li W, Rich T, Watson CJ. PML: a tumor suppressor that regulates cell fate in mammary gland. Cell Cycle. 2009; 8:2711–2717. [PubMed: 19652541]
139. Saitoh N, et al. Proteomic analysis of interchromatin granule clusters. Mol Biol Cell. 2004; 15:3876–3890. [PubMed: 15169873]
140. Salichs E, et al. Genome-wide analysis of histidine repeats reveals their role in the localization of human proteins to the nuclear speckles compartment. PLoS Genet. 2009; 5 e1000397.
141. Brown JM, et al. Association between active genes occurs at nuclear speckles and is modulated by chromatin environment. J Cell Biol. 2008; 182:1083–1097. [PubMed: 18809724]
142. Dent MA, et al. NeuN/Fox-3 is an intrinsic component of the neuronal nuclear matrix. FEBS Lett. 2010; 584:2767–2771. [PubMed: 20452351]
143. Sunwoo H, et al. MEN epsilon/beta nuclear-retained non-coding RNAs are up-regulated upon muscle differentiation and are essential components of paraspeckles. Genome Res. 2009; 19:347–359. [PubMed: 19106332]
144. Clemson CM, et al. An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. Mol Cell. 2009; 33:717–726. [PubMed: 19217333]
145. Bond CS, Fox AH. Paraspeckles: nuclear bodies built on long noncoding RNA. J Cell Biol. 2009; 186:637–644. [PubMed: 19720872]
146. Sasaki YT, et al. MENepsilon/beta noncoding RNAs are essential for structural integrity of nuclear paraspeckles. Proc Natl Acad Sci U S A. 2009; 106:2525–2530. [PubMed: 19188602]
147. Zhang Z, Carmichael GG. The fate of dsRNA in the nucleus: a p54(nrb)-containing complex mediates the nuclear retention of promiscuously A-to-I edited RNAs. Cell. 2001; 106:465–475. [PubMed: 11525732]
148. Prasanth KV, et al. Regulating gene expression through RNA nuclear retention. Cell. 2005; 123:249–263. [PubMed: 16239143]
149. Ramskold D, et al. An abundance of ubiquitously expressed genes revealed by tissue transcriptome sequence data. PLoS Comput Biol. 2009; 5 e1000598.
150. Chen LL, Carmichael GG. Altered nuclear retention of mRNAs containing inverted repeats in human embryonic stem cells: functional role of a nuclear noncoding RNA. Mol Cell. 2009; 35:467–478. [PubMed: 19716791]
151. Hata K, et al. Paraspeckle protein p54nrb links Sox9-mediated transcription with RNA processing during chondrogenesis in mice. J Clin Invest. 2008; 118:3098–3108. [PubMed: 18677406]
152. Brown SA, et al. PERIOD1-associated proteins modulate the negative limb of the mammalian circadian oscillator. Science. 2005; 308:693–696. [PubMed: 15860628]
153. Sone M, et al. The mRNA-like noncoding RNA Gomafu constitutes a novel nuclear domain in a subset of neurons. J Cell Sci. 2007; 120:2498–2506. [PubMed: 17623775]
154. Biamonti G, Vourc'h C. Nuclear stress bodies. Cold Spring Harb Perspect Biol. 2010; 2 a000695.
155. Li L, et al. Dynamic nature of cleavage bodies and their spatial relationship to DDX1 bodies, Cajal bodies, and gems. Mol Biol Cell. 2006; 17:1126–1140. [PubMed: 16371507]

156. Gil J, et al. Polycomb CBX7 has a unifying role in cellular lifespan. Nat Cell Biol. 2004; 6:67–72. [PubMed: 14647293]
157. Downes M, et al. Identification of a nuclear domain with deacetylase activity. Proc Natl Acad Sci U S A. 2000; 97:10330–10335. [PubMed: 10984530]
158. Lafarga M, et al. Clastosome: a subtype of nuclear body enriched in 19S and 20S proteasomes, ubiquitin, and protein substrates of proteasome. Mol Biol Cell. 2002; 13:2771–2782. [PubMed: 12181345]
159. Li L, Monckton EA, Godbout R. A role for DEAD box 1 at DNA double-strand breaks. Mol Cell Biol. 2008; 28:6413–6425. [PubMed: 18710941]
160. Manfiolli AO, et al. FBXO25-associated nuclear domains: a novel subnuclear structure. Mol Biol Cell. 2008; 19:1848–1861. [PubMed: 18287534]
161. Scaffidi P, Misteli T. Lamin A-dependent nuclear defects in human aging. Science. 2006; 312:1059–1063. [PubMed: 16645051]
162. Bione S, et al. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. Nat Genet. 1994; 8:323–327. [PubMed: 7894480]
163. Gros-Louis F, et al. Mutations in SYNE1 lead to a newly discovered form of autosomal recessive cerebellar ataxia. Nat Genet. 2007; 39:80–85. [PubMed: 17159980]
164. Ozelius LJ, et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet. 1997; 17:40–48. [PubMed: 9288096]
165. Hakelien AM, et al. Expression of the myodystrophic R453W mutation of lamin A in C2C12 myoblasts causes promoter-specific and global epigenetic defects. Exp Cell Res. 2008; 314:1869–1880. [PubMed: 18396274]
166. Makatsori D, et al. The inner nuclear membrane protein lamin B receptor forms distinct microdomains and links epigenetically marked chromatin to the nuclear envelope. J Biol Chem. 2004; 279:25567–25573. [PubMed: 15056654]
167. Vuilleumier N, et al. Neuropathological analysis of an adult case of the Cornelia de Lange syndrome. Acta Neuropathol. 2002; 104:327–332. [PubMed: 12172920]
168. Wendt KS, Peters JM. How cohesin and CTCF cooperate in regulating gene expression. Chromosome Res. 2009; 17:201–214. [PubMed: 19308701]
169. Gard S, et al. Cohesinopathy mutations disrupt the subnuclear organization of chromatin. J Cell Biol. 2009; 187:455–462. [PubMed: 19948494]
170. Lefebvre S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995; 80:155–165. [PubMed: 7813012]
171. Ule J. Ribonucleoprotein complexes in neurologic diseases. Curr Opin Neurobiol. 2008; 18:516–523. [PubMed: 18929657]
172. Clelland AK, et al. The SMN protein is a key regulator of nuclear architecture in differentiating neuroblastoma cells. Traffic. 2009; 10:1585–1598. [PubMed: 19735367]
173. Fujimura K, Kano F, Murata M. Dual localization of the RNA binding protein CUGBP-1 to stress granule and perinucleolar compartment. Exp Cell Res. 2008; 314:543–553. [PubMed: 18164289]
174. Ricciardi S, et al. CDKL5 influences RNA splicing activity by its association to the nuclear speckle molecular machinery. Hum Mol Genet. 2009; 18:4590–4602. [PubMed: 19740913]
175. Casafont I, et al. TDP-43 localizes in mRNA transcription and processing sites in mammalian neurons. J Struct Biol. 2009; 167:235–241. [PubMed: 19539030]
176. Luciani JJ, et al. PML nuclear bodies are highly organised DNA-protein structures with a function in heterochromatin remodelling at the G2 phase. J Cell Sci. 2006; 119:2518–2531. [PubMed: 16735446]
177. Servadio A, et al. Expression analysis of the ataxin-1 protein in tissues from normal and spinocerebellar ataxia type 1 individuals. Nat Genet. 1995; 10:94–98. [PubMed: 7647801]
178. Zuhlke C, et al. Different types of repeat expansion in the TATA-binding protein gene are associated with a new form of inherited ataxia. Eur J Hum Genet. 2001; 9:160–164. [PubMed: 11313753]
179. Savitsky K, et al. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science. 1995; 268:1749–1753. [PubMed: 7792600]

180. Takashima H, et al. Mutation of TDP1, encoding a topoisomerase I-dependent DNA damage repair enzyme, in spinocerebellar ataxia with axonal neuropathy. Nat Genet. 2002; 32:267–272. [PubMed: 12244316]

181. Moreira MC, et al. The gene mutated in ataxia-ocular apraxia 1 encodes the new HIT/Zn-finger protein aprataxin. Nat Genet. 2001; 29:189–193. [PubMed: 11586300]