[Frontiers In Bioscience, Landmark, 23, 1445-1464, March 1, 2018]

Impact of epigenetics in aging and age related neurodegenerative diseases

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1. ABSTRACT

Epigenetics involves multiple processes such as DNA methylation, histone code modifications, and noncoding RNAs to regulate gene expression. In recent years the implications of epigenetic mechanisms have emerged in the field of neuroscience especially in brain development, memory, learning, and various cognition processes. Epigenetics also plays a pivotal role during the aging process of the brain which has led to various age-related neurodegenerative diseases. This manuscript portrays the findings of various epigenetic mechanisms that play a critical role and their implications in aging as well as age-related neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease.

2. INTRODUCTION

Aging is defined as a time-dependent loss of function causing increased vulnerability to death that affects most of the living organisms. Various factors that affect the aging process include genomic instability, somatic mutations, telomere shortening, loss of protein stability and function, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication such as inflammation (69). In addition to molecular, cellular, and physiological defects associated with aging, an epigenetic alterations that affects all types of cells and tissues throughout life is the major hall-mark of aging (8) (Figure 1). During aging, the epigenome undergoes a progressive loss of its configuration that results in a significant change in the genome integrity, chromatin architecture, and gene expression pattern. Alteration of the epigenetic pattern during aging is a phenomenon called epigenetic drift (23).

The term epigenetics is a heritable change in gene expression without altering the sequence of DNA. Epigenetic regulatory mechanisms include DNA methylation, histone code modifications, and small and long non-coding RNAs. DNA methylation involves covalent modification of cytosine residues of CpG dinucleotides by addition of methyl groups catalyzed by DNA methyl transferases. Another epigenetic alteration is histone code modifications which involve various chemical modifications such as acetyl, methyl, and phosphoryl groups attached to amino terminal tails of histones. Depending on the type of modification found on a particular amino acid residue, histone code modifications remodel the chromatin either euchromatin or heterochromatin. Euchromatin is loosely packed with histones and DNA, less condensed, transcriptionally active and characterized with hypomethylation of DNA, histones and hyper acetylation of histones. Heterochromatin is tightly packed with histones and DNA, highly condensed,

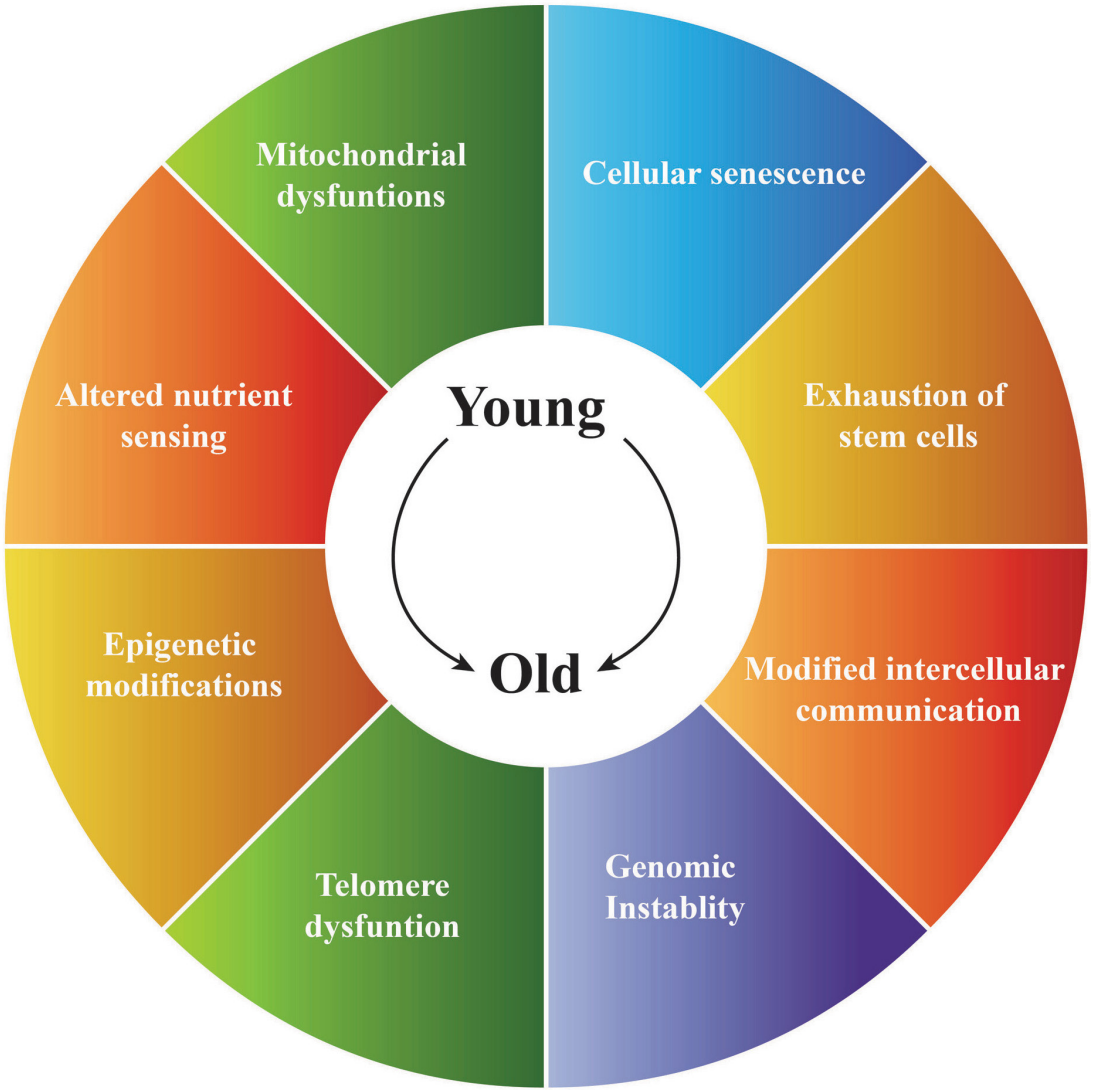

Figure 1. Hallmarks and mechanisms of aging.

transcriptionally repressive and characterized with hypermethylation of DNA, histones and hypoacetylation of histones. (Figure 2). In addition, non coding RNAs can affect both transcriptional and post-transcriptional gene silencing.

Few studies have reviewed the epigenetic changes occurring during aging (83, 95, 117). In this review, we describe various epigenetic mechanisms that occur in general and specify those changes in the aging process and their implications in some of the common age related neurodegenerative diseases.

3. EPIGENETIC CHANGES IN AGING

3.1. DNA methylation and aging

DNA methylation is one of the best-characterized epigenetic mechanisms which provide a stable and heritable epigenetic modification. It is essential for normal development and survival of mammalian cells. DNA methylation occurs on cytosine residue of CpG dinucleotides. The CpG dinucleotide rich regions are called CpG islands and are found in the promoter regions of genes. Promoter CpG island methylation plays an important role in gene silencing by preventing transcriptional factor binding on to the promoter and thereby recruiting transcriptional repressors including methyl binding proteins (10). DNA methyl transferases (DNMTs) catalyzes the addition of a methyl group on to the 5th carbon position of cytosine residue utilizing S-adenosyl methionine (SAM) as the methyl donor. Off all the DNMTs, DNMT1, DNMT3A and DNMT3B plays an important role in maintaining and establishing genome methylation.

One of the well-studied DNA methylation changes that occurs with advanced aging is global

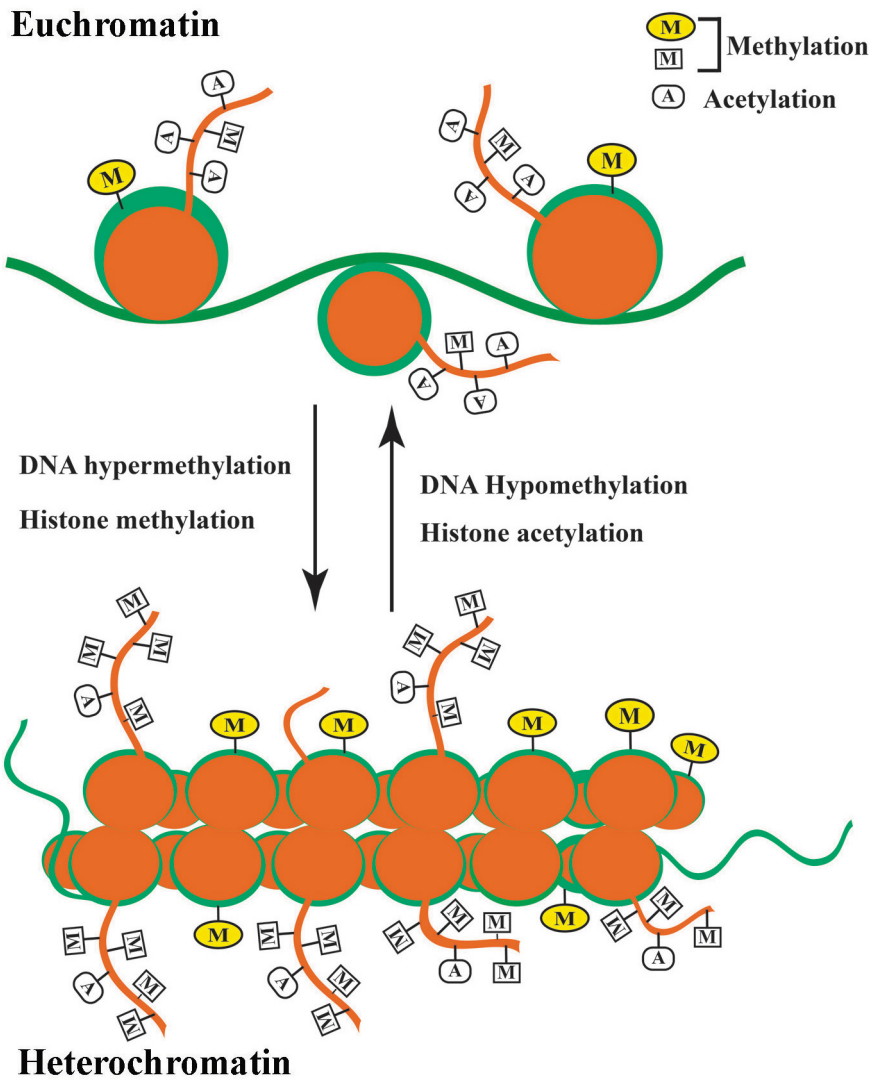

Figure 2. Eukaryotic chromatin organization. In eukaryotes chromatin is organized as open transcriptionally active euchromatin or compact, closed, transcriptionally inactive heterochromatin. Euchromatin is characterized with DNA hypomethylation and hyper acetylation of histone N terminal lysine residues. Heterochromatin is characterized with DNA hyper methylation, histone methylation at specific lysine residues. M is methyl CpG on DNA, M is methyl lysine and A is acetyl lysine of N terminal tail of histone.

DNA hypomethylation. During the aging process, DNA methylation drift occurs in mammalian cells that change the 5-methyl-cytosine distribution across the genome. This result in global DNA hypomethylation, while some promoters undergo aberrant DNA hypermethylation (139, 118, 42, 43, 44). DNA hypomethylation also takes place in transposable DNA repetitive elements including Alu and LINE-1 elements, resulting in increased transposition activity and genomic instability (139). Age dependent loss of DNA methylation also occurs at promoters of specific genes such as CD11a and IL17RC (146, 138). During aging, promoter hypermethylation affects the expression of certain transcription regulatory genes (29), apoptotic genes (84), development and differentiation regulatory genes (107). Global genome wide methylation changes and epigenetic pattern of specific genes predicting the aging have been reported (57, 6). Due to aging, promoter hyper-methylation has been observed in several tumor suppressor genes such as CDKN2A, LOX, RUNX3, and TIG1 (131, 119). In addition, promoter hypermethylation was also observed on estrogen receptor (ER) and insulin-like growth factor II (IGF2) due to aging (42, 43). Other genes with increased promoter methylation during aging include collagenα1, c-fos, and the myogenic differentiation antigen1 (13, 123, 144). Ribosomal DNA (rDNA) clusters also show increased promoter methylation that results in reduced expression of rRNA during aging (17, 91). Global DNA hypomethylation and promoter specific hypermethylation changes that occur during aging may be associated with altered expression of DNA

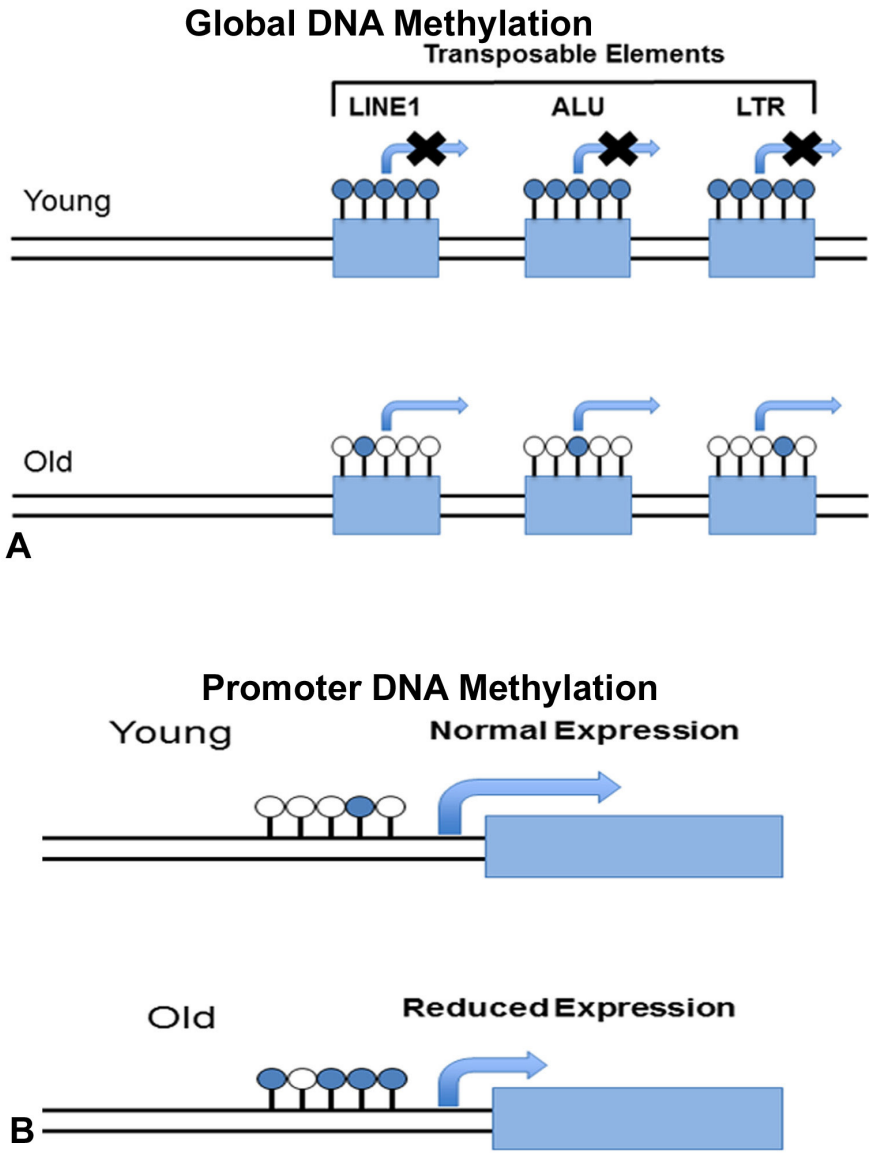

Figure 3. DNA methylation changes during aging. A. Global DNA hypermethylation occur at repetitive DNA elements such as Line 1, Alu and LTR in young individuals results in transcriptional repression. In Old individuals, hypomethylation of these repetitive transposable elements results in transcriptional activation. B. Promoter DNA hypomethylation observed in Young and hypermethylation in Old result in differential expression. Each CpG site is represented as lollipop structure with methyl (closed circle), unmethyl (open circle).

methyl transferases. It has been shown that DNMT1 expression was reduced while DNMT3b expression steadily increased with aging in cells (9, 51) (Figure 3).

3.2. Histone code modifications and aging

Genomic DNA packed in to highly ordered chromatin structures regulate various genomic processes such as DNA replication, transcription, recombination, and repair. In eukaryotes, the basic unit of chromatin structure is a nucleosome that consists of 147 base pairs of DNA wrapped around a histone octomer comprising two molecules of H2A, H2B, H3 and H4. Covalent as well as non-covalent modifications occur on histones to alter the chromatin structure. Covalent modifications occur at particular amino acid residues of the N-terminal tail of histones include acetylation, methylation, phosphorylation, ubiquitination and ADP ribosylation and sumoylation (133). Depending on the site and type of modification on amino acid residues, histone code modifications are associated with either transcriptional activation or repression. Acetylation of histone H3 and H4, di and tri methylation of H3K4 and H3K36 are associated with active transcription referred to euchromatic modifications. Methylation of H3K9, H3K27, and H4K20 are commonly associated with transcriptional repression and are considered heterochromatin

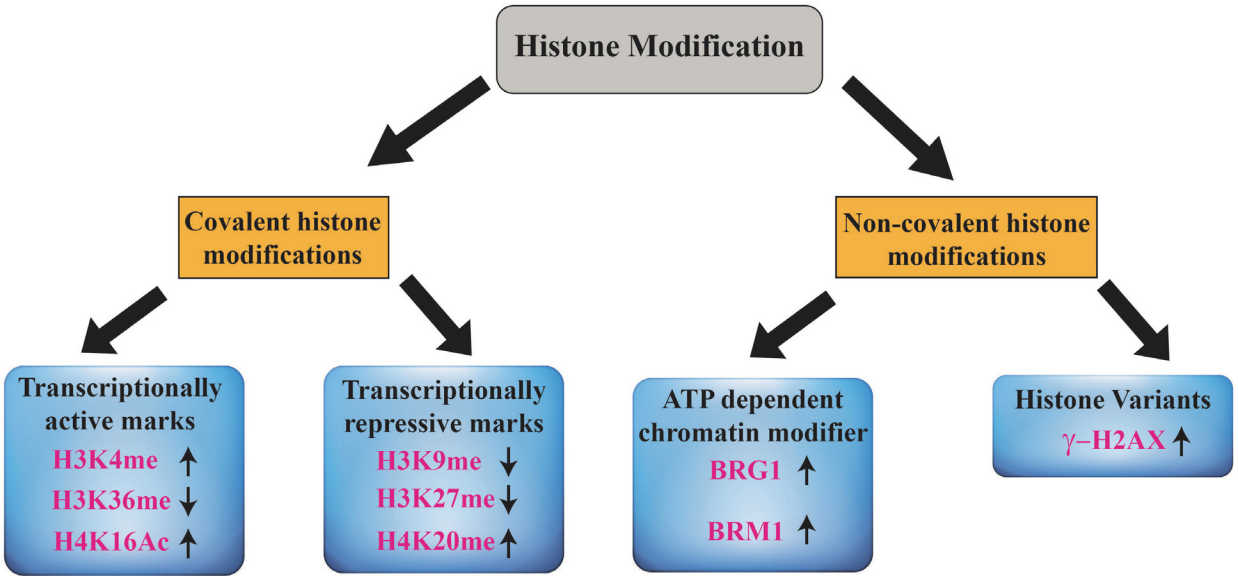

Figure 4. Histone code modifications during Aging. Covalaent and non-covalent histone modifications alter during aging. Covalent histone modifications include transcriptionally active (H3K4me, H3K36me, and H4K16ac) and transcriptionally repressive (H3K9me, H3K27me and H4K20me) marks. Non covalent histone modifications include ATP dependent chromatin modifiers such as BRG1, BRM1 and histone variants such as **γ**-H2AX. The increase and decrease in expressions were represented with corresponding arrows.

modifications (104). Non covalent histone modifications comprise ATP dependent mediated chromatin remodeling and histone variants incorporation in to the chromatin (134).

Among the histone code modifications, histone methylation and acetylation of lysine residues are the more prominent ones that affect the longevity process. The global histone methylation pattern differs in different organisms during aging process. McCauley and Dang (76) reported that there is an increase of transcriptionally active histone methylation marks and reduced levels of transcriptionally repressive histone methylation marks during aging suggesting a significant loss of heterochromatin marks in aging cells, tissues and organisms. Histone methylation marks such as H3K4me3, H3K9me, H3K27me3 and H3K36me3 change during aging which indicate a loss of heterochromatin. The increased level of H3K9me3 and SUV39H1 methyl transferase has also been reported in a premature aged mouse model (66). Increased methylation of H3K36 has been reported to promote life span in S.cervisiae. They identified that H3K36 methyl transferase mutants had a shortened life span (113). Studies from C. elegans and D. melanogaster suggest that loss of H3K36 methylation during aging leads to aberrant gene expression and causes transcriptional drift like effect and limit the life span (99). These studies together suggest that H3K36 methylation loss during aging led to aberrant gene expression result in limiting the life span. (99, 113). A significant increase of H4K20me3 was found in the kidney and liver of old rats whereas the amounts of mono and di methylated forms did not change significantly with age (108). The increase in H4K20me3 was accompanied by reduced levels of other histone modifications such as H3K9me3 and H3K27me3. H3K4me3 and H3K27me3 have been related to lifespan regulation and global reduction of the H3K4me3 increases the life expectancy (32). Histone acetylation also plays an important role during aging. The changes in the levels of two histone marks such as H3K56Ac reduction and increase in the levels of H4K16Ac occurs during replicative aging in cycling human fibroblasts (18). Global histone hypoacetylation occurs in the repetitive DNA elements in aged mice brains suggesting a loss of chromatin integrity with aging (106). In addition, it has been shown that histone H4K12 acetylation plays a critical role in the aged mouse brain (96). Deregulation of H4K12 acetylation showed memory impairment in the aged mouse brain. Whereas, restoration of H4K12 acetylation recovered learning behavior in aged mice (96) (Figure 4).

In addition to the loss of heterochromatin observed during the aging process, global loss of core histone proteins from the genome during aging has been observed in budding yeast (22). In human fibroblasts, it has been reported that reduced synthesis of new histones during replicative senescence results in shortened telomere length, which is one of the hallmarks of aging (94). H2AX, a minor histone H2A variant gets phosphorylated at serine 139 to produce γH2AX, which is an early cellular response to double stranded DNA breaks. The increased levels of DNA breaks represented by the formation of γ-H2AX foci have been observed in aged cells from multiple species including aged mice and senescent human cells. (67, 71, 111, 112). There are also studies emerging to link

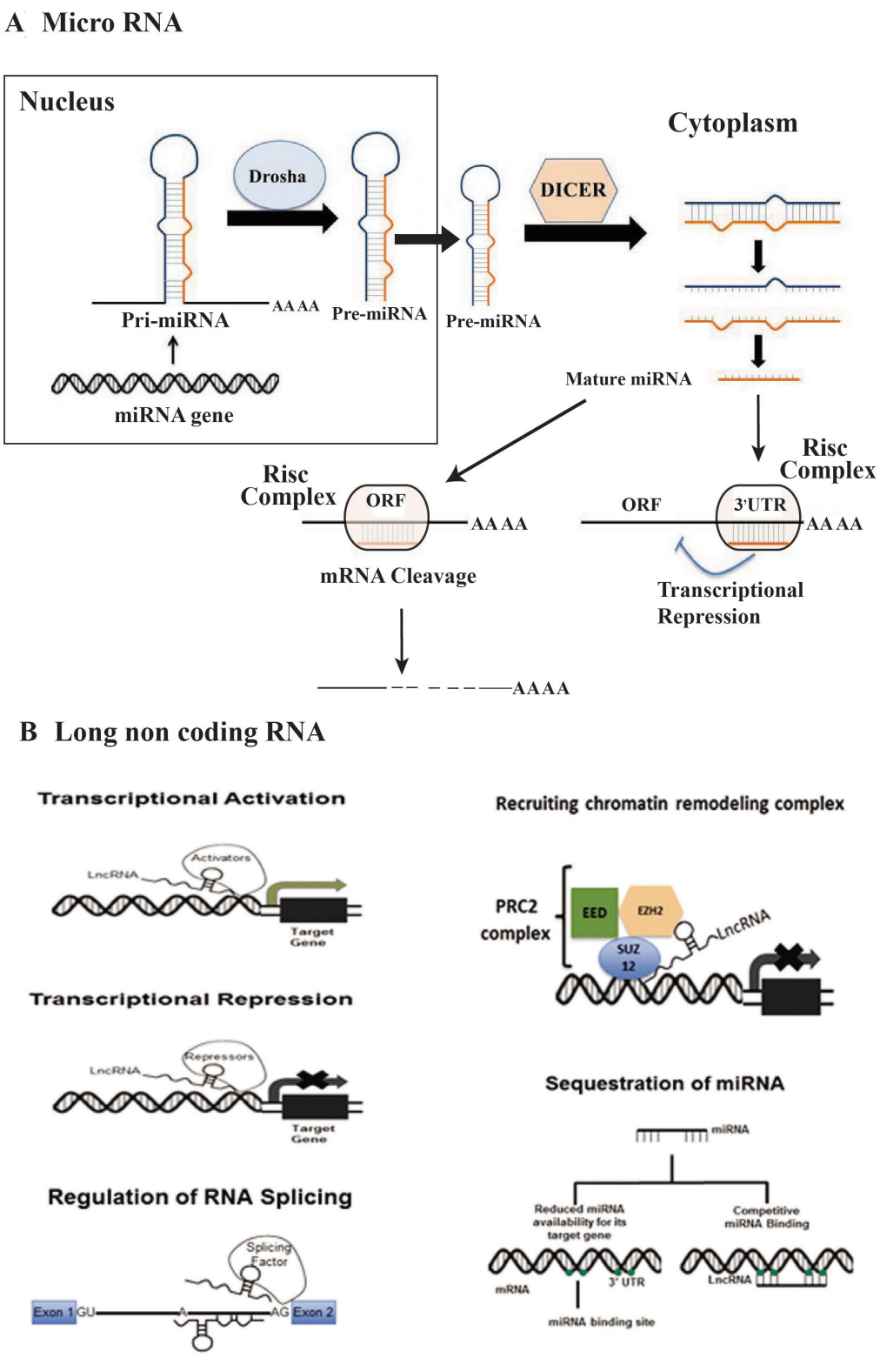

Figure 5. Non coding RNAs. A. MicroRNA biogenesis and function. MicroRNAs are synthesized from their gene as primary miRNA which are cleaved by Drosha results in premature miRNA. It is further processed by Dicer which cleaves hairpin loop structure to yield miRNA duplex. Unwinding of the duplex releases a mature miRNA which target the mRNA by binding to 3' UTR or ORF. B. Long noncoding RNA mechanism of action. Long noncoding RNAs regulate gene expression either by interacting with transcriptional activator led to gene activation or interacting with transcriptional repressor thereby suppress the transcription. LncRNA regulate RNA splicing by interacting with splicing factor or by binding the splicing junction of premRNA. LncRNAs recruit chromatin remodeling complex such as PRC2 on to the promoter region thereby regulate the gene expression. LncRNA sequester miRNAs by occupying their target sites on the mRNA.

the ATP dependent chromatin remodeling complexes to aging. BRG1 a member of SWI/SNF complex induced cellular senescence (115). BRM is another member of SWI/SNF family that can regulate aging in the rat liver. Aging increases levels of BRM in the livers of aged animals (41). (Figure 4).

3.3. Non-coding RNAs and aging

Non-coding RNAs are another kind of epigenetic modifiers that regulate gene expression without altering the DNA sequence. Although most of the studies were focused on small non- coding RNAs such as microRNAs, the importance of long non-coding RNAs has become more evident in recent years.

MicroRNAs are small non coding RNAs which are about 20-24 nucleotides in length that regulate gene expression post transcriptionally either by blocking translation or by inducing mRNA degradation. They are transcribed as a primary miRNA transcript from their corresponding gene locus by RNA polymerase II. It is further processed by endonucleases Drosha and Dicer to generate a short RNA duplex. One strand of the duplex is loaded into the RNA induced silencing complex (RISC) to bind to the target mRNA, whereas the other strand is usually degraded (2) (Figure 5). Numerous miRNAs are expressed throughout the whole human body; the brain is especially enriched in miRNAs suggesting their role in neuronal development, function, and aging (31, 39). Global miRNA profiles associated with aging have been studied in peripheral blood mononuclear cells and it was found that the majority of miRNAs were decreased with age. There were about 144 miRNAs down regulated and 21 miRNAs were upregulated in elderly individuals (90). They further validated nine different miRNAs, miR-103, miR-107, miR-128, miR-130a, miR-155, miR-24, miR-221, miR-496, miR-1538 that were significantly lower in older individuals compared to young ones. Predicted targets for several of these miRs were found to be PI3K, c-Kit, and H2AX, which were elevated with advanced age supporting a possible role in aging process. However, two miRNAs (miR-496, miR-1538) were found to be upregulated in the old participants (90). Another study in a mouse model of senescence revealed that miR-29, which targets type IV collagen gene was increased in elderly mouse tissue which in turn reduced the type IV collagen expression and weakened the basement membrane (122). Another study revealed that the miR-34 family is an important determinant for brain aging in Drosophila (68). Various members of miR-17-92 clusters were reported to be down regulated during aging in humans (34). Several studies reported that certain miRNAs were specific to aging in the brain. Mir-144 was reported to be upregulated in the cortex and cerebellum of humans, chimpanzees and macaque monkeys (97).

Long non coding RNAs (lnc RNAs) are heterogenous regulatory elements that are >200 nucleotides in length, and poorly conserved (49, 75). Based on genomic location, relative to a protein-coding gene, they are classified as intergenic, intronic, exonic, antisense, and overlapping. They regulate many biological processes such as development, differentiation, cell survival, apoptosis, gene imprinting, maintainance of stem cells, and reprogramming of differentiated cells (5, 78, 102, 89, 137). The function of lncRNAs in gene regulation is quite complex and involves epigenetic mechanisms. They couple with chromatin-remodeling or histone modifying complexes such as polycomb repressive complexes (PRCs) and HDACs (140, 77). They also serve as scaffolds that mediate the recruitment of PRCs to certain genomic regions to guide the regulation of transcription. They also involve in post transcriptional modification such as mRNA stability, splicing and translation (128). LncRNAs can serve as molecular sponges by targeting miRNA binding sites thereby sequester miRNAs from their mRNA targets (98). (Figure 5). Recent evidence also suggests a role for lncRNAs in gene regulation via influencing the activity of gene enhancers. These lncRNAs are transcribed from gene enhancers are called enhancer RNAs (eRNAs) (132). LncRNAs have also been shown to regulate gene expression in both cis- and trans- based on their regulations that are local or distant from their genetic locations (103). Long noncoding RNAs mainly execute their function via modulating chromatin structure and function. During aging, the aberrant expression of these noncoding RNAs results in defects in many chromatin related biological processes. The important lncRNAs that are functionally associated with chromatin stability and integrity and could also be implicated in aging process are H19, Kcnq1ot1, ANRIL and AIR. H19 lncRNA is found to be strongly expressed during embryogenesis and acts in trans to negatively regulate various conserved genes in the imprinted gene locus IGN including H19 and IGF2 (25, 26). Recently it has been shown that H19 forms a complex with MBD1 which then recruits histone lysine methyltransferases at DMR1 region resulting in repressive H3K9me3 marks at the imprinted locus (81). Loss of imprinting at the H19-IGF2 locus in mice has been implicated in aging (101). This loss of imprinting results in higher levels of expression of H19 in human prostate tissue during aging (149). Kcnq1ot1 is a nuclear localized, paternally expressed lncRNA that regulates imprinting of nearby imprinted genes including Cdkn1c and, Kcnq1 during embryonic development. It interacts with and recruits chromatin remodeling complexes such as G9a and PRC2 to the paternal DMR-LIT1 (differentially methylated region- long QT intronic transcript 1) locus to maintain the repressive state of the chromatin (59, 80). Kcnq1ot1 can affect the aging process by regulating cell growth and proliferation via epigenetically modulating the expression of various cell regulated genes. ANRIL is an antisense noncoding

RNA in the INK4 cyclin-dependent kinase inhibitor 2A, (CDKN2A) locus. It regulates the expression of CDKN2A and CDKN2B genes which plays roles in the regulation of cell proliferation, senescence, and aging. It binds and recruits Chromobox 7 (CBX7) a component of PRC1 to p16, SUZ12 a component of PRC2 on to p15 result in the increased repressive histone mark, H3K27 methylation (61, 143). Recent reports also suggest that this lncRNA is positively linked to TNF-α, NF-κB, and other inflammation factors contributing to aging (148). AIR (antisense Igf2r RNA) is a nuclearly localized and, paternally expressed imprinting lncRNA that is transcribed in the antisense direction towards the Igf2r promoter region. Silencing of AIR expression resulted in bi-allelic expression of Igf2R which lead to various developmental defects. AIR can be indirectly implicated in the senescence and aging process through its regulation of Igf2 expression. Other lncRNAs involved in the aging process are LincRNA-p21 and HOTAIR. LincRNA-p21 showed p53 mediated upregulation following DNA damage (40). It has been associated with repressing somatic cell pluripotency a characteristic feature found in aging cells through hnRNPK mediated recruitment of H3K9 methyl transferase, SETDB1 and DNMT1 to the promoters of pluripotency genes (4). HOTAIR (HOX transcript antisense RNA) regulates expression of genes located in HOXD1 gene locus. It acts in trans- by targeting SUZ12, EZH2 and LSD1 complex leading to altered H3K27methylation and H3K4 demethylation at the HOXD locus (140, 142, 145).

4. EPIGENETIC DYSREGULATION IN AGE RELATED NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are characterized by a progressive loss of neuronal integrity and function followed by neuronal death. Age associated neurodegenerative changes include abnormal and dysfunctional axons, neurites, a decline in neurotransmitter network, and the presence of amyloid plaques. Depending on the brain region where the changes occur, various functional disabilities may arise as the disease progresses. The exact cause for various neurodegenerative diseases varies, suggesting in some cases it is genetic mechanism. Recent evidence also suggests, epigenetic mechanisms play an important role in neurodegenerative processes. We and others recently reviewed DNA methylation and histone code modification changes in various neurological disorders (63, 27). Some of the most common age related neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD).

4.1. Alzheimer's disease

AD is the most common type of age related neurodegenerative disease characterized by cognitive decline, progressive motor abnormalities, mood instabilities, loss of memory, and decreased ability to focus and reason. It is a complex multifaceted disorder involving dysregulated energy metabolism, inflammation, and cell cycle control (72). There is a complex interplay between genetic, epigenetic and environmental factors that contribute to AD (15, 73). The two major hallmarks of AD pathology are amyloid β (Aβ) plaques and phosphorylated tau protein (127). The amyloid precursor protein (APP) is concentrated in neuronal synapses and cleaved to produce β-amyloid plaques, which are responsible for neurodegeneration and dementia in AD patients. The hyper-phosphorylated microtubule associated protein tau is expressed in neurons and is capable of forming neurofibrillary tangles (130).

Growing evidence suggests that epigenetic mechanisms mediate the risk for AD. Studies revealed a reduction in genome wide DNA methylation in aging and AD (73). Global DNA hypomethylation observed in AD patients were attributed to significant decreases in folate and S-adenosyl methionine, whose metabolites are critically involved with DNA methylation mechanism (7, 82). Evidences also suggest that the expressions of genes associated with synapatic plasticity are selectively reduced, while inflammatory and immune response genes were significantly increased in AD brains. The locus specific epigenetic changes and chromatin alterations associated with this targeted gene expression correlate with impaired synaptic plasticity (8). Bakulski *et al*., 2012 (3) studied global genome wide CpG methylation of several genes in the frontal cortex of AD patients brains and demonstrated promoter hypomethylation of transmembrane protein 59 (TMEM59) which is implicated in amyloid-β precursor post-translational processing. Other studies also reported changes in methylation status of transcription factor binding sites of tau promoter (135). In addition to DNA methylation, histone code modifications also have been reported in AD. APP/presenilin 1 double mutant transgeneic mice exhibit a marked reduction in histone H4K14 acetylation which was associated with impaired learning (24). It has also been reported that in pre-plaque AD transgenic mice exhibit increased levels of H3K14 and H3K9me2 compared with wild-type non-transgenic mice (24). An accumulation of phospho-H2AX, an indicator of DNA strand breaks has been reported in AD (86). The increased level of global H3 phosphorylation in frontal cortex and hippocampus in AD has been reported (93, 100). Guan *et al*., 2009 (33) studied HDAC2 deficiency and found that it results in increased synapse number and memory facilitation supporting the role of histone acetylation and deacetylation in AD. Non-coding RNAs have also been associated with AD. Preliminary evidence suggesting the role of miRNAs in AD came from the studies of Dicer knock-out in adult forebrain which caused abnormal tau hyperphosphorylaion and

neurodegeneration as observed in AD brain (109). Studies reported that miR-9, miR-125b and miR-146 are increased in the temporal lobes, neocortex and hippocampal regions from Alzheimer's disease patients (70, 114). Various other miRNAs were also dysregulated in sporadic Alzheimer's disease patients. Mir-29a/b-1 was found to be downregulated in AD patient's brains. These miRNAs are potential regulators of BACE1 which contribute to Aβ in sporadic AD (35). Mir-34a is upregulated in the cerebral cortex of AD mouse model (55). Another study showed miR-107 expression decreased in AD patient's brains. Mir-107 seems to regulate BACE1 expression which is associated with AD pathology (136, 87). Various long noncoding RNA dysregulation has been implicated in Alzheimer's disease (37). BACE1-AS is one of the long noncoding RNA abundantly expressed in several brain regions of AD patients. It regulates BACE1 expression, which is crtical for AD pathophysiology (21). BC200 is another long noncoding RNA involved in regulation of synaptic plasticity and is found to be elevated in the prefrontal association area and hippocampus regions in AD brains (85, 126).

4.2. Parkinson's disease

PD is the second most common age related neurodegenerative disease affecting humans over the age of 65. The clinical manifestations of the disease include motor dysfunctions such as rigidity, tremors at rest, slowness or absence of voluntary movement, and posture instability. Other non-motor symptoms are cognitive defects, depression, sleep, and emotional problems (Jankovic 2008). Loss of dopaminergic neurons in the substantia niagra brain region and formation of α-synuclein protein aggregates named levy bodies are the two major hall marks of the disease. Although a number of studies reported genetic predisposition remains high risk factor for sporadic PD, studies are emerging to suggest the role of epigenetic machinery in the development of this neurodegenerative disease (53).

Epigenetic regulation of PD linked genes is emerging in the field of neuroepigenetics and it was recently reviewed (62, 28). The relationship between methylation potential and cognitive performance in PD patients revealed that higher methylation potential is correlated with better cognitive capabilities (92). The SCNA gene which encodes α-synuclein known to form levy bodies is potentially regulated by DNA methylation. Hypomethylation of the SCNA intron1 negatively correlates with its expression and was reported in the substantia nigra of brains in PD patients (50, 74). Promoter CpG2 site of SCNA gene was found to have reduced methylation in PD patients (124). In addition, it has been shown that α-synuclein can associate with DNMT1, sequestering it in the cytoplasm resulting in global DNA hypomethylation observed in PD cases (19). A few other genes including PARK16, MAPT, and Cyt P450 2E1 (CYP2E1) are implicated in PD pathogenesis showed differential methylation status in PD patients suggesting the critical role of DNA methylation in PD (16, 54). Chromatin remodeling including histone code modifications also have been reported in PD. α-Synuclein, a major contributor of PD-linked neurodegeneration is neurotoxic with increased nuclear targeting. It has been found that α-Synuclein binds to histones and reduces the levels of histone H3 acetylation resulting in neurotoxicity (58). In PD patients, PGC1-α expression was significantly reduced in substantia nigra neurons. The epigenetic mechanism by which PGC1-α expression reduced in PD was suggested with binding of α-Synuclein on to the PGC1-α promoter which causes histone deacetylation thereby reduces the expression of PGC1-α (147, 116). Dieldrin, a neurotoxin implicated in PD pathogenesis has been found to increase histone H3 and H4 acetylation (120, 53). MicroRNAs also play an important role in PD. Mir-7 negatively regulates α-synuclein expression by binding to its 3' UTR (52). Mir-133b is another miRNA that plays a role in PD by acting as a negative regulator of dopaminergic neuron differentiation. It regulates dopaminergic neuron differentiation by targeting Pitx3 a transcription factor critically involved during this process (56). Another miRNA, miR-153 represses α-synuclein (20). In addition to the SCNA gene, the LRRK2 gene is also implicated in PD. It has been reported that Mir-205 targets the 3'UTR of LRRK2 which was found to be downregulated in PD cases (12). Mir-34b/c are thought to modulate DJ-1 and Parkin proteins that have been associated with PD. These miRs are down regulated at the early stages of the disease in brains of PD patients (79). The two lncRNAs namely RP11-462G22.1 (lnc-FRG1-3) and RP11-79P5.3 are differentially expressed in PD cases were identified from studies of whole transcriptome RNAseq analysis of leukocytes from PD patients (141). Another lncRNA, naPINK1 is transcribed antisense to the PINK1 gene and is involved in dopamine release, mitochondrial function, and motor function affected in PD (110).

4.3. Huntington's Disease

HD is an autosomal dominant neurodegenerative disease prevalent in aged individuals. It is the most common polyglutamine (polyQ) disorder which is caused by an aberrant expansion of trinucleotide sequence CAG repeats in exon1 of the HTT gene. This misfolded mutant protein can affect several cellular processes such as endocytosis, vesicle trafficking and synaptic functions. It is cleaved and forms intracellular aggregates in the cell nucleus, cytoplasm, neurites, and neuron terminals which constitutes a major hallmark of the disease (150). The most characteristic symptom of the disease is chorea, an involuntary jerk or movement of

the face and limbs. Other prominent symptoms include cognitive deterioration and psychiatric disturbances.

Altered epigenetic modifications have been reported in HD. DNA methylation pattern were found to be altered in striatal cells of HD mouse model. The promoter regions of Ap-1, Sox2, Pax6 and Nes genes were hypermethylated in HD mutant cells resulting in reduced expression. These genes are associated with neurogenesis and neuronal differentiation (88). Adenosine A_{2A} receptor ($A_{2A}R$) also known as ADORA2A, is a G-protein coupled receptor highly expressed in striatum. Decreased expression of this receptor is also epigenetically regulated in HD patients as well as in a mouse model. The increased levels of 5-mC in the 5'-UTR region of the $A_{2A}R$ gene correlate with its reduced expression in the putamen of HD patients. The reduced levels of 5-hmC correlates with this receptor reduced expression in the striatum of HD transgenic mice (129). Another DNA methylation modification observed in HD is 7-methylguagnine (7-mG), which also plays an important role in transcriptional regulation. It has been found that 7-mG was significantly altered in human HD brains and also in animal models (125). Loss of histone acetylation and hypermethylation of histones are associated with HD pathogenesis (11, 121). Mutant huntingtin was shown to interact with CBP, an important histone acetyl transferase (HAT) in mediating neuronal survival response and also implicated in neurodegenerative diseases (1, 60). It has been reported that disruption of CBP function by mutant HTT is indirectly induced by histone hypermethylation (64). CBP is thought to repress SUV39 and SETDB1 which are histone lysine methyl transferases that methylate H3K9. The reduction of CBP by mutant HTT can cause increase in levels of SETDB1 resulting in increased H3K9me3 in striatal neurons of transgenic HD mice and HD patients (106). In addition to DNA methylation and chromatin modification, the non-coding RNAs are also implicated in HD. In general, miRNA expression was found to be decreased in HD patients and animal models resulting in an upregulation of their target mRNAs (48, 65). Mir-9, miR-9*, and miR-124 were shown to be down regulated in the cortex of HD patients (47). These miRs target REST and CoREST chromatin repressor complexes shown to be implicated in HD. There are other miRNAs such as miR10b-5p, miR196a-5p, miR-196b-5p, and miR615-3p, which are upregulated in the prefrontal cortices of HD brains correlated to aberrant polycomb repressive complex2 (PRC2) regulation (38). In addition, it was also reported that mutant HTT expression decreased miR-125b and miR-150 expression (30). LncRNAs are also involved in HD pathogenesis. A natural antisense lncRNA, HTT-AS, expressed antisense to HTT has been identified to regulate the expression of HTT gene. In HD brain cortex this lncRNA is reduced in its expression. Its overexpression or knock-down shows the inverse effect on HTT transcript (14). In addition to HTT-AS, there are other lncRNAs such as TUG1, NEAT1, MEG, DGCR5 and some novel lncRNAs such as LINC00341, RPS20P22, and LINC00342, which are differentially expressed in HD brain versus control (36, 46). Another study reported that HTT acts as a molecular coordinator of PRC2, which associates with many lncRNAs for its function suggesting HD pathophysiology is related with impaired lncRNA expression, its chromatin, and transcriptional regulatory processes.

5. CONCLUSION

Epigenetic mechanisms regulating gene expression plays a critical role in various cellular processes. Here we reviewed various epigenetic mechanisms and how they regulate gene expression. We discussed in detail each epigenetic modification involved in the aging process and their role in common age-related neurodegenerative diseases. The involvement of the epigenetic factors in the brain during the aging process and age-related neurodegenerative diseases provides new insight in understanding how epigenetic based therapy is emerging as an alternative approach to treat neuropsychiatric diseases. The current knowledge of epigenetic changes that occur during aging and age-related disorders is of great importance and epigenetic based therapies need to be developed in the near future.

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Key Words: Epigenetics, Aging, DNA methylation, Histone code, Micro RNA, Long non coding RNA, Neurodegenerative disease, Review

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