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Epigenetic Regulation in Neurodegenerative Diseases

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INTRODUCTION

Mechanisms of epigenetic regulation, including DNA methylation, chromatin remodeling and histone post-translational modifications, are involved in multiple aspects of neuronal function and development. Recent discoveries have shed light on critical functions of chromatin in the aging brain, with an emerging realization that the maintenance of healthy brain relies heavily on epigenetic mechanisms. Here we present recent advances, with a focus on histone modifications and the implications for several neurodegenerative diseases including Alzheimer's, Huntington's and ALS. We highlight common and unique epigenetic mechanisms among these situations and point to emerging therapeutic approaches.

EPIGENETIC REGULATION OF CHROMATIN IN THE BRAIN

Eukaryotic genomic DNA must be packaged to fit inside the nucleus, the diameter of which is roughly 100,000 times smaller than the length of the DNA. By maintaining specific loci at a more 'open' state and other loci tightly packed, chromatin structure regulates various processes that require access to DNA. The nucleosome, which is the basic unit of DNA packaging, consists of 147bp DNA wrapped around a histone octamer (made of two copies of histones H2A, H2B, H3 and H4). Multiple mechanisms that regulate the interaction between histones and DNA control access and recruitment of factors critical for DNA replication, transcription and the DNA damage response.

DNA methylation, histone post-translational modifications, chromatin remodeling, histone protein variants and long non-coding RNA have all been shown to control chromatin structure and regulate a plethora of cellular and organismal processes (Box 1). Established and emerging techniques for the study of chromatin structure enable genome-wide characterization of DNA and interacting proteins at the single cell and single base resolution [1, 2].

Epigenetic regulation has critical implications in human health, with alterations in chromatin known to be involved in multiple illnesses, most notably cancer, where drugs that inhibit DNA methylation and histone deacetylation have been approved for clinical use by the FDA [3]. With specific relevance to the brain, mutations in several chromatin-associated factors lead to neurological disorders, including autism spectrum disorder, mental retardation, intellectual disability and epilepsy [4], highlighting the important roles of epigenetic mechanisms for brain development and function. The brain has unique metabolic

characteristics [5], and metabolism controls important aspects of epigenetic regulation [6]. For example, production of acetyl-CoA, a substrate for histone acetylation, is carried out in neurons in proximity of genomic loci that are critical for learning and memory. This ‘on-site production’ likely allows efficient acetyl-transferase reaction and supports neuronal gene expression [7]. The protein levels of multiple epigenetic factors are also altered by mutations in the translational regulator FMRP in Fragile X syndrome [8], the leading cause of intellectual disability and autism. A shared histone acetylome profile characterizes cortical chromatin in autism spectrum disorders [9]. These recent findings suggest a unifying underpinning in the heterogeneous group of neurological disorders encompassed by intellectual disability and autism.

DNA CpG demethylation occurs in brain-specific genes related to neuronal plasticity following neuronal activation [10], and non-CG methylation (mCH) accumulates in neurons but not glia during development [11]. Interestingly, preliminary analysis identified common changes in DNA methylation in several neurodegenerative diseases [12], suggesting the involvement of shared regulatory programs. Human neurodegenerative diseases including Alzheimer’s disease, Huntington’s disease and amyotrophic lateral sclerosis (ALS) are associated with dramatic changes to the transcriptional profile [13–15]. A critical emerging question is therefore if chromatin structure is altered during neurodegenerative processes, and if such changes are causally involved in disease.

AGING AS A RISK FACTOR FOR EPIGENETIC ALTERATIONS LEADING TO NEURODEGENERATION

The most notable risk factor for neurodegenerative diseases is age, and aging itself is associated with a decline in cognitive capacities. Chromatin alterations that occur as the brain ages might therefore be important targets to prevent cognitive deterioration [16]. In addition, such alterations could contribute to the development of degenerative diseases. Altered levels of histone acetylation and methylation have been associated with advanced age. In general, an increase in repressive marks of H3K9me2, H3K9me3 and H3K27me3 and a decrease in activating marks of H3K36me3 and H3K27ac have been observed in cerebral cortex and hippocampus of aged animal models [17]. In aged mice, impaired memory functions measured by fear conditioning correlate with inability to upregulate acetylation of H4K12 [18]. Hippocampal gene expression analysis demonstrated minor changes in gene expression in old mice. Remarkably however, fear conditioning induces large scale changes to gene expression of young mice, but the transcriptome of old mice remains fairly unchanged one hour after the stressful stimuli. Therefore, aging may block transcriptome dynamics in a mechanism dependent on H4K12ac [18].

An important candidate gene that could be involved aged-associated reduced cognitive capacities is brain derived neurotrophic factor (*Bdnf*). BDNF is critical for learning and memory, and *Bdnf* mRNA levels are reduced in hippocampi of aged mice. In the *Bdnf* promoter, reduced H3K27ac and increased H3K27me3 levels were observed in aged mice, suggesting that a shift from ‘open’ to ‘closed’ chromatin underlies the reduced transcriptional output [19]. Reduced levels of the histone acetyltransferase (HAT) CREB-

binding protein (CBP) and increased levels of the histone deacetylase HDAC4 at *Bdnf* promoter regions in aged mice support this notion. CBP is recruited by active CREB following N-methyl-D-aspartate receptor (NMDAR) activation [20]. Interestingly, age-associated reduction in membrane cholesterol in the hippocampus leads to reduced NMDAR signaling and low H3K27ac levels at the *Bdnf* promoter. Prevention of age-associated cholesterol loss rescues *Bdnf* transcription and enhances cognitive performance of old mice [19], linking H3K27ac to age-associated neuronal physiology and cognitive performance.

Could epigenomic analysis of the aging brain point to pathways that are relevant to neurodegenerative diseases? Transcriptomic analysis of the human brain as it ages identified reduced expression of targets of repressor element 1-silencing transcription factor (REST), predicting that REST levels should increase in normal aging [21]. Indeed, REST levels are high during neurodevelopment but remain low until advanced age, when they increase again. In neurodegenerative diseases including Alzheimer's disease and frontotemporal dementia, REST levels fail to increase with age, leading to reduced levels of neuroprotective genes such as *FOXO*, which mediates oxidative stress resistance, and the anti-apoptotic *BCL2*[21]. Conversely, increased levels of genes that promote Alzheimer's pathology (e.g *PSEN2*) and cell death (e.g the proapoptotic *BID*, *PUMA* and *BAX*) result from reduced REST expression [21], and could promote neuronal fragility in these diseases.

ALZHEIMER'S DISEASE AND TAUOPATHIES

Alzheimer's disease (AD) is the leading cause of dementia in the elderly and a major public health concern with a current estimation of 5.5 million AD patients in the United States alone [22]. Both beta-amyloid (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated Tau are pathological hallmarks of the disease, and soluble oligomers as well as aggregated proteins contribute to neuronal toxicity [23]. A study in the CK-p25 AD mouse model [24] showed increased expression in genes associated with immune response functions, while reduced expression for genes involved insynaptic and learning functions. Corresponding ChIP-seq analyses revealed changes in promoter (H3K4me3) or enhancer (H3K27ac) marks that correlated with the gene expression alterations, while very few alterations in heterochromatin or polycomb regions were found (H3K9me3 and H3K27me3, respectively). Human orthologues of increased level enhancers were enriched for genetic variants associated with AD, suggesting a role for immune- related enhancer elements in AD predisposition [24]. Further implicating a role for H3K4me3 in AD, deletion of the lysine methyltransferase Kmt2a in mouse forebrain neurons partially recapitulates the loss of H3K4me3 in the CK-p25 model, and Kmt2a itself is downregulated in CK-p25 [25].

H4K16ac is a histone mark generally associated with active gene expresssion and is localized to both enhancers and promoters. By inhibiting the formation of the 30 nanometer-like fibers and inhibiting the ability of chromatin remodeling factor ACF to mobilize nucleosomes, H4K16ac alters chromatin structure [26]. H4K16ac has been linked to aging and DNA damage processes, both associated with neurodegenerative diseases [27–29]. ChIP-Seq profiling of H4K16ac in postmortem temporal lobe from Alzheimer's disease and controls spanning a range of ages show dramatic redistribution of H4K16ac in aging and disease. While both gains and losses are found, normal aging is associated predominantly

with increases of H4K16ac peaks, with the number of H4K16ac peaks doubling in the healthy aged cortex. By contrast, H4K16ac is dramatically lost in the AD cortex, pointing to an inability to upregulate H4K16ac in the aged AD brain. H4K16ac peaks positively correlate with expression of nearby genes suggesting that altered H4K16ac landscape could have functional implications. Importantly, disease-altered H4K16ac peaks are associated with AD-associated single nucleotide polymorphisms (SNPs) and with expression quantitative train loci (eQTL) of AD, but not other diseases. H4K16ac peaks that are altered in AD appear, therefore, to represent critically important loci as many of them are identified as AD associated by genetic association studies (Nativio et al.).

Histone deacetylase 2 (HDAC2) levels are upregulated following neurotoxic insults in cultured cells, in the hippocampus and prefrontal cortex of AD mouse models and in the hippocampus of postmortem samples from human AD patients [30]. In a mouse AD model, increased binding of HDAC2 to promoter coding regions of genes with critical roles in learning and memory and synaptic plasticity is accompanied by reduced acetylation levels of H2BK5, H3K14, H4K5 and H4K12, reduced RNA polymerase II binding and reduced gene expression [30]. Thus, increased HDAC2 levels may lead to impaired synaptic function, a well characterized pathological feature of AD [31]. Pointing to a direct effect of chromatin alterations, acetylation of non-histone proteins such as P53 and TAU are not altered in this model. Strikingly, hippocampal HDAC2 knockdown rescues gene expression levels, enhances synaptic density and mitigates memory impairments but has no effect on neuronal survival [30]. Therefore, epigenetic blockade of memory functions in the surviving neurons might play critical roles in dementia, in addition to the impairments that are caused by loss of neurons.

In addition to reduced transcription of genes that are critical for proper neuronal function, aberrant upregulation of genes that are normally silenced may also occur in AD. In *Drosophila* models of tauopathies, which include AD, both wild-type and mutated Tau (pseudohyperphosphorylated Tau^{E14}) cause a reduction in H3K9me2 and heterochromatin protein 1 (HP1) [32]. Loss of these heterochromatin marks and proteins is associated with promiscuous expression of genes that are normally silenced or expressed at low levels in the fly head (e.g *Nvd*, *Ir41a*, *Ago3* and *CG15115*), while highly expressed genes are not affected [32]. Tau also causes reduced lamin levels in *Drosophila*, and abnormal lamin invaginations are present in nuclei from AD postmortem frontal cortex. Because of the interactions of heterochromatin with the lamin nucleoskeleton, it is expected that such alterations will impact chromatin structure. Indeed, lamin dysfunction leads to heterochromatin relaxation, neurodegeneration and DNA damage, likely through stablization of F-actin and dysruption of the linker of nucleoskeleton and cytoskeleton (LINC) which bridges the actin cytoskeleton and the lamin nucleoskeleton [33]. It is hence possible that lamin dysfunction mediates several toxic effects of hyperphosphorylated Tau in multiple different tau-associated pathologies.

H3K9 methylation might also be relevant in Parkinson's disease as α-synuclein, a major aggregated protein in the disease, increases global mono and di-methylation of H3K9 in *Drosophila* and cultured neuroblastoma cell models [34] (see [35] for additional details on the effect of α-synuclein on epigenetic regulation in PD).

HUNTINGTON'S DISEASE

Huntington's disease (HD) was one of the first neurodegenerative diseases to be studied in the context of epigenetic regulation. Excellent reviews summarize these data [36–38], and here we highlight more recent findings. HD impacts multiple abilities in patients and can cause movement, cognitive and psychiatric disorders. An autosomal dominant disease, HD is caused by polyglutamine expansion in the first exon of the *huntingtin* gene. Chromatin alterations found in HD are therefore likely downstream effects of these repeat expansions. HD models and HD human brain tissue show alterations in gene expression, increased H3K9me3 heterochromatin domains, and importantly, the histone acetyl transferase CBP is mislocalized to polyglutamine aggregates in HD cultured cells, mouse models and HD postmortem brain [39]. Additionally, multiple other transcriptional regulators are impaired by mutant huntingtin [40]. Work with *Drosophila* HD models initially identified a beneficial effect of histone deacetylase inhibitors to dramatically mitigate neurodegeneration [41]; these findings were corroborated by mammalian models [42–45] and suggested that decreased histone acetylation might be involved in HD mechanisms. Surprisingly, in the HD82Q mouse model, histone hypoacetylation of hundreds of H3K9 H3K14 and H4K12 loci is not correlated with severe hippocampal and cerebellar transcriptional dysregulation [46]. These results suggest that histone deacetylation and transcriptional impairments might be somewhat independent. Even though HDAC inhibitors showed some initial promise in clinical trials for HD, unwanted side effects led to efforts to develop more selective inhibitors [36].

Recent efforts to target histone methylation in HD show that reduced H3K9me3 levels with the chromatin remodeling drug nogalamycin slows disease progression in an HD mouse model [47]. Accordingly, the levels of H3K4me3, a mark associated with gene activation, are lower at promoters of down regulated genes in HD postmortem brain and in HD mouse models. Increasing the levels of H3K4me3 by targeting H3K4me3 demethylase was protective in mouse and *Drosophila* HD models [48]. ChIP-Seq analysis of neuronal nuclei isolated by sorting postmortem human prefrontal cortex of HD cases and controls identified neuronal-specific alterations in H3K4me3 with many of the altered H3K4me3 peaks located near genes with synaptic functions [49, 50].

Another approach to characterize chromatin alterations associated with brain diseases is the use of cultured neurons that are differentiated from induced pluripotent stem cells (iPSC). Such neurons derived from juvenile onset HD patients show altered expression of nearly 2000 genes, compared to neurons derived from controls. More than a quarter of these genes are centered on neurodevelopment, with Neurod1 and TGFbeta identified as critical hubs [51]. Chromatin profiling of H3K4me3, H3K27ac and H3K36me3 revealed that genes near altered H3K4me3 peaks are associated with cell adhesion, and genes near altered H3K27ac are associated with synaptic transmission, neuron differentiation and the actin cytoskeleton [51]. These and other studies suggest that alterations in histone methylation and acetylation marks occur in HD and that a full understanding of these changes could allow the development of more directed and hopefully selective therapeutics.

Further alterations to the epigenome in HD include changes in expression of histone variants. In a study aimed at defining biomarkers for HD, *H2AFY* which encodes the histone variant macroH2A1 was identified as upregulated in cellular blood of patients with HD, compared to healthy controls or patients of other neurodegenerative diseases [52]. H2AFY protein levels were reduced in blood from HD patients treated with HDAC inhibitor, but not placebo [52]. Genes related to chromatin structure may thus serve as peripheral biomarkers and assist in monitoring the pharmacodynamic responses to treatment.

ADDITIONAL INSIGHT INTO THE DISEASE STATE

Neurons as postmitotic cells rely on various mechanisms to maintain their identity thoughout life. Epigenetic mechanisms are required, but are not sufficient, to maintain the gene expression state of differentiated neurons [53]. For example, a combination of transcription factors (*die-1* and *che-1*) as well as a MYST-type histone acetyltransferase are required to induce and maintain left/right laterality in *C. elegans* ASE sensory neurons [54].

Alterations in histone modifications as they occur in aging or disease may contribute to neuronal reentry to the cell cycle, a unifying theme in many neurodegenerative diseases [55]. Supporting a role for repressive histone methylation to maintain neuronal-specific transcriptional states, reduced H3K27me3 in medium spiny neurons (MSN) of the striatum in mice resulted in the perturbed expression of genes, both upregulated and down regulated. However, genes whose expression was reduced were not identified as H3K27me3 targets in wild-type MSNs, suggesting that their decrease is a secondary effect [56]. H3K27me2/3 is deposited by the PRC2 complex, which contains the enzymatic components EZH1 or EZH2, as well as non-enzymatic proteins SUZ12 and Jarid2. While most H3K27me3 target genes in MSNs were insensitive to PRC2 deficiency, transcriptional regulators that were upregulated generated positive feedback loops that maintained high expression of their targets [56]. Interestingly, most upregulated genes show bivalent H3K27me3 and H3K4me3 marks in MSNs indicating that the loss of H3K27me3 results in release of a barrier to their transcription. Several genes with cell death promoting functions were among those upregulated, and mice with neuronal PRC2 deletion developed progressive neurodegeneration, impaired motor performance and died early [56]. Increased H3K27me3 levels, however, can also be deletious, as loss of A-T mutated (ATM) in Ataxia-telangiectasia leads to increased stabilization of EZH2 and increased H3K27me3 levels in human and mouse cerebellum [57]. Knockdown of *EZH2* in an ATM-deficient mouse model of ATM mitigates neurodegeneration and behavioral impairments, indicating that the increased H3K27me3 levels contribute to toxicity [57]. Strikingly, increased H3K4me3 in ATM deficient neurons was also associated with cell cycle reentry suggesting that proper balance of H3K27me3 is critical for maintaining healthy neurons, with reduced or increased levels associated with aberrant gene expression, imapired cell cycle control and neurodegeneration.

While many of the examples above involve global alterations in histone modifications, changes in the nuclear localization or recruitment of chromatin remodeling factors also play important roles to maintain neuronal integrity. ALS and frontotemporal dementia (FTD) are neurodegenerative diseases that share both pathological hallmarks and genetic causes. ALS

is characterized by progressive demise of motor neurons which leads to muscle weakness and paralysis, while in FTD variants present with behavior, personality and/or language deficits. However, significant clinical overlap suggesting that ALS and FTD form a disease spectrum. TDP-43, an RNA and DNA binding protein which forms insoluble aggregates in ALS and FTD subtypes (FTD-TDP) limits the recruitment of the chromatin remodeling factor Chd1 to stress response genes in *Drosophila*. This in turn limits nucleosome clearance from the gene body of heat shock protein genes, reduces their expression and impairs the cellular capacity to cope with various toxic insults [58]. While mass-spectrometry analysis revealed no alterations in global histone posttranslational modifications in postmortem temporal cortex of FTD cases, the protein levels of CHD2, the human orthologue of fly Chd1, were dramatically reduced in this brain region [58]. In addition, mutant TDP-43 or fused in sarcoma (*FUS*), an additional ALS associated gene, reduced the protein levels of Brg1 [59], a component of the chromatin remodeling complex nBAF which is a critically important complex in neuronal differentiation and function [60]. Therefore, an inability to maintain dynamic epigenetic responses due to altered levels and recruitment of remodeling factors may also contribute to age-dependent neuronal vulnerability.

III. IMPLICATIONS FOR THERAPY AND OUTSTANDING OPEN QUESTIONS

In cellular and animal models and in the postmortem human brain, disease-associated alterations of chromatin point to specific pathways that might be perturbed in disease. Critical questions include whether these changes are causally involved with disease initiation, progression or severity, and whether their discovery can direct the development of novel therapeutics.

As we consider the global changes in the epigenetic landscape and gene expression that occur in neurodegenerative diseases, it will be important to understand if disease modulation can be achieved by epigenetic editing of specific genes via precision medicine. Alternatively, if disease etiology involves the deregulation of multiple different genes, global strategies to collectively correct global expression levels might be preferable or necessary.

Locus-specific epigenetic changes can be achieved by fusing chromatin modifying enzymes to DNA binding platforms, including zinc finger proteins (ZFPs), transcription activation-like effectors (TALE), or the clustered regularly interspaced short palindromic repeats (CRISPR)/Cas system [61]. These systems offer methods by which to alter chromatin structure without systemic administration of inhibitors (such as HDAC inhibitors) which could have pleiotropic side effects or impact non-histone proteins. The applicability of such techniques in the adult brain remain to be tested, and will likely involve major delivery, safety and efficacy hurdles. However, some recent findings suggest that epigenetic editing might offer future therapeutic approaches. In one such study study, the expression of *Dlg4*, which encodes PSD95 a major component of the postsynaptic density with critical scaffolding functions, was manipulated by ZFN targeting the *Dlg4* promoter. PSD95 levels are reduced in mouse models of Alzheimer's disease, suggesting that restoring PSD95 expression could ameliorate synaptic deficits [62]. ZFN was fused to G9a and SUV39-H1 to promote the repressive marks H3K9me2 and H3K9me3, respectively, or to the activation domain of the viral protein VP16 (tetrameric VP64) [63]. Increased expression of *Dlg4* by

targeting VP16 to the *Dlg4* promoter rescued memory impairments in AD mouse models, while reduced expression with SUV39 led to strong reduction in NMDA excitatory postsynaptic currents (ePSC) [63].

In several neurodegenerative diseases, repetitive sequences result in heterochromatization of nearby chromatin followed by reduced gene expression. In Friedreich's ataxia (FRDA), GAA repeats cause reduced elongation and impede transcription of the *frataxin* (*FXN*) gene. Conjugating JQ1, the bromodomain extraterminal domain (BET) inhibitor, and BRD4 ligand, to polyamides that target GAA microsatellite repeats (termed synthetic transcription elongation factors, Syn-TEFs), specifically recruits BRD4 to *FTN* and promotes the switch from paused RNA Polymerase II to productive elongation [64]. These findings support a future role of epigenome editing to alter specific genomic locations and restore the normal balance of gene expression in the brain. Interestingly, conflicting data exists on the effects of JQ1 itself to regulate memory. Korb et al. [65] found that JQ1 reduces the expression of immediate early genes (IEG) following BDNF stimulation in cultured neurons, and disrupts long-term memory formation in mice. Benito et al. [66], however, found that JQ1 enhances long-term potentiation (LTP), promotes long-term memory in controls and models of AD, and predominantly increased IEGs. Adding another complication, a third study [67] found no effect of a BET inhibitor (I-BET858) to alter BDNF stimulated IEGs, and identified a group of secondary and late response genes as targets of BET inhibition. Due to these data and because BET inhibition causes autism-like behavior in mice [67], BET inhibition as possible therapeutic strategy requires more studies to delineate mechanisms and possible complications. Indeed, the brain imposes a unique challenge to genomic and transcriptomic profiling due to the multitude of cell types in the single tissue (neurons, astrocytes, microglia, oligodendrocytes) and subtypes (excitatory and inhibitory neurons, unique anatomical location, cortical layer identity, neurotransmitter, and so forth). Novel techniques now allow cell-type specific analysis of transcription [68] and DNA methylation in the brain [69]. Single cell analysis of DNA-protein interactions [70] and chromatin 3D structure [71] might be applied in future studies to uncover neuronal cell-type specific chromatin structure and interneuronal variations (see [72] for a review of epigenetic control on gene expression in the brain).

CONCLUDING REMARKS

We are only beginning to understand the changes in chromatin structure and function that occur in neurodegenerative diseases and how they contribute to disease pathogenesis [73, 74]. Emerging insights, however, highlight the critical importance of maintaining chromatin dynamics and proper levels of histone and DNA modifications, with imbalances leading to catastrophic degenerative outcomes. The age-dependence of all neurodegenerative diseases suggests that such imbalances may accumulate over time until repair and stress response pathways finally collapse leading to irreversible neuronal damage. Technologies aimed at restoring chromatin dynamics and proper gene expression may provide novel therapeutic strategies, if applied sufficiently early, and could be combined with therapies addressing other aspects of these diseases, for example protein misfolding and aggregation. The continuous development of novel techniques to examine chromatin structure and function [68–71, 75], some of which are already applied to study of the nervous system, will provide

exciting advances in our understanding of epigenetic regulation in neurodegenerative diseases.

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MECHANISMS OF CHROMATIN STRUCTURAL REGULATION

DNA methylation.

DNA can be methylated on cytosine residues at the carbon 5 position (5mC by a family of methyltransferases (DNMT)). Methylation occurs in the context of CpG or CpHpG (H denoting A, T or C). Classic functions of DNA methylation include X chromosome inactivation in mammalian females, genomic imprinting and gene silencing. 5mC can be converted to 5-hydroxymethylcytosine (5hmC), a mark that is particularly abundant in the brain [76]. Demethylation occurs through a series of deamination and oxidation reactions.

Histone acetylation.

Acetylation occurs on the epsilon amino group of lysine residues in the N-terminal region of histone proteins (on the histone “tails”). Generally, acetylation is associated with gene activation and is mediated by histone acetyltransferase (HAT) enzymes, while removal of the mark is catalyzed by histone deacetylases (HDACs). Several mechanisms may explain the positive effect of acetylation on transcription: the acetyl group removes the positive charge of lysine side chain thus reducing the electrostatic interactions between positively charged histones with the negatively charged DNA backbone. In addition, chromatin ‘readers’ that bind acetylated histones can mediate chromatin remodeling and allow a more ‘open’ chromatin structure.

Histone methylation.

The effect of histone methylation on transcription is context-specific with several histone methylated marks promoting gene activation and others enhancing heterochromatization and reducing access to specific loci. Methylation can occur on lysine or arginine residues and does not alter the charge of the affected residues. Methylation, as other histone modifications, is dynamic with histone methyltransferases adding the methyl group and histone demethylases removing it. Arginine residues can be methylated in one or two locations on the guanidine group and the methylation could be symmetric or asymmetric resulting in four possible states. Lysine methylation can add mono, di, or trimethyl groups (me1, me2 and me3), each state conferring unique structural alterations that are recognized by appropriate ‘reader’ proteins.

Histone phosphorylation.

Phosphorylation of serine, threonine or tyrosine side chains is catalyzed by protein kinases and can be dephosphorylated by phosphatases. This well studied protein modification also takes place in histone tails and regulates multiple processes, the best known of which is the DNA damage response where the phosphorylated H2A(X) histone variant (γH2AX) accumulates at DNA damage sites. Histone phosphorylation also regulates gene expression and has been linked to acetylation events. In addition, phosphorylation is associated with chromatin condensation during mitosis and meiosis [77].

Histone variants.

Canonical histones can be replaced by histone variants which introduce sequence variations, with all histones except histone H4 having multiple gene variants in humans. Incorporation of histone variants occurs both during replication or in a replication-independent manner. Histone variants promote unique interactions with chromatin associated proteins, such as chromatin remodeling factors, or alter chromatin structure, and play important roles during mammalian development, X- chromosomal inactivation and gene expression in the brain [78].

Chromatin remodeling.

The association of DNA with histones, which serves as a barrier to transcription and other processes, can be altered by chromatin remodeling factors which use ATP hydrolysis to mobilize nucleosomes [79]. Nucleosome sliding, as well as ejection or insertion, change chromatin structure and the interaction with auxiliary factors. The ATPase motor is accompanied by additional domains that are characteristic of specific chromatin remodeling subfamilies [80]. Four major families of chromatin remodeling factors are: SWI/SNF, ISWI, INO80/SWR1 and NuRD.

Histone chaperones.

Histone chaperones are a diverse set of proteins regulating histone storage, transport, post-translational modifications, nucleosome assembly and turnover [81]. Newly synthesized histones, as well as replacement variants and recycled histones, may be deposited on DNA following replication, transcription, DNA damage repair or other nuclear processes. Major histone chaperones include HIRA, DAXX, CAF1 complex, and ASF1.

Long non-coding RNAs.

LncRNAs allow allele-specific chromatin alterations by tethering RNA-protein complexes to a specific locus [82]. One of the best examples is Xist, a lncRNA transcribed from the X inactivation center (*Xic*) which covers the entire mammalian inactive X chromosome and promotes silencing.

Three-dimensional organization.

Within the nucleus, chromatin is organized in a 3D structure that brings selective regions to close proximity and sets other regions apart. Genome-wide techniques that study such interactions (e.g. Hi-C), led to the identification of topologically associated domains (TADs) [83], which are remarkably conserved between cell types and mammalian species. Regulatory interactions, such as those between enhancers and promoters, mainly occur within the same TAD. Similarly, genes within the same TAD show co-regulatory properties, suggesting a functional and regulatory role for TADs [84].

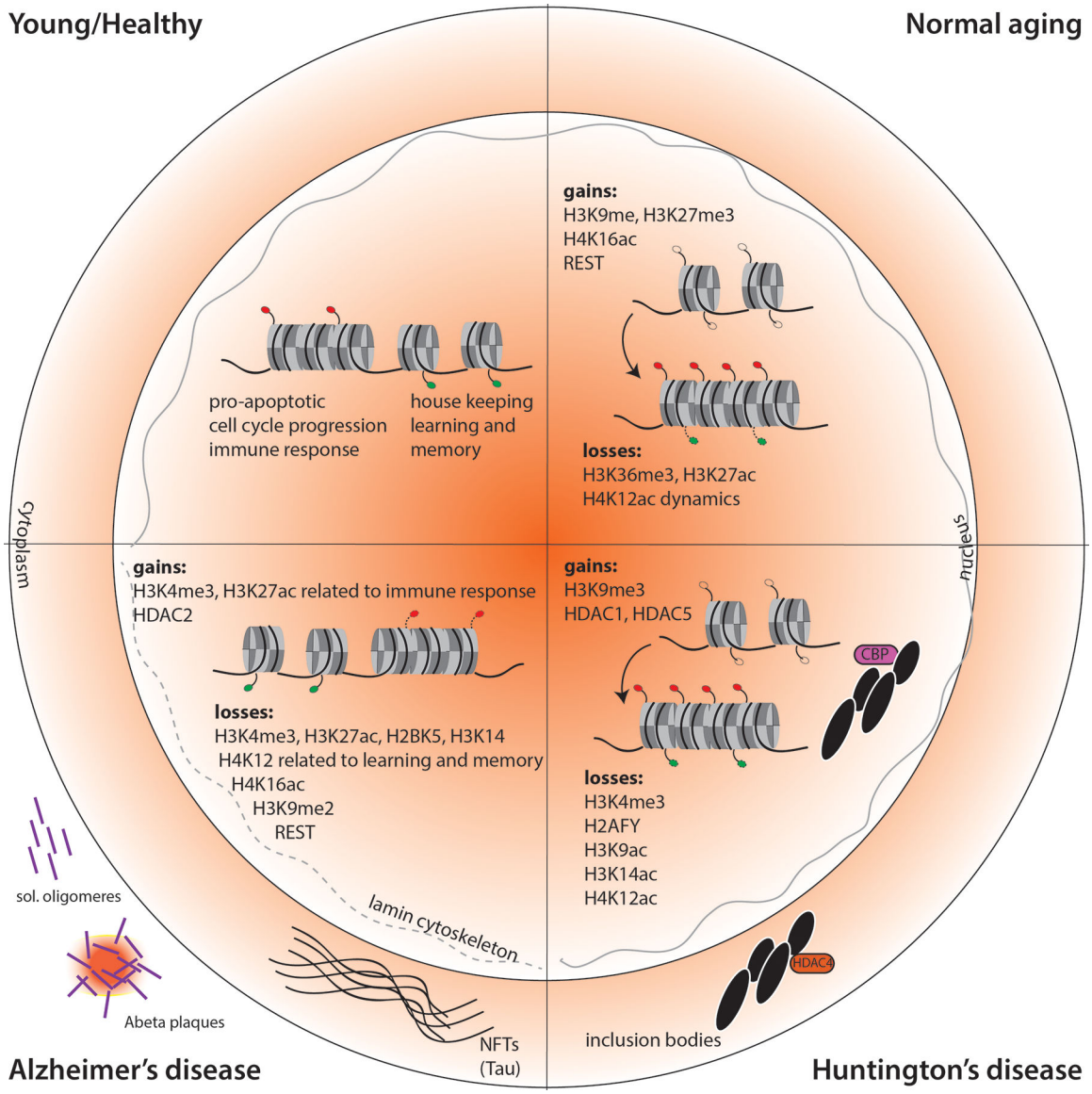

Figure 1.

Chromatin Alterations in Brain Aging and Disease. We summarize global changes to histone modifications and related alterations that occur in aging, AD, and HD. We note that due to the complexity of the genome, with both losses and gains usually reported for histone marks in these conditions, this schematic represents a simplified model of more intricate changes. From the studies highlighted here, a general theme emerges in which aging and HD are primarily characterized by reduced levels of modifications usually associated with open chromatin (in aging, H3K36me3 and H3K27ac [17]; in HD, H3K4me3, H3K9ac, H3K14ac, and H3K12ac [54, 91]) and increases in marks associated with closed chromatin (in aging, H3K9me and H3K27me3 [17]; in HD, H3K9me3 [43, 45]). In Drosophila heads however, reduced levels of H3K9me3 and HP1 with age are associated with increased expression of genes that are normally silenced [18]. In AD, the alterations appear to be distinct with global losses of heterochromatin marks (H3K9me2 in Drosophila τ model [36]), as well as locus-

specific losses and gains of activating marks (H3K4me3 and H3K27ac in a mouse model [27], and H4K16ac in the human AD brain [33]). Changes to the nuclear architecture, for example loss of the lamin cytoskeleton in tauopathies, may also contribute to reduced levels of heterochromatic marks and gene expression imbalances. In HD, the pathological accumulations of nuclear and cytoplasmic inclusion bodies interact with several chromatin factors including CBP and HDAC4, providing a direct mechanism by which these pathologies promote alterations to chromatin structure. Abbreviations: AD, Alzheimer's disease; CBP, CREB-binding protein HD, Huntington's disease; HDAC, histone deacetylase; NFTs, neurofibrillary tangles; REST, Repressor element 1-silencing transcription factor.