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The epigenetics of aging and neurodegeneration

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Abstract

Epigenetics is a quickly growing field encompassing mechanisms regulating gene expression that do not involve changes in the genotype. Epigenetics is ofincreasing relevance to neuroscience, with epigenetic mechanisms being implicated in brain development and neuronal differentiation, as well as in more dynamic processes related to cognition. Epigenetic regulation covers multiple levels of gene expression; from direct modifications of the DNA and histone tails, regulating the level of transcription, to interactions with messenger RNAs, regulating the level of translation. Importantly, epigenetic dysregulation currently garners much attention as a pivotal player in aging and agerelated neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, where it may mediate interactions between genetic and environmental risk factors, or directly interact with disease-specific pathological factors. We review current knowledge about the major epigenetic mechanisms, including DNA methylation and DNA demethylation, chromatin remodeling and noncoding RNAs, as well as the involvement of these mechanisms in normal aging and in the pathophysiology of the most common neurodegenerative diseases. Additionally, we examine the current state of epigenetics-based therapeutic strategies for these diseases, which either aim to restore the epigenetic homeostasis or skew it to a favorable direction to counter disease pathology. Finally, methodological challenges of epigenetic investigations and future perspectives are discussed.

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Keywords

Epigenetics; Aging; Neurodegeneration; Alzheimer's disease; Parkinson's disease; Huntington's disease

1. Epigenetics

Conrad Hal Waddington coined the term "epigenetics" in 1942, an event commonly viewed as the birth of epigenetics as it developed from a phenomenon to an immensely studied branch of science (Choudhuri, 2011). A merger between the terms "genetics" and "epigenesist", the concept of epigenetics in a way represents the association of two views on development that have been clashing at least since the time of Hippocrates and Aristotle (Muller and Olsson, 2003). Hippocrates proposed what became known as the preformationist view of development; all parts of a mature organism are already present at the embryonic stage, albeit in a miniature stage, and they simply grow during development. Aristotle argued against this preformationist view, providing an alternative explanation that lies at the foundation of the epigenesis concept: embryonic development involves the formation of new parts. After numerous scientific discoveries these views evolved over the centuries. A contemporary preformationist would hold that all that is needed to generate a mature organism is its genetic code, whereas a supporter of epigenesis would argue that the genome only holds the information of building blocks - but that how these are put together depends on environmental influences. The contemporary perspective of "epigenetics" is that of the field of science that studies how changes in gene expression occur without changes in the DNA sequence (Choudhuri, 2011). Such changes can be induced by environmental factors, while some are more programmed, as seen during cell differentiation. As such, these epigenetic alterations can be highly stable, such as those resulting from genetic imprinting, or dynamic such as the epigenetic changes associated with memory. Many Epigenetic modifications can be inherited through mitosis and some have even found to be transgenerational (Handel et al., 2010; Hsieh and Eisch, 2010; Hu et al., 2012; Ma et al., 2010). Thus, whereas genetic alterations usually reflect permanent changes of the DNA sequence, epigenetic changes are mediated through processes that are in principle reversible (Henikoff and Matzke, 1997). While environmental influences can potentially alter the phenotype of an organism by interacting with and by acting on both the genome and epigenome (Liu et al., 2008), the reversible nature of epigenetic changes makes them more suitable as candidates for clinical interventions (Feinberg, 2008). Over the past decade there have been ample studies investigating the contributions of epigenetic modifications to aging and age-related neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). The epigenetic machinery covers multiple levels of control, including DNA methylation and hydroxymethylation, chromatin remodeling, and non-coding RNA (ncRNA) regulation (Adwan and Zawia, 2013). See Fig. 1 for a general overview of the epigenetic mechanisms discussed below.

1.1. DNA methylation

The best characterized epigenetic modification, DNA methyl-ation involves the addition of a methyl group at the 5 position on the pyrimidine ring of cytosines, creating 5-methylcytosine

(5-mC) (Razin and Riggs, 1980). These modifications primarily occur at cytosine-phosphate-guanine (CpG) islands. Recently, however, non-CpG methylation has received increased attention (Guo et al., 2013). Apart from cytosines, there are also reports of guanine and adenine methylation, resulting in 7-methylguanine (7-mG) and 3- methyladenine, respectively (Thomas et al., 2013). In this review, however, DNA methylation refers exclusively to 5-mC, unless mentioned otherwise. Generally, DNA methylation is associated with transcriptional repression and is mostly found in heterochromatin (Miller and Sweatt, 2007), while the euchromatin typically contains low amounts of methylated DNA. Some genes, however, are suspected to show enhanced expression when hypermethy-lated (Silva et al., 2008). Additionally, DNA methylation within gene bodies (the transcribed portion of a gene) has been implicated in alternative splicing (Flores et al., 2012; Lyko et al., 2010). How DNA methylation exactly affects gene transcription is highly dependent on the location in or around the gene (Ziller et al., 2013). In promoter regions, methylated DNA can directly disrupt the transcriptional process by interfering with the binding of transcription factors (Klose and Bird, 2006). Additional repression can be established through the attraction of methyl-CpG-binding domain proteins (MBDs) and subsequent activation of the histone tail modifying machinery, leading ultimately to chromatin compaction (Portela and Esteller, 2010). How gene expression is enhanced through methylation of gene bodies remains unclear.

Although DNA methylation is the most stable epigenetic modification, the DNA methylation profile, or ‘methylome’, is highly dynamic (Bhattacharya et al., 1999; Levenson et al., 2006; Weaver et al., 2004). DNA methylation profiles are, at least partly, heritable, both after cell division, as well as in a transgenerational fashion (Bergman and Cedar, 2013; Guerrero-Bosagna and Skinner, 2012). Heritable DNA methylation needs to be copied to the newly synthesized DNA strand, a process that is referred to as maintenance DNA methylation. The addition of completely new DNA methylation marks is called *de novo* DNA methylation. DNA methyltransferases (DNMT) are responsible for maintenance and *de novo* DNA methylation (Mastroeni et al., 2010). There are four known types of DNMTs; DNMT1, DNMT2, DNMT3a and DNMT3b, all of which use S-adenosylmethionine (SAM) as the methyl donor (Klose and Bird, 2006; Mastroeni et al., 2010). Note, however, that DNMT2 was actually found to be a RNA methyltransferase (Jurkowski et al., 2008). Furthermore, there is another DNMT, DNMT3-like (DNMT3L), which exhibits no enzymatic activity, but detects unmethylated lysine 4 of histone H3 tails (H3K4) and recruits or activates DNMT3a (Ooi et al., 2007). Interestingly, the DNMT3B splice variants DNMT3B3 and DNMT3B4 are also inactive and play a regulatory role in *de novo* DNA methylation (Gordon et al., 2013). DNMT1 is the most common variant in somatic cells and primarily involved in maintenance DNA methylation, and DNMT3a and DNMT3b are responsible for *de novo* DNA methylation (Okano et al., 1999). DNMT3a and DNMT3b isoforms are expressed in a more cell-type-specific manner (Guo et al., 2013; Okano et al., 1999).

It is worth mentioning that the methyl donor of the DNMTs, SAM, is generated through a complex cycle and is the methyl donor of numerous additional transmethylation reactions (Mastroeni et al., 2011; Wang et al., 2013). This cycle starts with the conversion of tetrahydrofolate (THF) to 5,10-methylenetetrahydrofolate (MTHF) by vitamin B_6-dependent serine hydroxymethyltransferase (SHMT), and the subsequent conversion of 5,10-MTHF to

5-MTHF by B_2-dependent MTHF reductase (MTHFR). 5-MTHF acts as the methyl donor for the methylation of homocysteine (Hcy), producing methionine, by cobalamin-dependent methionine synthase (MetH). SAM is subsequently generated from methionine by methionine adenosyltransferase (MAT). During methyltransferase reactions SAM is converted to S-adenosylhomocysteine (SAH), which is further hydrolyzed to Hcy and adenosine by SAH hydrolase (SAHH). Folate serves as cardinal input for this cycle and the proper elimination of Hcy and adenosine is important to maintain homeostasis. For instance, global DNA hypomethylation could be induced through folate deficiency and high levels of Hcy (Mastroeni et al., 2011).

As DNA methylation can be relatively simple and robustly assessed using genomic DNA, it has been the primary focus of human epidemiological epigenetic research (Lunnon and Mill, 2013). Early investigations into DNA methylation showed its cardinal importance in the proliferation and differentiation of neural stem cells (Mattson, 2003). More recently, it has been established that DNA methylation is pivotal for synaptic plasticity, neuronal repair, neuronal survival, and learning and memory (Fan et al., 2001; Feng et al., 2010; Iskandar et al., 2010). Such dynamic processes are more dependent on *de novo* methylation, although the importance of maintenance DNA methylation should not be underestimated, as a loss of DNMT1 was shown to result in increased histone acetylation, a disruption of the nuclear organization and eventually cell death (Chan et al., 2001; Espada et al., 2007; Fan et al., 2001; Jackson et al., 2004; Milutinovic et al., 2004). Because these are factors disturbed in a neurodegenerative state, DNA methylation is a valid target when investigating neurodegeneration.

1.2. DNA demethylation

While DNA methylation is a well-established epigenetic mechanism, the existence of active DNA demethylation in animals has long been a point of controversy (Ooi and Bestor, 2008). Observations such as high levels of DNMTs in nondividing cells (Sharma et al., 2008) and a significant decrease in methylated DNA levels when DNA methylation is blocked (Levenson et al., 2006; Miller and Sweatt, 2007), despite the stability of the 5-mC mark, have led to an avid search for the players responsible for an active demethylation process. This search generated several mechanisms, including an RNA-dependent pathway by which the methyl group is removed from 5-mC, a pathway involving the nucleotide excision repair mechanism, and a base excision repair based pathway (Barreto et al., 2007; Bhattacharya et al., 1999; Gavin et al., 2013; Zhu et al., 2000a,b).

Although still a point of discussion, the base excision repair pathway is a prime candidate as the primary road to demethyla-tion in post-mitotic neurons (Gavin et al., 2013), which does not exclude the possibility of multiple overlapping demethylation pathways. DNA demethylation is thought to be initiated by the oxidation of 5-mC into 5-hydroxymethylcytosine (5-hmC) by the ten-eleven translocation (TET) proteins (Guo et al., 2011; Ito et al., 2011). There are 3 TET proteins, TET1, TET2 and TET3, which are differentially expressed and regulated throughout the body (Delatte and Fuks, 2013). Interestingly, in the last few years 5-hmC was shown to be an important epigenetic marker that is functionally different from 5-mC (van den Hove et al., 2012). While DNA

hydroxymethylation is generally associated with increased gene activity, work by Jin et al. (2011b) indicates that this correlation does not always hold and depends on the location of 5-hmC in the gene and the CpG content. 5-hmC is present in most tissues and cell types, but is especially enriched in the brain (Globisch et al., 2010), with cerebellar Purkinje cells exhibiting some of the highest levels (Kriaucionis and Heintz, 2009). Furthermore, in the frontal cortex, 5-hmC is selectively enriched in promoter and intragenic regions (Jin et al., 2011b). Interestingly, 5-hmC levels are particularly low in stem cell-rich areas (Globisch et al., 2010; Orr et al., 2012). In addition to the formation of 5-hmC, it has recently been discovered that TET enzymes can further oxidize 5-hmC to 5-formylcytosine (5-fC), and 5-fC to 5- carboxylcytosine (5-caC) (Ito et al., 2011). Although it is generally accepted that 5-hmC is a functional epigenetic marker, such a role remains to be established for 5-fC and 5-caC (Raiber et al., 2012; Song et al., 2013). Apart from oxidation, 5-mC and 5-hmC can be deaminated instead, by either activation-induced cytidine deaminase (AICDA) or apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like protein (APOBEC), resulting in thymidine or 5-hydroxymethyluracil (5-hmU) (Guo et al., 2011; Popp et al., 2010). 5-caC, thymidine or 5-hmU present a mismatch in the base pairing of the DNA sequence (5-caC:G, T:G or 5-hmU:G, respectively). Such a mismatch can be detected and mended through the removal of the transformed bases by thymidine or uracil glycosylases (Cortellino et al., 2011; Guo et al., 2011; He et al., 2011; Matsubara et al., 2004). Alternatively, 5-fC and 5-caC can be changed back to cytosine by removal of formic acid or decarboxylation, respectively (Ito et al., 2011). In addition to the aforementioned enzymes, the growth arrest and DNA damage 45 (GADD45) proteins are crucially involved in directing the activity of these enzymes, thereby assisting in the localization of demethylation activity to specific gene promoters (Barreto et al., 2007; Ma et al., 2009; Rai et al., 2008; Schmitz et al., 2009). Clearly, the exact mechanisms underlying DNA demethylation remain to be elucidated.

1.3. Chromatin remodeling

Chromatin can be seen as a string ofnucleosomes, which mainly consist of DNA and the histones around which it is wrapped. There are five types of histone proteins; H2A, H2B, H3, and H4 forming the octameric core of the nucleosome, and H1 serving as a linker and stabilizer, binding to DNA among nucleosomes (Luger et al., 1997; Wang et al., 2013). The conformation of these histones largely determines the accessibility of the DNA for transcription, and can be adjusted through reversible modifications of their N-terminal tails. Such modifications include lysine (K), arginine (R) or histidine (H) methylation (Murray, 1964), K acetylation (Gershey et al., 1968), serine (S), threonine (T) or tyrosine (Y) phosphorylation (Kleinsmith et al., 1966), ubiquitination (Hunt and Dayhoff, 1977), adenosine diphosphate (ADP)-ribosylation (Ueda et al., 1975), crotonylation (Tan et al., 2011), hydroxylation (Houston et al., 2013), proline isomerization (Kouzarides, 2007) and K SUMOylation (Shiio and Eisenman, 2003), which together constitute the histone code. A specific state of the histone code may either lead to gene activation or silencing (Jenuwein and Allis, 2001). The endless possible combinations of the various modifications and target sites, allows the histone code for highly versatile fine tuning of gene expression, but is also critically involved in DNA repair and replication (Day and Sweatt, 2011). Owing to the attention that chromatin-modifying enzymes have received over the past years, many

enzymes that had been identified as modifying histones, were later found to have many additional substrates. In view of this, Allis et al. (2007) have proposed an updated nomenclature that better reflects the full spectrum of functions of these enzymes. For instance, histone (lysine) acetyltransferases (HATs) were renamed to lysine acetyltransferases (KATs). As, however, this new nomenclature has only sporadically been adopted, both old and new names will be stated to avoid confusion.

Acetyl coenzyme A serves as donor of the acetyl group, which is transferred to lysines of histone tails by KATs (Marmorstein and Roth, 2001). There are a multitude of proteins with KAT activity, which can be divided into five main groups, comprising KAT2A (or general control of amino acid synthesis [GCN] 5), KAT2B (or P300/ CBP-associated factor [PCAF]), KAT6–8, cyclic adenosine monophosphate (cAMP) response element-binding protein binding protein (CREBBP or CBP) and adenovirus early region 1A (E1A)-binding protein P300 (EP300 or P300) (Huynh and Casaccia, 2013).

Currently, there are 18 known histone deacetylases (HDACs) in humans, generally subdivided into four classes; class I (HDACs 1,2, 3 and 8), class IIa (HDACs 4, 5, 7 and 9), class IIb (HDACs 6 and 10), class III (sirtuins [SIRTs] 1,2, 3, 4, 5, 6 and 7) and class IV (HDAC11) (Dokmanovic et al., 2007). Although their name suggests that histones are the primary targets of HDACs, phylogenetic analysis indicates that de evolutionary development of HDACs preceded that of histones (Gregoretti et al., 2004). Indeed, over 50 nonhistone targets of HDACs have been identified, including proteins important for proliferation, migration, and cell death (Marks and Breslow, 2007; Minucci and Pelicci, 2006; Rosato and Grant, 2005). Thus, as for HATs, it was suggested that HDACs should be more appropriately referred to as lysine deacetylases (Xu et al., 2007). The different HDACs fulfill many different roles, either by affecting gene expression or by directly regulating protein functioning. Class I HDACs for instance, are thought to play a general role in cell survival and proliferation, whereas class II HDACs have a more tissue-specific role (Chang et al., 2006; Harms and Chen, 2007; Kim et al., 2007b; Laggeret al., 2002; Parra et al., 2007; Vega et al., 2004; Zhang et al., 2002). The SIRTs further differ from the others HDACs in that their activity is nicotine adenine dinucleotide (NAD+)-dependent, whereas the other classes require the presence of zinc. Not all SIRTs are even primarily deacetylases. This has led to the suggestion that SIRTs should be classified as deacylases, as opposed to deacetylases (Hirschey, 2011). Although class I and class IV HDACs are mainly nuclear, class Ila shuttles between the nucleus and cytoplasm and class llb is primarily cytoplasmic. The sirtuins of class lll are most varied in their localization, and can be either expressed in the nucleus (SIRTs 1, 2, 6 and 7), cytoplasm (SIRTs 1 and 2) or mitochondria (SIRTs 3, 4 and 5) (Michan and Sinclair, 2007). The expression of the different HDACs is also highly region- and cell-type-specific, for instance, while HDAC2 is expressed in most brain regions, it is predominantly active in mature neurons and weakly or not in progenitor and glial cells (Guan et al., 2009; MacDonald and Roskams, 2008).

Methylation of histone tails happens at K or R residues of H3 or H4, and is executed by histone lysine methyltransferases (HKMTs) and protein arginine methyltransferase (PRMT), respectively, whereas demethylation is performed by histone lysine demethy-lases (HKDMs) and histone arginine demethylases (HRDMs) (Chang et al., 2007; Habibi et al., 2011). The

other histone modifications are less well characterized. Phosphorylation and dephosphorylation of histones is executed by protein kinases, such as mitogen- and stress-activated protein kinase (MSK)-1, and protein phosphatases, such as protein phosphatase (PPT) 1, respectively (Brami-Cherrier et al., 2009; Koshibu et al., 2009). Histone phosphorylation is dynamic in function; H3 phosphorylation, for instance, marks open chromatin during active gene expression, whereas during mitosis this marker associates with condensed chromatin (Sawicka and Seiser, 2012). Ubiquitination can either enhance or inhibit gene expression, whereas SUMOylation is primarily thought to suppress transcription (Habibi et al., 2011).

The actual effect and interplay between these modifications are complex, and depend on the type of histone protein and the specific amino acid that is modified, and a combination of certain modifications can even have a function that is different from that of these modifications in isolation (Bernstein et al., 2006; Greer and Shi, 2012; Hwang et al., 2013; Jenuwein and Allis, 2001; Sawicka and Seiser, 2012). For instance, acetylation of K 9 (H3K9ac) and 14 (H3K14ac) of H3, or tri-methylation at K 4 of H3 (H3K4me3), H3K36me, H3K79me, H3R2me, H3R17me, H3R26me and H4R3me are associated with gene activation, whereas H3K9me2/3, H3K27me3, H3R8me, H4K20me3 and H4R3me are generally associated with gene repression (Habibi et al., 2011). Interestingly, in case of histone methylation, the number of attached methyl groups also matters, as the previously mentioned H3K9me3, H3K27me3 and H4K20me3 marks that are associated with gene repression, all have monomethylated counterparts that are associated with gene activation (Barski et al., 2007). Of note, recent studies mapping histone tail modifications to genomic regions found that many transposable elements (TEs) are enriched with certain histone marks (Kondo and Issa, 2003; Martens et al., 2005; Pauler et al., 2009) and it has therefore been suggested that TEs may attract certain histone marks to induce heterochromatic and euchromatic states, or serve as boundary elements that prevent the propagation of such states (Huda and Jordan, 2009).

In addition to histone modifications, chromatin remodeling also occurs through adenosine triphosphate (ATP)-dependent multiprotein chromatin remodeling complexes. Four distinct remodeling complex families have been identified, including the Brg1/hBrm associated factor (BAF; previously known as switching defective/sucrose nonfermenting [SWI/SNF]), imitation SWI (ISWI), chromodomain, helicase, DNA-binding (CHD) and inositol requiring 80 (INO) families (Clapier and Cairns, 2009; Hargreaves and Crabtree, 2011; Vogel-Ciernia and Wood, 2014). These complexes, or remodelers, can bind nucleosomes, disrupt nucleosome-DNA binding, and then move, destabilize, eject or restructure them, using ATP hydrolysis as energy source. In doing this, remodelers can either induce transcriptional activation or repression, through the recruitment of coactivator or corepressor complexes. The different remodeling complexes are defined by their ATPase subunits, but variation in their remaining subunit composition, possibly altering the DNA and protein binding properties of the complex, allows for great diversity, leading to cell-type specific roles (Ho and Crabtree, 2010; Ronan et al., 2013). Furthermore, multiple functionally different versions of a complex may be present within one cell (Wang et al., 2004). The BAF complex, consisting of at least 15 subunits, is of particular interest, as it is the only chromatin remodeling complex with a neuron-specific subunit, BAF53b. The BAF complex

is thought to play an important role in neuronal development and functioning, with unique subunit compositions in embryonic stem cells, neuronal progenitors and mature neurons (Vogel-Ciernia and Wood, 2014). The BAF53b subunit was shown to be important for dentritic development *in vitro* and long term memory in mice (Vogel-Ciernia et al., 2013). See the excellent review by Hargreaves and Crabtree (Hargreaves and Crabtree, 2011) fora detailed discussion of the different chromatin remodeling complexes.

1.4. Non-coding RNAs

Until recently it was widely believed that most of the human genome consisted of so-called 'junk', or nonfunctional DNA. It was later revealed that almost the whole genome is transcribed, but that only about 2% is actually translated into proteins (Amaral et al., 2008). Most of the 'junk' actually is functional and is primarily involved in the regulation of gene expression, usually in the form of ncRNAs. There are many types of ncRNAs, including microRNAs (miRNAs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), small Cajal body-specific RNAs (scaRNAs), piwi-interacting RNAs (piRNAs), splice junction- associated RNAs (spliRNAs), small modulatory RNAs (smRNAs), repeat-associated small interfering RNAs (rasiRNAs), transcription initiation RNAs (tiRNAs), promoter-associated short RNAs (PASRs), transcription start site-associated RNAs (TSSa-RNAs), promoter upstream transcripts (PROMPTS), ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), and small double-stranded RNAs (dsRNAs) (Jady et al., 2004; Mattick, 2011; Preker et al., 2008; Schouten et al., 2012; Seila et al., 2008). These are small ncRNAs (sncRNAs), of <200 nucleotides, whereas there are also long ncRNAs (lncRNAs), which can exceed 100,000 nucleotides, often including TE-derived sequences that may confer specific protein or nucleic acid interacting properties (Johnson and Guigó, 2014). Examples of lncRNAs are intergenic ncRNAs (lincRNAs), natural antisense transcripts (NATs), ncRNA expansion repeats, promoter-associated RNAs (PARs), and enhancer RNAs (eRNAs) (Kapranov et al., 2007; Khalil et al., 2009; Kim et al., 2010b; Nakamori and Thornton, 2010; Werner, 2005). The sncRNAs fulfill various functions, including infrastructural (rRNAs, tRNAs and snRNAs) and regulatory roles (miRNAs, siRNAs, snoRNAs, piRNAs and spliRNAs), whereas the lncRNAs are primarily regulatory. Interestingly, lncRNAs are expressed in a highly cell-specific manner, may undergo alternative splicing, and may even have protein-coding isoforms (Cabili et al., 2011; Chooniedass-Kothari et al., 2004; Djebali et al., 2012; Johnsson et al., 2013). Alternatively, some mRNAs may function as *trans*-acting regulatory RNAs (Ashe et al., 1997; Dinger et al., 2011; Mercer et al., 2011). In terms of epigenetics, ncRNAs are cardinally involved in gene expression control, in the silencing of TEs, X-chromosome inactivation, alternative splicing, and DNA imprinting (Jeon et al., 2012; Lisch, 2012; Morrissy et al., 2011). Additionally, some lncRNAs have been proposed to direct epigenetic enzymes to their target sites (Khalil etal.,2009; Koziol andRinn, 2010; Mercer and Mattick, 2013), while others are thought to bind and sequester other epigenetic players, such as DNMTs and miRNAs, thereby hampering their activity (Di Ruscio et al., 2013; Johnsson et al., 2013; Mercer and Mattick, 2013).

The best characterized of the ncRNAs are miRNAs. These begin their lives as primary miRNAs, after which they are cleaved by ribonuclease type III Drosha to form precursor

miRNAs (pre-miRNAs) (Han et al., 2009). These pre-miRNAs are then transported from the nucleus to the cytosol by Exportin-5, where Dicer makes the final adjustment to produce double-stranded mature miRNAs. Mature miRNAs span 21–25 nucleotides and regulate protein production through an RNA interference pathway, involving the association of one of the strands of the miRNA duplex with the RNA-induced silencing complex (RISC) (Ambros, 2004; Han et al., 2004). They interfere with gene expression through binding to messenger RNA (mRNA), usually to the 3' untranslated region (UTR), which hampers the initiation of translation and affects mRNA stability. MiRNAs can potentially regulate the translation of multiple genes, whereas genes can also be regulated by several miRNAs, as the sequences of the miRNA and its target are not required to be a perfect match for interference to take effect (He and Hannon, 2004; Lim et al., 2005). While siRNAs are processed and function similarly, they require stricter matching with their target sequence when compared to miRNAs (Zeng et al., 2003). Apart from interacting with RISC, some miRNAs have been observed to promote mRNA translation and gene transcription, by binding to gene promoter regions (Eulalio et al., 2008; Fabian et al., 2010). There are numerous miRNAs, many of which are expressed according to strict spatial and temporal patterns. Currently, there are 1881 precursors and 2588 mature human miRNAs registered in the fast growing miRBase (The University of Manchester, 2014). While expressed throughout the whole human body, the brain is especially enriched in miRNAs, suggesting an important role for them in neuronal development, functioning, and aging (Gokey et al., 2012; Hu et al., 2011a). Their biological role has been further characterized, and reviewed by Santosh, and colleagues, as well as Qu and Adelson (Qu and Adelson, 2012; Santosh et al., 2014). Both the reviews extend beyond the aforementioned functions, and present the key role of ncRNA in RNA splicing, transcriptional, post-transcriptional, and translational regulation by either binding directly to transcriptional factors or by generating siRNAs, that consequently interact with the translational machinery.

1.5. Additional epigenetic mechanisms

DNA methylation, chromatin remodeling, and ncRNAs represent the best-studied epigenetic mechanisms, especially in relation to aging and neurodegenerative diseases. Epigenetic regulation goes much deeper, however, and also includes the rising subfields of RNA editing, RNA methylation, and mitochondrial epigenetics, which will be briefly touched upon in this section, but will not be further discussed in relation to aging and neurodegeneration due to the as of yet extremely limited findings in this respect. Clearly, more studies on the role of these additional layers of epigenetic regulation in aging and neurodegeneration are waranted.

1.5.1. RNA editing—The observation of discrepancies in genomic and cDNA sequences led to the discovery of RNA editing (Bass, 2002). The finding that RNA can be edited, a process that seems particularly important in the brain, adds another layer to the transcriptional and post-transcriptional regulation of gene expression. It has even been proposed that a dramatically increased RNA editing capacity was crucial for the evolution of the mammalian brain as it may function as a mechanism driving phenotypic adaptability, which ultimately led to the superior cognitive abilities of humans (Mattick, 2010; Mattick and Mehler, 2008). In support of this, roughly 35 times more RNA editing is observed in

humans compared to mice. This surplus appears to be mainly directed to retrotransposed Alu elements that are primate-specific and constitute 10.5% of the human genome (Athanasiadis et al., 2004; Kim et al., 2004; Lander et al., 2001; Levanon et al., 2004; Umylny et al., 2007).

In contrast to RNA and DNA modifications, RNA editing involves a change in RNA sequence by deamination of either adenosine (A) or cytosine (C), to inosine (I) (Bass, 2002; Valente and Nishikura, 2005) or uracil (U) (Conticello, 2008; Navaratnam and Sarwar, 2006), respectively. A to I editing is performed by adenosine deaminases that act on RNA (ADARs), while C to U editing is carried out by APOBECs. APOBECs are related to AICDAs, which targets DNA and is pivotal in the generation of the immunoglobulin repertoire (Muramatsu et al., 1999). Although not much is known about the targeting, regulation and functional impact of ADARs and APOBECs, they are thought to be evolved from adenosine deaminases that act on tRNAs (ADATs) and thus bind doublestranded RNA regions, such as those seen in hairpin formations that are also present in tRNAs (Bass, 2002; Conticello, 2008).

ADAR1 and ADAR2 are ubiquitously expressed and they appear to be enriched in the brain, while the expression of ADAR3 seems to be restricted to the brain. A to I RNA editing has been observed in coding transcripts, for instance leading to changes in the amino acid sequence of glutamate and serotonin receptors. Most editing, however, happens to noncoding sequences, such as miRNAs (Blow et al., 2006; Kawahara et al., 2008; Nishikura, 2006) and transposon-derived repetitive sequences (Morse et al., 2002), suggesting that RNA editing not only directly affects gene expression, but also indirectly by regulating other epigenetic players (Mattick, 2010). APOBECs, together with overall RNA editing, appear to have undergone a substantial expansion over the course of evolution, with APOBEC3 being especially favored in humans with eight orthologs, compared to one in mice (Conticello et al., 2005; Navaratnam and Sarwar, 2006; Sawyer et al., 2004). Although it has been suggested that these enzymes have evolved to combat retrotransposons and endogenous retroviruses (Aguiar and Peterlin, 2008; Schumann, 2007), there is also evidence indicating that these elements actually have been harnessed as epigenetic regulators involved in growth and differentiation, including the generation of neuronal diversity (Coufal et al., 2009; Dunlap et al., 2006; Faulkner et al., 2009).

Recently, the implication of RNA editing in the etiopathogenesis and progression of neurodegenerative disorders as well as normal aging processes has gained momentum and the few available studies begin to elucidate this connection. The majority of these studies are focusing on aging. Sebastiani et al. observed that 5 SNPs in the ADAR encoding genes *Adarb1* and *Adarb2* are associated with extreme longevity in 4 independent human studies. The observation of the critical role of ADARs in aging was also verified in a *Caenorhabditis elegans (C. elegans)* model with loss of function of *adr1* and *adr2 (Adarb1* and *Adarb2* orthologues), which had a 50% decrease in lifespan (Sebastiani et al., 2009). After this study a lot of RNA editing targets were discovered, such as gamma-aminobu-tyric acid receptor subunit alpha-2 *(Gabra2),* cytoplasmic FMR1-interacting protein 2 *(Cyfip2),* potassium channel gene *(Kcnal),* filamin a *(Flna),* bladder cancer associated protein *(Blcap),* golgi complex subunit 3 (*Cog3*), nuclear paraspeckle assembly transcript 1 and 2 *(Neat1, Neat2),*

metastasis associated lung adenocarcinoma transcript 1 (*Malat1*) and phosphatidylserine decarboxylase-pseudogene 1 *(Pisd-ps1)* that are differentially edited in the aging murine and human brain. Among them Cyfip2 and Pisd-psl have gained considerable attention (Holmes et al., 2013; Nicholas et al., 2010; Stilling et al., 2014). Nicholas et al. demonstrated that A to I editing declines with age in humans, in a gene-specific manner, resulting in downregulation of an ADAR2 target gene, *Cyfip2,* which is responsible for synaptic maintenance (Nicholas et al., 2010). In the hippocampal formation of aged mice Stilling et al. showed that the altered RNA editing levels of Pisd-ps1 results in higher editing frequency with age and thus upregulation of gene expression (Stilling et al., 2014).

In case of AD, Akbarian et al. observed a decrease in the RNA editing levels of glutamate receptor 2 (GluR2) in the prefrontal cortex of AD human brains (Akbarian et al., 1995). Rechavi's team following the aforementioned research line, examined the GluR2 Q/R RNA editing levels in the hippocampus of AD brains, which they found to be decreased in comparison to controls. Additionally, they showed lower GluR2 Q/R RNA editing in the hippocampus of APOEε4 carriers. The mRNA expression of ADARs was also investigated in this specific study; unexpectedly no differences were found in the hippocampus but a 37% decrease of ADAR2 mRNA expression was noticed in the caudate (Gaisler-Salomon et al., 2014). Finally, Akbarian et al. extended his study on HD where he also showed a decrease in GluR2 RNA editing levels in the striatum (Akbarian et al., 1995).

1.5.2. RNA methylation—Although the discovery of methylated RNA was done decades ago (Desrosiers et al., 1974; Rottman et al., 1974), over a hundred RNA nucleotide modifications have been identified across different organisms (Behm-Ansmant et al., 2011; Kellner et al., 2010). In eukaryotes the best-studied mRNA modifications are N6-methy-ladenosine (m6A) and 5-mC, which mainly occur at 3' UTRs and stop codon sites (Meyer et al., 2012). As in DNA, 5-hmC has also been observed in RNA (Fu et al., 2014). m6A is the most prevalent mRNA modification in mammals and has also been observed in tRNAs, rRNAs and snoRNAs(Bringmannand Luhrmann, 1987; Choi and Busch, 1978; Epstein et al., 1980; Harada et al., 1980; Munns et al., 1977; Perry et al., 1975; Shimba et al., 1995; Tanaka and Weisblum, 1975). In humans the m6A modification shows high tissue specificity, with the highest levels occurring in the brain, in transcripts such as *Bdnf, Dscam, Lis1* and *Ube3a* (Dominissini et al., 2012). In mice and humans m6A methyltransferase methyltrans- ferase-like protein 3 (METTL3) (MT-70) is responsible for the post- transcriptional m6A RNA modification (Bujnicki et al., 2002). Additionally, METTL14 and Wilm's tumor-associated protein (WTAP) have been shown to interact with METTL3 and are thought to be additional components involved in RNA methylation (Ping et al., 2014; Wang et al., 2014b). Just as DNA methylation, the identification of m6A demethylases fat mass and obesity-associated protein (FTO) and AlkB, alkylation repair homolog 5 *(E. coli)* (ALKBH5)(Jia et al., 2011; Zheng et al., 2013), indicates that RNA methylation is a dynamic regulatory mechanism. FTO, a dioxygenase, demethylates RNA via a similar oxidation procedure as is employed by the TET enzymes that are thought to be involved in DNA demethylation, namely through the generation of intermediates N6-hydroxymethyladenosine (hm6A) and N6-for-myladenosine (f6A), before being reversed to A (Fu et al., 2013). Although these intermediates remain stable for several hours, no separate regulatory roles for hm6A and f6A have been reported

yet. ALKBH5 is thought to remove m6A directly, without the generation of intermediates (Zheng et al., 2013). Although the exact regulatory functions of m6A RNA methylation remain to be elucidated, its main occurrence at 3' UTRs and stop codons has been suggested to indicate a role in switching genes on or off (Chandola et al., 2014). Alternatively, the observation that players involved in m6A RNA methylation were located at splice sites suggests that the m6A RNA modification may modulate splicing (Meyer et al., 2012). More recent findings show a relation between the m6A modification and mRNA degradation, as m6A selectively binds human YTH domain family 2 (YTHDF2) proteins, which can bind and target mRNA to decay sites, such as processing bodies (P-bodies) (Wang et al., 2014a). Other members of the YTH domain family, YTHDF1 and YTHDF3 also selectively bind m6A modified RNA. Another study, however, indicated that m6A does not lead to RNA decay through the YTHDF2 pathway, but by interacting with miRNAs, and that the removal of m6A promotes human antigen R (HuR) binding, a protein that protects against RNA decay (Wang et al., 2014b). These studies suggest that the m6A mark may dynamically regulate mRNA lifetime.

An alternative pathway of RNA methylation involves the versatile regulatory ncRNAs snoRNAs, which can guide 2'-O-methylation and pseudo-uridylation of RNA transcripts, including mRNAs (Bachellerie et al., 2002). 2'-O-methylation is important for the functioning of certain rRNAs (Maxwell and Fournier, 1995), but also determines the guide strand and targeting specificity of siRNAs (Chen et al., 2008). Apart from their role in RNA modifications, snoRNAs can be further processed into snoRNA-derived small RNAs (sdRNAS), which are similar to miRNAs (Ender et al., 2008; Politz et al., 2009; Saraiya and Wang, 2008; Taft et al., 2009).

The pathway that most closely resembles DNA methylation involves DNMT2, which, despite its name, transfers methyl groups to cytosines in RNA (Jurkowski et al., 2008; Schaefer et al., 2009). Apart from tRNA, the exact substrates of DNMT2 still need to be identified. Nevertheless, DNMT2 has been implicated in brain development and retrotransposon silencing (Phalke et al., 2009; Rai et al., 2007). Other known RNA methylation modifications include Nl-methyladenosine (m1A) and Nl-methylguanine (mlG), which occur mainly in tRNAs and are thought to enhance tRNA stability, and mlG also decoding accuracy (Anderson et al., 2000; Bjork et al., 1989; Jackman et al., 2003; Saikia et al., 2010).

The only reported studies connecting RNA methylation to aging, as well as neurodegenerative disorders, were performed by Giordano et al. (2012) and Thomas et al. (2013), respectively. Bellizzi's team studied the methylated cytosine residues in two mitochondrial genes, 12S and 16S rRNA and they showed that the methylation levels of 12S rRNA are decreased with age in males. Thomas et al., while attempting to develop a novel method for detecting trace amounts of 7-mG in biological samples, observed differential methylation patters in murine HD models and significantly increased levels of 7-mG in postmortem human HD brain samples.

1.5.3. Mitochondrial epigenetics—Apart from the nuclear genome, human cells can harbor thousands of copies of the mitochondrial genome. Both the nuclear and

mitochondrial genome consist of DNA, but there are some striking differences (Byun and Baccarelli, 2014). The mitochondrial genome is only 16 kb long, contains 37 genes without introns and is much more prone to mutations than the nuclear genome. With respect to epigenetics, its regulation seems to be less complex, as mitochondrial DNA (mtDNA) is thought not to be wrapped around histones and not to contain CpG islands; the 435 CpG sites in the mitochondrial genome are almost evenly dispersed.

Over 40 years ago, methylated mtDNA was discovered in loaches, and it was shown there is DNMT activity in mitochondria that is independent from DNMT activity outside mitochondria (Kudriashova et al., 1976; Nass, 1973). Later, mtDNA methylation was also observed in humans (Shmookler Reis and Goldstein, 1983), and a mitochondrial DNMT, (mtDNMT1) was discovered (Shock et al., 2011). Of note, however, more recent studies cast doubt on the general notion that DNA methylation is the prime epigenetic mechanism at work in mitochondria. For instance, Hong et al. (2013) were unable to detect CpG methylation in the genome of human mitochondria, whereas Choi et al. (2011) report on the possible existence of mitochondrial histones, and Barrey et al. (2011) found miRNAs in mitochondria. Nevertheless, there are also many recent reports supporting the presence of methylated mtDNA and even hydroxymethylated mtDNA (Chestnut et al., 2011; Dzitoyeva et al., 2012; Iacobazzi et al., 2013; Manev et al., 2012), showing that it is not always located at CpG sites (Bellizzi et al., 2013; Sun et al., 2013), and that mtDNA methylation plays a role in mitochondrial gene regulation (Feng et al., 2012; Pirola et al., 2012). Clearly, these rapid developments within the field of mitochondrial epigenetics warrant further attention. In the recent study of Dzitoyeva et al. not only the hydroxymethylation of mtDNA was reported but they also demonstrated that solely the levels of hydroxymethylated mtDNA reduce with age in the frontal cortex of mice (Dzitoyeva et al., 2012). This decrease in 5-hmC is associated with an increase in complex I components (ND2, ND4, ND4L, ND5, ND6) in the same area. Furthermore, they observed region-specific differential expression of epigenetic players; the mRNA levels of TET2 and TET3, which are also responsible for the hydroxymethylation of mtDNA, are only increased in the cerebellum, whereas the mRNA levels of mtDNMT1 decrease solely in the frontal cortex.

1.6. Epigenetic processes are interdependent

The epigenetic processes of DNA (de)methylation, chromatin remodeling, and miRNAs do not act independently, but closely interact to form a complex, multilayered regulatory system that can dynamically fine-tune gene expression. DNA methylation stability in promoter regions, for instance, is enforced by methyl CpG binding protein (MeCP) 1, which also binds the nucleosome remodeling and histone deacetylase (NuRD) core and cyclin-dependent kinase 2 associated protein (CDK2AP) 1, forming a protein complex not only able to stabilize DNA methylation, but also to modify the histone code (Grewal and Jia, 2007; Zhang and Reinberg, 2001). MeCP1 is attracted to methylated DNA through its affinity for MBD2, which directly binds to DNA methylated at CpG sites. As such, DNA methylation and histone modifications act in concert to regulate gene expression, through interference with transcription factor binding and chromatin compaction (Klose and Bird, 2006). Another interesting interplay, between DNMT3a-dependent DNA methylation and Polycomb-group (PcG)-depen- dent H3K27me3 marks was discovered by Wu et al. (2010).

They showed that DNMT3a activity at non-promoter regions correlated with increased expression of neurogenic genes, by interfering with PcG binding and H3K27me3-mediated gene repression. In contrast, DNMT3a activity at the promoter regions inhibited gene expression. Alternatively, MBD1 can antagonize H3K4me3, leading to chromatin compaction. DNA methylation can thus in a bottom-up fashion induce changes on the chromatin level (Liu et al., 2010a). The other way around is also possible, as exemplified by Detich et al. (2003). They showed that increases in H3 acetylation can induce DNA demethylation, and thereby gene expression *in vitro.* Conversely, HDAC activity is thought to inhibit gene expression through the induction of DNA methylation (Sun et al., 2007). There are additional complex interactions between miRNAs and other components of the epigenetic machinery. Where some miRNAs regulate the expression of proteins involved in epigenetic regulation, the expression of various miRNAs themselves is also subject to factors such as DNA methylation and histone modifications (Saito and Jones, 2006). For example, miRNA 184 (miR-184), involved in the regulation of proliferation and differentiation of neural stem cells, is surrounded by CpG islands, attracting MBD1, which can suppress its expression as described above (Liu et al., 2010a).

2. Aging

Before delving into the aberrant epigenetic processes associated with neurodegeneration, it is important to consider the epigenetic changes associated with normal aging and related hallmarks, such as oxidative stress, as these can already be quite dramatic. Bocklandt et al. (2011) for instance, devised a method to determine the age of an individual based on the methylation of specific sites in the ectodysplasin-A receptor-associated death domain *(EDAR-ADD),* target of myb1 (chicken)-like 1 *(TOM1L1)* and neuronal pentraxin II *(NPTX2)* genes. At these sites a linear correlation between methylation and age was observed, allowing for a prediction of age with an average accuracy of 5.2 years. Horvath later devised an even more accurate method to determine the ‘DNAm age’, based on the methylation status of 353 CpGs (Horvath, 2013). The DNAm age of Horvath has a chronological age correlation of about 0.96 and an error of 3.6 years and is applicable in many different tissue and cell types. Note, however, that epigenetic processes are not the only players involved in aging. According to the “free radical theory of ageing”, oxidative stress is thought to play an integral role in the aging process (Beckman and Ames, 1998). Oxidative stress refers to the generation of reactive oxygen species (ROS), which are damaging to proteins, nucleic acids and lipids and are known to also affect epigenetic players (Cencioni et al., 2013). Furthermore, as aging is the prime riskfactor of most neurodegenerative diseases, it is possible that age-related processes including epigenetic alterations and oxidative stress, facilitate the development of these illnesses.

2.1. DNA (de)methylation in aging

Early research established that DNA methylation plays a crucial role during development. Later studies identified aging to be a pivotal modulator of the epigenome. The DNAm age of Horvath offers some interesting insights in this respect (Horvath, 2013). Of the 353 CpG sites used to predict the DNAm age, 193 got hypermethylated and 160 got hypomethylated with age, and most are associated with genes involved in cell death and survival, cell growth

and proliferation, organismal and tissue development, and cancer. Additionally, DNAm age shows a logarithmic relationship with chronological age until adulthood, and a linear relationship later in life, indicating that the epigenetic clock 'ticks' faster during growth and development. While highly accurate in most tissues, Horvath found that the DNAm age was consistently lower in tissues which may be renewed through the presence of stem cells, such as skeletal and heart muscle. It was, however, also observed that DNAm age does not reflect cellular senescence, as it highly correlated with chronological age in short and long lived cells, as well as immortal cells. As could be expected, embryonic stem cells appeared to have a DNAm age close to zero. Interestingly, the DNAm age of induced pluripotent stem cells did not differ significantly from that of embryonic stem cells. While the clock CpGs used for Horvath's DNAm age are enriched in cancer genes, there are some important differences between normally aging and cancerous tissue. In general, cancer tissue exhibits an accelerated DNAm age. Due to the heterogeneity of cancer types, however, general statements about its use should be interpreted with caution, as for example thyroid cancer progression negatively correlates with age acceleration. Additionally, Horvath observed that an increased DNAm age may promote genomic stability, as he found in several cancer types a negative relation between DNAm age acceleration and somatic mutations. He proposes that cancer triggers a hypothetical epigenetic maintenance system that promotes genetic stability, a process that is dependent on P53, as mutations in the TP53 gene are associated with a lower DNAm age acceleration. Interestingly, in glioblastoma multiforme TP53 mutations appear to be associated with an increased DNAm age acceleration. While it thus seems that in general cancer is associated with an increased DNAm age profile and aging with global DNA hypermethylation, neurodegenerative diseases such as AD and PD are associated with global DNA hypomethylation (Mastroeni et al., 2010; Obeid et al., 2009). Note, however, that the DNAm age itself has not yet been assessed in neurodegenerative tissue. Nevertheless, despite having age as a common risk factor, cancer and age-related neurodegenerative diseases seem to involve (at least partly) different epigenetic dysregulation or compensatory mechanisms.

Taking a more specific approach, Siegmund et al. (2007) investigated the DNA methylation status of 50 CpG islands associated with genes involved in brain growth and development in subjects of various ages, and they observed a robust and progressive increase in DNA methylation of multiple genes with age (Table 1). They also confirmed that a rise in DNA methylation typically results in a decline of corresponding mRNA levels. In addition, it was observed that DNMT3a was expressed across all ages, supporting the notion that DNA methylation can be dynamically altered throughout the lifespan. Interestingly, in relation to AD, the promoter region of the amyloid β precursor protein (APP) gene becomes hypomethylated with age (Tohgi et al., 1999). Additionally, binding sites for granulocyte chemotactic factor (GCF), known to repress CG-rich promoters and interaction sites for specificity factor (SP) 1, which enhances gene expression in the tau promoter, became hypo- and hypermethylated, respectively, with age, decreasing its overall expression. This finding suggests that certain age-related epigenetic changes might facilitate the development of AD. Although expressed across all ages, levels of DNMT3a and 5-mC actually increase with age in the dentate gyrus (DG), cornu ammonis (CA) 1–2, and CA3 regions of the mouse hippocampus (Chouliaras et al., 2011a, 2011b), which is in line with previous reports

(Lopatina et al., 2002). An interesting study by Oliveira et al. (2012) showed that hippocampal levels of DNMT3a2, an isoform of DNMT3a, decrease with age and that this decrease correlated with age-related cognitive decline in mice. Importantly, experimental restoration of DNMT3a2 levels alleviated this age-related cognitive impairment. Additionally, Hernandez et al. (2011) investigated 27,000 CpG sites in brain samples of varying ages and detected a general positive correlation between age and methylation levels. In contrast, it was found that expression levels of DNMT1 decrease with aging in human fetal lung fibroblasts, which would be in support of reports of global DNA hypomethylation with aging and cell senescence, including non-coding regions and repetitive sequences in the blood (Bollati et al., 2009; Lopatina et al., 2002; Pan et al., 2013). Mazin (Mazin, 2009) put forward an interesting hypothesis, proposing a DNA methylation-dependent aging process. This model is based on the observation that methylation of cytosines may induce C>T mutations, which is suggested to result in age-related genome disintegration, and eventually cell apoptosis, organism aging and death. Due to the age-related increase in 5-mC>T transitions, this model predicts an age-related depletion of 5-mC.

Note, however, that DNA methylation profiles are not only known to be different between different tissues, regions and cell types, but that these also seem to be differentially affected by the aging process (Brown et al., 2008; Ladd-Acosta et al., 2007; Thompson et al., 2010). An interesting study by Fraga et al. (2005), investigating DNA methylation and histone acetylation during the lifetime of monozygotic twins, illustrates that the epigenome not only changes with age, but also that differences in the epigenome might explain phenotypic disparity in genotypically identical individuals.

In addition to the age-related increases of DNMT3a and 5-mC levels, a significant age-related increase in 5-hmC levels was found in the DG, CA1–2, and CA3 regions of the mouse hippocampus (Chouliaras et al., 2012), which is in line with previous investigations into the spatial and temporal distribution of 5-hmC in the brain (Münzel et al., 2010; Song et al., 2011b). While some of the genes that exhibit age-related increases in 5-hmC levels are associated with age-related neurodegenerative diseases (Song et al., 2011b), further investigations are required to elucidate the functional consequences of these findings, taking into account the differential functions of the 5-mC and 5-hmC markers. Table 1 summarizes the age-related alterations regarding DNA (de)methylation.

2.2. Chromatin remodeling in aging

Apart from widespread changes in the neuronal DNA methyl-ation profile throughout the lifespan, the neuronal histone code also undergoes age-related alterations (Table 2). An example is the observation of lower levels of histone acetylation with aging *in vitro* (Ryan and Cristofalo, 1972), and an age-related progressive decline of H3 and H4 methylation (Thakur and Kanungo, 1981) and monoacetylated H4 levels, discovered in neurons from the rat cerebral cortex (Pina et al., 1988). Apart from detecting decreased levels of H3K9ac and increased levels of H3S10p (Kawakami et al., 2009), Nakamura et al. (2010) detected decreased acetylation of extranuclear proteins. In senescence-accelerated prone mouse 8 (SAMP8) brains it was shown that many histone marks are alterated with age (Wang et al., 2010a; Table 2). In rats, however, some of these markers were observed not to undergo

significant age-related changes (Sarg et al., 2002). These not always compatible findings between species illustrate the necessity of translating results regarding epigenetic changes to the human situation. Apart from changes in specific histone methylation marks, the HKMTs polycomb repressive complex member Bmi1 (PRC1) and polycomb repressive complex member enhancer of zeste homolog (EZH) 2 *(Drosophila)* (PRC2) have been observed to decrease with cell senescence, a common, but limited, *in vitro* model of aging, while the HKDM jumonji domain containing (JMJD) 3 increased (Agger et al., 2009; Jung et al., 2010). The balance between PcG and JMJD3 gene expression is in turn thought to be regulated by HDAC activity.

The finding that HDAC2 expression increases with age in the mouse hippocampus is in line with findings of decreased acetylation levels (Chouliaras et al., 2013b). Age-associated reduction in acetylated H4 is thought to reduce chromatin structural plasticity and may result in a decreased accessibility of the DNA for repairing enzymes and other regulatory factors (Perry and Chalkley, 1982; Pina et al., 1988). Other studies are more specific, pointing towards a role of deregulated H4K12ac in age-related memory impairment (Peleg et al., 2010), a negative influence of HDAC2 on synaptic plasticity and memory formation through the suppression of neuronal gene transcription (Fischer et al., 2007; Guan et al., 2009), and a dependence of histone acetylation on citrate levels (Wellen et al., 2009), which decline in the aging brain (Jiang et al., 2008). Furthermore, the KAT CREBBP is important for long-term memory formation and late-phase long-term potentiation in the hippocampus of mice (Alarcón et al., 2004; Korzus et al., 2004). Apart from histone acetylation, H3K4me3 (Gupta et al., 2010) and H3 phosphorylation (Chwang et al., 2006) are also involved in memory formation. The SIRT HDACs have also been implicated in aging. In contrast to HDAC2, SIRT1 levels were found to drop with age, a change not limited to the brain (Quintas et al., 2012; Sommer et al., 2006) and also observed in senescent cells (Sasaki et al., 2006). Reduced levels of SIRT1 have been associated with increased levels of H4K16ac *in vitro* (Pruitt et al., 2006). SIRT1 can in addition directly deacetylate the HKMT suppressor of variegation 3–9 homologue (SUV39H) 1, which increases the activityofSUV39H1 (Vaqueroetal., 2007).This HKMT is responsible for H3K9me3, which is important for the formation of facultative heterochromatin. Despite the association between senescence and decreased H3K9me3 levels, H3K9me3 is thought to accumulate in senescence-associated heterochromatin foci (SAHF), a form of facultative heterochromatin, which are thought to induce senescence through the repression of the pro-proliferation E2F transcription factor family (Narita et al., 2003; Ye et al., 2007). Alternatively, in *C. elegans,* it has been observed that sir-2.1, the ortholog of mammalian SIRTI, can extend lifespan through its product nicotinamide (Schmeisser et al., 2013). Nicotinamide can be methylated by nicotinamide-*N*-methyltrans-ferase-1, producing 1-methylnicotinamide, and 1-methylnicotina-mide in turn is processed by aldehyde oxidase gastrulation defective 3 (GAD-3) to generate hydrogen peroxide. This hydrogen peroxide is thought to play a mitohormetic role, inducing longevity (Ristow and Zarse, 2010). Reinstating SIRT levels, for instance through caloric restriction, has in addition been reported to increase lifespan in yeast, invertebrates, and vertebrates (Guarente and Picard, 2005; Rutten et al., 2010), and has been argued to facilitate healthy aging in humans, thereby slowing the development of age-related neurodegenerative diseases such as AD (Baur et al., 2006; Haigis and Sinclair, 2010).

2.3. Non-coding RNAs in aging

One of the first ncRNAs reported to affect the aging process was miRNA lin-4, whose expression was observed to modulate lifespan in *C. elegans* (Lee et al., 1993). In neurons of *C. elegans,* miR-71 promotes longevity through the dauer 16/forkhead box O (DAF-16/FOXO) pathway, increasing resistance towards heat shock and oxidative stress (Boulias and Horvitz, 2012). Other studies found increased levels of some miRNAs with age, but did not detect any significantly downregulated miRNAs in mice (Maes et al., 2008; Table 3). In human blood mononuclear cells, however, various miRNAs were significantly decreased in older participants (Noren Hooten et al., 2010; Table 3). Altered expression of various miRNAs, has been linked to age-related cardiovascular problems (Boon et al., 2011, 2013; Menghini et al., 2009; Olivieri et al., 2013; Vasa- Nicotera et al., 2011; Table 3). Moreover, various members of the miR-17–92 cluster were reported to be downregulated in humans (Hackl et al., 2010; Table 3). Another study in human endothelial cells detected additional miRNAs affected by age (Vasa-Nicotera et al., 2011; Table 3). Increased ROS levels in human endothelial cells were observed to induce miR-200c and concomitant initiation of apoptosis and senescence (Magenta et al., 2011). Several studies have recently shown the importance of certain miRNAs specific to the aging brain and their roles in the development of neurodegenerative diseases (Hebert and De Strooper, 2009; Somel et al., 2010). In the cortex and cerebellum of humans, chimpanzees, and macaque monkeys, miR-144 was observed to be upregulated (Persengiev et al., 2011). This miRNA targets the ataxin-1 gene, which is critically involved in the development of spinocerebellar ataxia type 1, and its age-related dysregulation could thus facilitate the development of this disease. Li et al. (2011) forged a link between aberrant miRNA expression and age-related declines in mitochondrial respiration rates. They found 70 miRNAs to be upregulated in the aging mouse brain, 27 of which were implicated in the downregulation of mitochondrial complexes III, IV and F_0F_1-ATPase that are all pivotal to the oxidative phosphorylation process. Interestingly, in the SAMP8, a mouse model of accelerated aging, miR-16 was found to be dysregulated. This miRNA modulates AD-related APP protein expression and with age APP levels were shown to drastically increase in the hippocampus of SAMP8 mice, leading to the suggestion that this model might serve as a model for AD (Liu et al., 2012b). Table 3 provides an overview of some of the ncRNAs that undergo age-related changes.

3. Neurodegeneration

Neurodegenerative diseases typically involve a progressive loss of neuronal integrity and function, followed by neuronal death. Depending on where in the brain the loss of integrity and neuronal loss occur, various functional disabilities may arise and which gradually worsen as the neurodegeneration spreads. The underlying cause and localization of the neurodegenerative processes, however, often vary between different neurodegenerative disorders. Some of the most common include AD, PD and HD, but also amyotrophic lateral sclerosis and prion diseases are well studied forms of neurodegeneration (Coppede et al., 2006). Multiple sclerosis is more recently also being investigated as a neurodegenerative disease (Trapp and Nave, 2008). The exact etiology of most neurodegenerative diseases is far from clear, while in some cases, such as for HD (Bates et al., 2006), it is clear that the origin is largely genetic, for others, including sporadic AD and PD, the link between

genetics and disease development is much more complex, possibly involving gene-gene and gene-environment interactions (Chouliaras et al., 2010a,b; Migliore and Coppede, 2009). Numerous studies have, where genetics did not give simple answers, investigated other possible instigators, of which epigenetic mechanisms seem to be most promising. Although it remains to be elucidated whether dysfunctional epigenetic machinery plays a causal role, it has been critically implicated in various neurodegenerative processes. Additionally, environmental factors enjoy much attention as either direct modulators of disease development, or indirect via genetic or epigenetic pathways (Babenko et al., 2012; Chouliaras et al., 2010a,b; Jaenisch and Bird, 2003).

3.1. Alzheimer's disease

The most ubiquitous neurodegenerative disorder and form of dementia is AD, with an estimated worldwide prevalence of over 35 million cases (Selkoe, 2012). Mainly characterized by cognitive decline, late-stage AD concomitantly involves progressive motor aberrancies, mood instabilities and other behavioral and physical abnormalities (Bediou et al., 2009; Budson and Solomon, 2012). Although most of these symptoms arise as a result of cortical degeneration, others are due to degeneration of subcortical or autonomic function-related areas. It should be noted, however, that AD pathology does not equally affect the whole brain, as certain brain areas and cell types are specifically vulnerable to AD pathology (Hardy, 2006). Among the areas mainly affected by degeneration in AD are the frontal cortex, temporal and parietal lobes, including the hippocampus and entorhinal cortex (EC), and the cingulate gyrus, whereas the cerebellum is largely spared (Wenk, 2003). Interestingly, there is some evidence indicating that, while the cerebellum is mostly spared, the Purkinje cells are specifically targeted by AD pathology (Fukutani et al., 1996). Despite numerous pre-clinical and clinical trials for AD treatments, only basic symptom management therapies are currently Food and Drug Administration-approved (some acetylcholinesterase inhibitors and an *N*-methyl-D-aspartic acid [NMDA] receptor antagonist), which cannot halt, or slow down the progressive neurodegeneration and the associated decline of memory, cognitive and executive functions. Apart from being a scourge among the elderly and the relatives of patients, dementia also incurs a tremendous socioeconomic burden; amounting to an estimated $200 billion in 2013 in the United States of America alone (Alzheimer's Association, 2013).

AD is a complex, multifaceted disorder, involving dysregulated homeostasis on various fronts, including energy metabolism, inflammation, and cell cycle control (Mastroeni et al., 2010), likely resulting from a complex interplay between genetic, epigenetic and environmental factors (Coppede et al., 2006; Mastroeni et al., 2011). Despite much research into the pathophysiology of AD, including amyloid β (Aβ) and phosphorylated tau proteins (Tiraboschi et al., 2004), its exact etiology remains to be elucidated (Mill, 2011). Aβ, which exists in monomeric, oligomeric, and aggregated forms (senile plaques), is the product of APP cleavage by the β- and γ-secretases (Citron et al., 1995; Shoji et al., 1992). APP cleavage by γ-secretases can result in either Aβ40 or Aβ42, of which Aβ42 is thought to be especially neurotoxic. APP can also be cleaved by α-secretases such as a disintegrin and metalloproteases domain 10 (ADAM10) and tumor necrosis factor alpha (TNF-α) converting enzyme (TACE), but that this cleavage does not result in Aβ, but generates APPs-

α, which is thought to be neuroprotective (Groen, 2010). One of the most prominent theories of AD pathology is the amyloid hypothesis, which states that Aβ is responsible for initiating the pathogenic pathway that leads to neurodegeneration and dementia in AD. Generally, this theory proposes that neurodegeneration is the result of impaired Aβ homeostasis, which leads to aberrant calcium homeostasis, triggering - and sensitizing cells to -damaging processes, including excitotoxicity and the formation of neurofibrillary tangles (NFTs) (Hardy and Higgins, 1992; Mattson etal., 1992; Selkoe, 1993). This hypothesis is applicable especially to early onset familial types of AD (fAD), which have a much more evident genetic component than the far more common late onset sporadic AD (sAD) (Tanzi, 2012). Mutations in the APP gene and the presenilin (PS) genes PS1 and PS2, have been observed in fAD cases (Czechetal.,2000; DeStrooperetal., 1998; Goateetal., 1991; Hardy and Higgins, 1992; Migliore and Coppede, 2009; Sherrington et al., 1995; Tanzi et al., 1996). PS1 and PS2 are γ-secretase-associated proteins involved in the generation of Aβ from APP, and PS mutations are able to bias this process towards Aβ42 production, the 42 amino acid-long Ab isoform that is more prone to aggregate then the shorter Aβ40 isoform, by either increasing Aβ42 production, or lowering Aβ40 production (Lemere et al., 1996). This relation has been corroborated by the detection of elevated Aβ42 levels in the blood and brains of fAD cases with PS mutations (Czech et al., 2000). Their major impact on disease development has led to the widespread use of mutant forms of the APP and PS genes to generate animal models of AD (see (Brasnjevic et al., 2013)). Although some mutations in the PS and APP genes seem to play a large role in disease development in fAD cases, most of the sAD susceptibility genes, including the risk factor with the highest population-attributable risk, the ε4 allele of the apolipoprotein E (*APOE*) gene and those identified through genome-wide association studies (ATP-binding cassette, sub-family A [ABC1], member 7 [ABCA7], clusterin [CLU], complement component receptor 1 [CR1], cluster of differentiation 33 [*CD33*], phosphatidylinositol-binding clathrin assembly protein [*PICALM*], membrane-spanning 4-domains, subfamily A, member 6A [*MS4A6A*], membrane-spanning 4-domains, subfamily A, member 4E [*MS4A4E*], cluster of differentiation 2-associated protein [*CD2AP*]) have a relatively minor influence on AD progression when altered (Cacabelos, 2005, 2007; Slooter et al., 1998). Moreover, despite the robust association with sAD of some of these common sequence variants, it remains largely unknown how they influence the development and course of sAD (Harold et al., 2009; Hollingworth et al., 2011; Naj et al., 2011; Sleegers et al., 2010). The same applies to the rare mutations recently discovered in the triggering receptor expressed on myeloid cells 2 (*TREM2*) gene, although they confer a much larger increase in risk to develop sAD than the common sequence variants (Guerreiro et al., 2013; Jonsson et al., 2013; Neumann and Daly, 2013). Although these genetic risk factors may be informative in screening for populations at risk to develop sAD, it has not yet been discovered how they exactly affect AD development (Slooter et al., 1998). Most is known about the involvement of the major risk factor APOEε4. For instance, increased levels of brain APOEε4 mRNA in AD cases, compared to controls with the same allele, were detected (Yamagata et al., 2001). Interestingly, the *APOE*ε3 allele is thought to protect against Ab neurotoxicity (Caesar and Gandy, 2012). Additionally, a study with a transgenic mouse model of AD expressing human APOE isoforms indicated that different *APOE* alleles might influence clearing soluble Ab from the brain (Castellano et al., 2011). This is in line with evidence indicating that sAD is characterized by an inability to clear Aβ from

the brain and not an increase Aβ production (Mawuenyega et al., 2010). A similar effect is suggested for the *CLU* gene, another important risk gene associated with sAD, implicating it in the aggregation and clearance of Ab, thereby mainly influencing age of onset and progression (Yu and Tan, 2012). Apart from the gene, CLU levels were shown to be elevated in the cerebrospinal fluid and brains of AD patients and CLU plasma levels were associated with several AD hallmarks (Schrijvers et al., 2011; Thambisetty et al., 2010).

Besides an abnormal Aβ homeostasis, dysfunctional tau has also been pointed out as a pivotal player in AD pathology. Tau, a microtubule-associated protein that promotes microtubule assembly (Weingarten et al., 1975), becomes hyperphosphorylated in AD. This causes it to dissociate from microtubules and aggregate, which induces cytoskeletal disorganization, neuronal dysfunction and cell death (Lee et al., 2001; Lovestone and Reynolds, 1997). This pathological process of aggregation is thought to play a part in the neurodegeneration and memory deficits as seen in AD (Alonso et al., 1997; Iqbal et al., 2009). Interestingly, while a similar process occurs in other tauopathies, diseases involving pathological tau aggregation, these generally involve mutations of the tau encoding microtubule-associated protein tau (*MAPT*) gene, whereas such mutations are usually not found in AD cases (Klafki et al., 2006; Lee et al., 2001). Mitochondrial abnormalities have also been investigated as contributors to AD pathogenesis, mainly in relation to energy imbalances and increased reactive oxygen species (Khairallah and Kassem, 2011).

Aβ and tau have long been the direct focus of treatment strategies, involving potential aggregation inhibitors, immunotherapy, and enzyme modulators (Hardy and Selkoe, 2002). More recently, however, while the epigenetic involvement in neurodegeneration is being explored, the epigenetic machinery has become an attractive target for novel intervention strategies. That minor aberrancies in the epigenetic machinery can have widespread consequences on gene expression, combined with the sporadic and complex nature of AD, has led to a recent interest in the role of epigenetic factors in the etiology of AD (Lahiri et al., 2009; Mastroeni et al., 2011).

3.2. Parkinson's disease

PD is the second most common progressive neurodegenerative disorder, affecting the dopaminergic neurons of the midbrain substantia nigra. Because the dopaminergic projections from the substantia nigra are crucially involved in the initiation of motor events, PD is mainly known for symptoms such as tremor, rigidity, bradykinesia, and gait disturbances (Jankovic, 2008). These motor disturbances are, however, complemented by psychiatric symptoms, autonomic impairments, sleep disturbances, and cognitive dysfunctions, including dementia, that are intrinsic to the disease pathology and may even precede the motor symptoms (Aarsland et al., 1999; Naimark et al., 1996; Riedel et al., 2008). These nonmotor symptoms are related to imbalances in other neurotransmitter systems, including serotonergic, noradrenergic, and cholinergic malfunctions (Francis and Perry, 2007). Furthermore, cognitive impairments in PD are generally accompanied by the occurrence of Lewy bodies in brain areas including the midbrain and cortex (van de Berg et al., 2012). Lewy bodies are cytoplasmic protein aggregates, consisting mainly of α-synuclein, parkin, and ubiquitin (Jellinger, 2009). Exactly what part Lewy bodies play in PD

pathophysiology warrants additional investigation. As with AD, PD exists as a familial (fPD) and a sporadic (sPD) variant, of which the former is again much rarer. Synuclein alpha (*SNCA*), the gene encoding the presynaptic protein α-synuclein, is one of the cardinal risk genes for PD; increased expression of only this gene (through point mutations and multiplications) can already induce familial Parkinsonian syndromes (Singleton et al., 2003; Thomas and Beal, 2011). In addition to *SNCA, MAPT,* Parkinson disease 16 (*PARK16*) and leucine-rich repeat kinase 2 (*LRRK2*) are also indicated as risk genes, with *SNCA* and *MAPT* SNPs conferring the highest risk (Edwards et al., 2010; Simon-Sanchez et al., 2009). Although genetic predisposition remains a high risk factor for sPD, age and environmental variations are also thought to be highly influential (Ammal Kaidery et al., 2013; Houlden and Singleton, 2012; Veldman et al., 1998), with factors such as a rural environment increasing the risk to develop PD, while smoking and the consumption of coffee decrease the risk (de Lau and Breteler, 2006). Additionally, the development of sPD has often been linked with exposure to environmental toxins, of which 1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has the most prominent link to developing PD, leading to its widespread use to induce PD-like symptoms in animal models (Fukuda, 2001; Kopin, 1987). A causal role in the development of PD of most other toxins, however, remains a point of controversy (Franco et al., 2010). Nevertheless, evidence is accumulating pointing towards a cardinal role of the epigenetic machinery in mediating the effect of chronic environmental exposures on alterations in gene expression that can lead to the development of late-onset neurodegenerative diseases (Kanthasamy et al., 2012). At least for some genes a mechanism of DNA methylation-induced allelic skewing is proposed as the underlying mechanism of how an epigenetic process can modulate the interaction between genotype and environment. DNA methylation-induced allelic skewing is the process by which the paternal and maternal alleles are differentially methylated, leading to the preferential expression of either one.

3.3. Huntington's disease

In contrast to AD and PD, HD is primarily a genetic, autosomal dominant neurologic disorder, with the sporadic variant being rarer. When symptoms start to occur progress can be fast and will result in death, with no treatment options currently available to change this devastating process (Ryu et al., 2005). The most characteristic symptom of HD is chorea, but other prominent symptoms include cognitive deterioration and psychiatric disturbances. It is known that HD pathology is ignited by an expansion of a cytosine-adenine-guanine (CAG) repeat section, coding for glutamine, in the coding region of the Huntingtin (*HTT*) gene on chromosome 4p16.3 (MacDonald et al., 1993). Note that the familial and sporadic variants thus have the same genetic origin. A CAG repeat number of 36 units leads to the development of HD and sporadic cases are caused by *de novo* mutations that increase the repeat number to above the critical number, with high repeat numbers leading to a younger age of onset (Kremer et al., 1994; Myers et al., 1993). The primary risk factor for developing HD is thus having family members with HD, or members with a high CAG repeat number. The expansion results in a dysfunctional HTT protein, which has been shown to disrupt transcription via multiple pathways (Okazawa, 2003; Sugars and Rubinsztein, 2003). It remains, however, unclear exactly how the production of mutant HTT leads to the lethal neurodegeneration associated with HD (Thomas, 2006). Curiously, HD neurodegeneration is very region and cell-type specific, mainly affecting the medium-sized spiny neurons of the

neostriatal nuclei, caudate nucleus and putamen, explaining the grave motor symptoms (Ferrante et al., 1985,1986,1987,1991; Graveland etal., 1985; Kowall etal., 1987; Lee et al., 2013a; Vonsattel et al., 1985). Despite the specificity of neurodegeneration in HD, the HTT protein can be found in neurons throughout the whole brain (Ross, 1997). Wildtype HTT is mainly situated in the cytoplasm, its exact function, however, remains elusive, with proposed roles in intracellular transport, autophagy, transcription, mitochondrial functioning and signal transduction (Cattaneo, 2003; Mangiarini et al., 1996; Nucifora et al., 2001; Ross and Poirier, 2004). Nevertheless, HTT is critical for survival, as complete deletion of the *HTT* gene results on nonviable offspring (Zhang et al., 2003). Mutant HTT was shown to impair fast axonal transport, destabilize microtubules, and through its interactions with a multitude of proteins it disrupts important cellular pathways leading to hampered proteolysis, mitochondrial dysfunction, oxidative damage, inflammatory reactions, excitotoxicity and induction of apoptosis (Beal and Ferrante, 2004; Szebenyi et al., 2003; Trushina et al., 2004). Additionally, evidence indicates that mutant HTT has a widespread impact on gene expression, through interactions with specific transcription factors (Li et al., 2002), interference with the core transcriptional machinery and posttranscriptional modifications of histones, skewing the chromatin towards a more condensed state (Thomas et al., 2008).

4. DNA (de)methylation in neurodegeneration

4.1. DNA (de)methylation in Alzheimer's disease

Early epigenetic investigations related to AD by West et al. (1995) focused on DNA methylation, reporting an AD-specific hypomethylation of the APP gene promoter region in a single patient. This was confirmed by another study and linked to elevated Ab levels (Tohgi et al., 1999). A later study with a larger sample was, however, unable to replicate this finding, nor find any other significant AD-related abnormalities in *MAPT, APP* and *PS1* methylation (Barrachina and Ferrer, 2009). Others also did not find significant AD-related methylation changes in the APP promoter Barrachina et al. did report the presence of low and high methylated CpG sites in and close to the *APP* promoter region, as did Fuso et al. for the APP, PS and BASE genes (Fuso et al., 2005). Conversely, Brohede et al. (2010) observed no methylation at the investigated CpG site of the APP gene in a small sample of fAD patients, in all brain areas investigated, including the frontal cortex, parietal cortex, temporal cortex and cerebellum, concluding that *APP* is not transcriptionally regulated by methylation. All in all, these studies provide inconclusive evidence of whether *APP* methylation is involved in AD, raising the need for studies clearly separating between sAD and fAD, investigating multiple CpG sites and ideally also differentiate between cell types instead of using homogenates of whole regions. Wang et al. (2008b) observed a high interindividual variance in promoter methylation of the *PS1, APOE, MTHFR,* and *DNMT1* genes, and a particularly marked epigenetic drift in AD cases.

A finding relevant not only to global DNA methylation, but also for many other biochemical pathways, is a severe AD-associated reduction of SAM (up to 85%) and its demethylated metabolite SAH (up to 79%) in several neocortical areas, the hippocampus and putamen (Morrison et al., 1996). Additionally, cerebrospinal fluid levels of folate and SAM, and levels of SAM in the frontal cortex, occipital cortex, temporal cortex, putamen and

hippocampus, were found to be decreased in AD cases (Bottiglieri etal., 1990; Morrison et al., 1996; Serot et al., 2001), concomitant with an increase in brain SAH levels (Kennedy et al., 2004). Accordingly, lower serum folate levels and increased plasma Hcy levels were observed in sAD patients versus controls (Coppede et al., 2012). Cell culture work has indicated that increased Hcy levels can be linked to enhanced tau hyperphosphorylation and subsequent NFT formation (Sontag et al., 2007), which may be the result of the inhibitory effect of Hcy on methyltransferases, thereby preventing the methylation of protein phosphatase 2A (PP2A), which is required for its proper activation. PP2A can dephosphorylate phosphorylated tau and its decreased activity thus promotes the hyperphosphorylation of tau. In both mouse Neuro-2a (N2a) cells expressing human mutant APP and transgenic mice expressing human mutant PS1 and APP, PP2A was also found to be hypomethylated, resulting in elevated tau phosphorylation (Zhou et al., 2008). Furthermore, antagonizing folate with methotrexate in rat primary neuron cultures heightened phosphorylated tau, APP and BACE levels (Yoon et al., 2007). Interestingly, hypomethylated PP2A, but not normally methylated PP2A colocalized with hyperphosphorylated tau in the hippocampus of rats and AD cases (Zhang et al., 2008).

The apparent importance of folate and vitamins B_{12} and B_6 in maintaining SAM levels has stimulated investigations into the potentially protective effects of supplementing these vitamins to counteract cognitive decline and possibly the onset of dementia (Cacciapuoti, 2013). *In vitro* folate deprivation was able to induce global DNA hypomethylation, leading to an increased expression of BACE and PS1, but unaltered TACE, ADAM10 and APP expression (Fuso et al., 2005). SAM supplementation successfully restored the folate deficiency-induced abnormalities. In a follow-up study, mutant human APP transgenic mice deprived of folate, vitamin B_{12} and vitamin B_6 (Fuso et al., 2008), showed increased SAH to SAM ratios and increased PS1 and BACE levels, thus corroborating the *in vitro* findings. These increases in PS1 and BACE expression were paired with elevated Aβ aggregation, early appearance of intraneuronal Ab and mild spatial learning and memory impairments. In a similar study, it was later shown that SAM supplementation was also able to remedy the vitamin B deficiency-induced detrimental effects in mice, resulting in a reduction in PS1 and BACE1 expression, amyloid production, tau phosphorylation, and subsequent enhanced spatial memory (Fuso et al., 2012). Vitamin B deficiency induced hypomethylation of CpG sites near the PS1 promoter, indicating that PS1 expression is indeed regulated by methylation (Fuso et al., 2011). Another group also found benefical effects of dietary SAM supplementation in the 3xTg-AD mouse model (Lee et al., 2012). Additionally, a vitamin/nutriceutical formulation including folate and vitamin B was shown to delay the progression of dementia in a small sample of early stage (Chan et al., 2008), and moderate to late stage AD (Remington et al., 2009).

Observations of an overall reduction in DNA methylation in AD patients are in line with these findings and further stress the importance of DNA methylation in AD (Mastroeni et al., 2010, 2011; Wang et al., 2008b). Interestingly, despite this AD-associated global DNA hypomethylation, specific loci of the *MTHFR* gene, which is crucial for SAM synthesis, were found to be hypermethy-lated, in both postmortem prefrontal cortex and peripheral lymphocyte samples of AD patients (Wang et al., 2008b).

Studies focusing on the hippocampus, one of the brain areas early affected by AD and aging, have observed that levels of 5-mC (Chouliaras et al., 2011b) and DNMT3a (Chouliaras et al., 2011a) increase with age in mice, whereas these levels are significantly decreased in the hippocampus of AD patients (Chouliaras et al., 2013a).

Siegmund et al. (2007) found an increase in the methylation of sorbin and v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog homology 3 domain containing 3 (*SORBS3*) and a decrease in the methylation of S100 calcium-binding protein A2 (*S100A2*) in AD subjects, compared to controls of 60 years and older. Interestingly, although a progressive increase in *SORBS3* and decrease in *S100A2* methylation is normal with aging, this process is accelerated in AD. *SORBS3* encodes a cell adhesion molecule and the product of *S100A2* is observed in *corpora amylacea,* which are a hallmark frequently found in human brain aging and, in greater numbers, of neurodegenerative diseases (Hoyaux et al., 2000). A decline in *SORBS3* expression might have a hand in the synaptic abnormalities associated with AD (Urdinguio et al., 2009). Intriguingly, recent epigenome-wide association studies identified another gene that encodes an adaptor protein and its methylation signature is highly associated with AD pathology. More specifically, a differential cortex-specific hypermethylated region of *ankyrin 1(ANK1*) was found to be associated with the early stages as well as the progression of AD neuropathology (De Jager et al., 2014; Lunnon et al., 2014).

Remarkably, Aβ has also been implicated as a trigger of epigenetic changes. Chen et al. (2009) found that Aβ induces global DNA hypomethylation, while promoting hypermethylation of *NEP,* a gene that encodes neprilysin. Neprilysin is one of the enzymes involved in Aβ degradation and its expression is known to decrease with aging and AD. This finding indicates that Aβ is able to induce a vicious cycle that depends on epigenetic processes and favors Aβ deposition. Other regulatory players may further enforce this cycle, for instance TNF-α and cysteine-dependent aspartate-directed protease (caspase)-3 were found to increase Aβ production, and they are increasingly expressed in response to hypomethylation (Muerkoster et al., 2008; Sommer et al., 2009; Wilson, 2008; Xiong et al., 2008).

Tau gene expression is also subject to complex epigenetic regulation, involving differentially methylated binding sites for transcription factors. It was found that with age, the activator-binding site for transcription factor SP1 became hypermethylated in the tau gene promoter region, whereas the repressor-binding site for GCF was hypomethylated in the human cerebral cortex (Tohgi et al., 1999), which might be relevant to AD and other age-related tauopathies. This points toward an age-related decrease in tau expression, which has indeed been detected in the human frontal cortex and hippocampus, but this did not correlated with NFT pathology (Mukaetova-Ladinska et al., 1996).

The *APOE* gene promoter has a low CpG count and generally exhibits low levels of DNA methylation. There is, however, a CpG island located at the 3’ end that is usually heavily methylated, and which contains the sequence of the *APOE* ε4-haplotype, the prime genetic risk factor for sAD (Wang et al., 2008b). It has been suggested that the £4 allele might disturb the epigenetic regulation of the *APOE* gene, as this allele is associated with a C>T

transition, preventing this site from being methylated (Wang et al., 2008b). The *CLU* gene is more clearly regulated by epigenetic mechanisms, as its promoter regions contain a CpG island, the demethylation of which after 5- aza-2'-deoxycytidine (decitabine; DAC) treatment was shown to enhance CLU expression in cancer cell lines (Rauhala et al., 2008). A similar demethylating treatment in addition to the administration of HDAC inhibitors (HDACIs) has also been observed to increase CLU expression and secretion in human neurons and retinal pigment epithelial cells (Nuutinen et al., 2005; Suuronen et al., 2007).

There is increasing evidence of disturbed cell-cycle control and subsequent induction of apoptosis in degenerating AD neurons and, although not directly investigated, many of the proteins involved in these processes that have been shown to be upregulated in these neurons and are also known to be regulated through DNA methylation (Jee et al., 2005; Moreira et al., 2009; Muerkoster et al., 2008; Robertson and Jones, 1998; Tschöp and Engeland, 2007). In addition to genes involved in cell-cycle control, the promoter regions of cyclooxygenase-2 (COX-2) and nuclear transcription factor kappa B (NF-κB) were found to be hypo-methylated, while the promoter regions of brain-derived neuro-trophic factor (BDNF) and cAMP response element-binding protein (CREB) were hypermethylated in the frontal cortex of AD patients (Rao et al., 2012).

Bollati et al. (2011) specifically investigated blood for the methylation status of repetitive elements, including *Arthrobacter luteus* elements (Alu), long interspersed element 1 (LINE-1) and satellite-α (SAT-α), which comprise a large portion of the human genome and are known to contain large numbers of CpG sites. Interestingly, they found that LINE-1 methylation was increased in AD patients and that within the AD group enhanced LINE-1 methylation was associated with a better cognitive performance.

Although not as well studied in relation to AD as DNA methylation, the DNA demethylation process is receiving increased attention. As for 5-mC, 5-hmC levels were also found to be greatly decreased in the hippocampus of AD patients (Chouliaras et al., 2013a). This is in line with previous findings indicating a global DNA hypomethylation in EC NFT-bearing neurons of AD patients (Mastroeni et al., 2010). Additionally, it was found that global 5-hmC levels were decreased in the EC and cerebellum of AD subjects, while no significant disease-related changes in 5-mC, 5-fC and 5-caC were detected (Condliffe et al., 2014). In contrast, levels of 5-mC and 5-hmC were immunohistochemically found to be increased in the mid frontal gyrus and mid temporal gyrus of AD patients and positively correlated with Aβ, NFT, and ubiquitin load (Coppieters et al., 2014). This study included a cell-type specific analysis and found that 5-hmC and 5-mC were mainly present in Neuronal Nuclei (NeuN; a neuronal marker)-positive cells, with glial fibrillary acidic protein (GFAP; an astrocyte marker)-positive cells and ionized calcium-binding adapter molecule 1 (1BA1; a microglial/ macrophage maker)-positive cells only presenting with weak or no immunoreactivity. This latter study is in line with findings from Bradley-Whitman and Lovell (Bradley-Whitman and Lovell, 2013), who observed increased levels of TET1, 5-mC and 5-hmC in the hippocampus and parahippocampal gyrus in subjects with preclinical and late-stage AD. In addition, it was found that 5-fC and 5-caC levels were significantly decreased. Another study detected global hypermethylation in the frontal cortex of AD patients (Rao et al., 2012). Whether global 5-mC and 5-hmC levels are thus decreased or

increased in AD remains to be conclusively determined. Possible factors contributing to the discordant findings have been suggested and include differences in the brain regions studied, tissue processing, and detection methods and protocols (Coppieters et al., 2014). An additional factor that could influence readings is whether a cell type-specific analysis is conducted, or different cell types are grouped together. Considering the uncertainty regarding global 5-mC and 5-hmC changes in relation to AD it might be a bit too early to speculate about the consequences of such changes. Nevertheless, Coppieters et al. (2014), who detected a global DNA hypermethylation and hyperhydroxymethy-lation argue that these changes may facilitate cell death, as the methylation of cytosines is thought to enhance the mutation rate of these cytosines and this increased mutation rate could facilitate the loss of neurons in AD. There are, however, also studies indicating that DNA hypomethylation leads to neuronal degeneration (Fan et al., 2001; Hutnick et al., 2009), suggesting that no simple conclusions can be made from observations of globally increased or decreased DNA methylation levels.

Münzel et al. (2010) observed an age-related increase in 5-hmC levels, which seemed to be especially prominent in genes associated with neurodegeneration. Another finding indicating DNA demethylation to play a role in the development of AD is a single nucleotide polymorphism (SNP) in the *TET1* gene that was associated with sAD (Morgan et al., 2008). See Table 4 for an overview of the aberrant DNA (de)methylation in AD.

4.2. DNA (de)methylation in Parkinson's disease

Obeid et al. (2009) explored the relation between the methylation potential, represented by the SAM/SAH ratio, and cognitive performance in PD patients, and found that a higher methylation potential correlated with better cognitive capabilities. In addition, it was found that α-synuclein can associate with DNMT1, sequestering it in the cytoplasm, resulting in global DNA hypomethylation. This property of α-synuclein was not only found in PD cases, but also in dementia with Lewy bodies and a transgenic mouse model expressing human a-synuclein (Desplats et al., 2011). Because α-synuclein can also be observed in AD (Trojanowski et al., 1998), this mechanism might also contribute to the global DNA hypomethylation observed there. *In vitro* overexpression of DNMT1, as well as in transgenic mice, was able to normalize the nuclear localization of DNMT1.Jowaed et al. (2010) specifically investigated methylation of human *SNCA* and showed that expression of this gene is regulated through methylation of the first intron. Interestingly, a negative correlation between *SNCA* intron 1 methylation and *SNCA* expression has also been identified, and that *SNCA* methylation is decreased in the substantia nigra, putamen, and cortex of sPD patients (Jowaed et al., 2010; Matsumoto et al., 2010). Another study, investigating the high-resolution methylome of Lewy body disease cases, including PD, found, however, no overall differences in *SNCA* intron 1 methylation (de Boni et al., 2011). Although this study reported some differences at the single CpG level, it signifies that the extent of erroneous DNA methylation in PD warrants additional research efforts. Apart from *SNCA,* however, additional genes, including *PARK16*, glycoprotein (transmembrane) nmb (*GPNMB*) and syntaxin 1B (*STX1B*) have also reported to be differentially methylated in PD (Plagnol et al., 2011). A very recent EWAS in blood from PD patients, using a discovery and replication cohort, identified additional differentially methylated genes, with the most reliable

differentially methylated CpGs being located in the Fanconi anemia, complementation group C (*FANCC*) and tankyrase, telomeric repeat binding factor 1 (TRF1)-interacting ankyrin-related ADP-ribose polymerase 2 *(TNKS2)* genes (Moore et al., 2014). How this aberrant DNA methylation exactly affects gene expression and ultimately influences PD pathology remains to be unveiled.

Interestingly, although a mutation in *parkin* has been associated with a juvenile form of PD, deviant methylation patterns in the promoter of this gene have been observed in myelogenous leukemia and acute lymphoblastic leukemia, but not PD (Agirre et al., 2006; Cai et al., 2011). Similar observations were made for deubiquitinating enzyme ubiquitin carboxy-terminal hydrolase L1 (*UCHL1*), a gene associated with PD, and ATPase type 13A2 (*ATP13A2,*) which causes a recessive form of Parkinsonism, failing to establish a relation between abnormal promoter methylation and PD, although the promoter of *UCHL1* was found to be hypermethylated in cancer (Barrachina and Ferrer, 2009; Coppede, 2012; Thomas and Beal, 2011). Table 5 summarizes the findings regarding dysregulated DNA (de)methylation in PD.

4.3. DNA (de)methylation in Huntington's disease

DNA methylation states have been investigated in transgenic models, and to a lesser extend in HD patients (Ng et al., 2013; Villar-Menendez et al., 2013; Wood, 2013; Table 6). Promoter regions of genes important for neurogenesis were found to be hypermethylated in the presence of mutant HTT (Ng et al., 2013; Table 6). Although these findings need to be replicated in HD patients, reduced hippocampal neurogenesis might partially underlie the cognitive impairments seen in HD (Lee et al., 2013a). Decreased expression of the adenosine A2a receptor in HD patients is also epigenetically regulated. In both HD patients and transgenic mice adenosine A2a receptor expression was observed to be downregulated (Wood, 2013). However, in patients this was associated with increased 5' UTR DNA methylation, whereas in the mouse model with decreased 5' UTR DNA hydroxymethylation of the adenosine A2a receptor gene (*ADORA2A*). This finding indicates that epigenetic regulation might differ between species and illustrates the importance of replicating findings in human cases. The widely neglected 7-mG form of DNA methylation, which also occurs in RNA, was found to be disturbed in HD mouse models and patients, in both the nucleus and cytoplasm, the latter primarily reflecting methylated RNA (Thomas et al., 2013).

5. Chromatin remodeling in neurodegeneration

5.1. Chromatin remodeling in Alzheimer's disease

Going from the DNA to the chromatin level, additional epigenetic dysregulation can be observed in AD (Table 7). Histone acetylation was found to be drastically decreased in the temporal lobe of AD patients when compared to aged controls (Zhang et al., 2012), but also in animal models of AD (Graff et al., 2011). The importance of gene-specific investigations apart from global changes in epigenetic markers is exemplified by the observation of increased H3 acetylation at the promoter region of the *BACE1* gene in AD patients (Marques et al., 2012). The increase in H3 acetylation enhanced promoter accessibility and subsequent gene expression. Importantly, it was found that indirectly enhancing histone

acetylation through chronic treatment with HDACIs was able to reverse cognitive deficits in double transgenic mice overexpressing human APP isoform 695 with the double KM670/671NL Swedish mutation (APPswe) and the human PS1 deleted in exon 9 mutation (PS1ΔE9) (APPswe/PS1ΔE9 mice) (Kilgore et al., 2009). The mechanism of action of HDACI treatment might be related to the finding that dysregulation of H4K12ac is implicated in mediating cognitive impairment exhibited seen in aged mice, impairments which were alleviated through HDACI administration (Peleg et al., 2010). Another study using transgenic APP/PS1 mice observed diminished acetylation of H4 and linked this to memory impairments, which could be alleviated through trichostatin A (TSA), an HDACI, administration (Francis et al., 2009). Decreased histone acetylation is in line with the discovery of elevated nuclear translocation of EP300 interacting inhibitor of differentiation 1 (EID1) in cortical neurons of AD subjects (Liu etal., 2012a). EID1 inhibits EP300 and CREBBP, important KATs, and the overexpression of EID1 in mice resulted in learning and memory impairments thought to be the result of this inhibition. In the triple transgenic mouse model of AD (3xTg-AD mice) CREBBP expression was also decreased, while overexpression of CREBBP elevated BDNF levels and restored memory function in this AD model (Caccamo et al., 2010). Additionally, expression of a truncated inhibitory form of EP300 impaired memory in transgenic mice (Oliveira et al., 2011; Oliveira et al., 2007). Curiously, while knockout of KAT2B resulted in memory impairments in mice (Maurice et al., 2008), such mice are resistant to the neurotoxic effects of Ab injected into the lateral ventricles in another study (Duclot et al.,2010).

Conversely, cultured neurons from 3xTg-AD mice and non-transgenic controls, harvested at different ages, revealed an increased H3 and H4 acetylation levels from an age of 4 months, which is before the onset of memory impairments in this model of AD (Walker et al., 2013). With normal aging, H3 acetylation levels seem to remain unchanged, whereas H4 acetylation levels decreased, but administration of Aβ to the non-transgenic neurons increased acetylation levels. The repressive H3K9 mark in these same neurons increased with age in both the transgenic and non-transgenic neurons, but was more prominent in the transgenic cells. This later finding has been corroborated in humans; comparing two monozygotic twins discordant for AD it was found that the one with AD exhibited higher levels of H3K9me3 in the temporal cortex and hippocampus (Ryu et al., 2008). Using transgenic mice overexpressing APPswe (Tg2576 mice), increased H3 acetylation levels were found in the prefrontal cortex, as well as increased H4 acetylation levels in the CA1 region of the hippocampus (Lithner et al., 2009). Additionally, they also reported elevated levels of H3 phosphorylation and methylation in the prefrontal cortex, but decreased H3 methylation in the striatum.

While the use of non-selective HDACIs is a promising strategy for the treatment of cognitive problems, it might be even better to target the specific HDACs that induce the memory problems. Currently, HDAC2 is a prime suspect (Graff et al., 2012; Guan et al., 2009). Especially the group of Graff and Tsai has contributed significantly in this respect, starting with their detection of increased levels of HDAC2 in the hippocampus and prefrontal cortex of a mouse model of AD, while levels of the related HDAC1 and HDAC3 were not affected. Note, however, that recently it was reported that MS-275 treatment, an HDACI that favors HDAC1, was able to partially alleviate behavioral deficits, neuroinflammation and plaque

load in transgenic mice overexpressing APPswe and human PS1 with the L166P mutation, line 21 (APP/PS1–21 mice) (Zhang and Schluesener, 2013), and that HDAC3 inhibition enhanced long-term memory formation in the C57 black 6 inbred mouse strain (C57BL/6 mice) (McQuown et al., 2011). To study the effects of this HDAC2 dysregulation at the gene level, Graff et al. (2012) focused on genes involved in learning, memory and synaptic plasticity that were previously shown to be down-regulated in the AD brain and found that HDAC2 was significantly enriched at the promoter and coding regions of these genes, in their mouse model. In addition, they found several acetylation marks, associated with neuroplasticity, to be hypoacetylated (Table 7). Subsequently, it was shown that increased localization of HDAC2 to the investigated genes and hypoacetylation negatively correlated with RNA polymerase II (RNAPII) binding and mRNA expression. Interestingly, knock-down of HDAC2 ameliorated the cognitive problems and aberrant synaptic plasticity. It was then investigated how HDAC2 could be induced in AD, by testing *in vitro* the effect of the AD associated neurotoxic stimuli hydrogen peroxide and Aβ in primary hippocampal neurons. Both stimuli were found to enhance HDAC2 mRNA level through activation of glucocorticoid receptor 1 (GR1). Importantly, HDAC2 was also investigated in human postmortem brain samples from AD patients revealing that in actual AD cases HDAC2 was markedly increased in the hippocampus and EC. Already at Braak stages I and II HDAC2 levels were found to be significantly elevated in hippocampal CA1 field and the EC, indicating that increased HDAC2 activity might be involved in the early stages of AD. In addition to HDAC2, HDAC6 levels were found to be significantly higher in the hippocampus of AD cases when compared to controls (Ding et al., 2008). Interestingly, HDAC6 is thought to interact with tau, affecting its phosphorylation and aggregation (Simões-Pires et al., 2013). HDAC6 has been suggested to make tau vulnerable to phosphorylation through deacetylation, a finding relevant to tauopathies in general (Cook et al., 2014). HDAC6 also indirectly affects tau clearance through deacetylation of chaperone protein heat shock protein 90 (HSP90), which affects its drive towards refolding or degradation (Cook et al., 2012). It has been reported that tau can actually act as a HDAC6 inhibitor (Perez et al., 2009). Accordingly, in a mouse model for AD, reduction of HDAC6 levels mitigated learning and memory problems (Govindarajan et al., 2013). Studies on HDAC6 suggest that the role of HDACs in neurodegeneration might not solely depend on the deacetylation of histones, but also on the deacetylation of other targets, such as a-tubulin in the case of HDAC6 (Govindarajan et al., 2013; Simoes-Pires et al., 2013; Xiong et al., 2013). The same holds true for KATs, as the KAT human immunodeficiency virus type 1 transactivating protein interactive protein (TIP60/KAT5), the proposed counterpart of HDAC6 (Fischer, 2014) that has been associated with microtubule acetylation (Sarthi and Elefant, 2011), has been shown to guard against Aβ toxicity (Pirooznia et al., 2012). KAT5 in addition regulates the expression of genes involved in apoptosis (Pirooznia et al., 2012), axonal transport (Johnson et al., 2013) and DNA damage control (Kaidi and Jackson, 2013), and was found to interact with the amyloid precursor protein intracellular domain (Muller et al., 2013).

Not all HDACs have a detrimental effect on learning and memory, as inhibition of the class IIa HDACs HDAC4 and HDAC5 impair these processes (Agis-Balboa et al., 2013; Kim et al., 2012). Moreover, SIRT1, also an HDAC, was found to be decreased in the parietal cortex

of AD patients (Julien et al., 2009). SIRT1 has been linked to neurogenesis, DNA repair, apoptosis, cell stress responses, and various other vital signaling pathways (Morris, 2013). SIRT1 expression is suggested to be beneficial in case of AD (Kim et al., 2007a), as it induces ADAM10 expression, an α-secretase that can cleave APP without producing Aβ (Donmez et al., 2010). Additionally, SIRT1 is able to deacetylate tau and its deficiency in AD is thus thought to enhance tau expression and pathology (Julien et al., 2009; Min et al., 2010). Note that this is in conflict with more recent findings regarding HDAC6, which is thought to increase tau pathology through deacetylation of tau, as stated above (Cook et al., 2014), although the SIRT1 study investigated global tau acetylation, whereas the HDAC6 study specifically investigated the acetylation of KXGS motifs. Nevertheless, enhancing SIRT1 expression attenuated axonal neurodegeneration and microglia-dependent Aβ toxicity (Araki et al., 2004; Chen et al., 2005; Kim et al., 2007a). Interestingly, SIRT1 was found to be upregulated in AD mouse models, but which might by a defense mechanism (Kim et al., 2007a; Morris, 2013), although it was found to be decreased in AD patients (Julien et al., 2009). Histone modification abnormalities in AD also include histone phosphorylation, as H3 phosphorylation was found to be increased in the frontal cortex of AD patients (Rao et al., 2012). Phosphorylation of histone protein H2A member X (H2AX) at S139, a marker of DNA damage, was shown to be increased in the AD hippocampus, but specifically in astrocytes (Myung et al., 2008).

Accumulating evidence indicates that dysfunctional protein localization might be a chief player in the incapacitation of the epigenetic machinery in AD, and possibly in neurodegeneration in general. Ogawa et al. (2003) made some fundamental observations in this respect. As some neurons in AD erroneously exhibit signs of cell cycle activation, they investigated H3S10 phosphorylation, a histone modification critical for chromosome compaction during cell division. Strikingly, it was not only found that H3 phosphorylation was increased in hippocampal AD neurons, but also that this epigenetic marker was abnormally restricted to the cytoplasm in these neurons. In addition, it has also been shown that the mitogen-activated protein kinase (MAPK) pathway involved in the phosphorylation of H3 is upregulated in degeneration vulnerable neurons in AD (Hyman et al., 1994; Perry et al., 1999; Zhu et al., 2001). Furthermore, the presence of high levels of histones in the cytoplasm of neurons in the HD brain (Iqbal et al., 1974) suggests that incapacitated nuclear transport might be a common denominator for neurodegenerative processes. In support of this, Mastroeni et al. (2013) found that Aβ could reduce rat sarcoma (Ras)-related nuclear protein (RAN) expression, a pivotal player in nucleocytoplasmic transport. As an apparent result, they observed DNMT1 and RNAPII to be erroneously sequestered in the cytoplasm of neurons from AD patients.

Histone 1 ADP-ribosylation has not been directly investigated in relation to AD, but the observations that a loss of poly[ADP]-ribose polymerase 1 (PARP-1) induces memory problems in mice (Fontan-Lozano et al., 2010) and that a dysregulation of PARP-1 is associated with amyloid pathology and sAD (Abeti et al., 2011; Liu et al., 2010b; Strosznajder et al., 2012) suggests that ADP-ribosylation might be a relevant target for future studies. Although various histone methylation marks and histone methylation and demethylation enzymes have been linked to cognitive functioning in mice and humans (shortly reviewed in Fischer, 2014), no links with AD have been firmly identified yet.

5.2. Chromatin remodeling in Parkinson's disease

α-Synuclein normally localizes to the nucleus and presynaptic nerve terminals, but increased nuclear targeting is neurotoxic, possibly contributing to PD-related neurodegeneration (Kontopou-los et al., 2006). This nuclear toxicity of α-synuclein is supported by the finding that fPD a-synuclein mutations A30P and A53T result in an increased nuclear targeting of α-synuclein. Kontopoulos et al. (2006) found that nuclear toxicity of α-synuclein might be the result of direct binding of α-synuclein to histones, reducing the levels of acetylated histone H3 and acetylation in general in cultured cells through interactions with S1RT2. In cell cultures and transgenic flies, it was further shown that a rescue of α-synuclein toxicity could be achieved through HDACIs (Outeiro et al., 2007; St Laurent et al., 2013). Similar findings were found after exposure to oxidative stress, which induces the relocation of α-synuclein to the nucleus, where it subsequently binds to the peroxisome proliferator receptor gamma coactivator-1 alpha (PGC1-α) promoter element (Siddiqui et al., 2012). This binding of α-synuclein causes histone deacetylation, lowering PGC1-α expression, which is deleterious for mitochondrial functioning. Interestingly, levels of PGC1-α were significantly reduced in post-mortem substantia nigra neurons of PD patients (Zheng et al., 2010).

Curiously, not only does α-synuclein interact with the epigenetic machinery, but the KAT EP300 interacts with protein aggregation in Lewy bodies. A specific domain of EP300, reminiscent of prion-like domains, was found to serve as a potential interaction site for misfolded proteins, such as α-synuclein found in Lewy bodies, and enhance their aggregation (Kirilyuk et al., 2012). Conversely, α-synuclein was found to have neuroprotective actions via its interactions with EP300 and NF-κB, downregulating the proapoptotic protein kinase Cδ (PKCδ) (Jin et al., 2011a).

In PD patients, most of the aforementioned findings regarding the involvement of histone modifications still need to be replicated, but there is a report of an fPD case with a heterozygous A53 T *SNCA* mutation, in which the affected allele was epigeneti-cally silenced through histone modifications and the normal allele displayed expression levels exceeding those of two normal alleles in controls (Voutsinas et al., 2010).

Previously, the mechanism of DNA methylation-induced allelic skewing was described as a mediator between the genotype and environment. Histone modifications, however, are the most common epigenetic modality affected by environmental toxins such as pesticides, herbicides and industrial agents (Ammal Kaidery et al., 2013). MPTP, for instance, has been shown to lower H3K4me3 levels in the striatum of mice and non-human primates (Nicholas et al., 2008). Interestingly, H3K4me3 levels could be restored through chronic L-3,4-dihydroxy-phenylalanine (L-DOPA) treatment. Additionally, the herbicide paraquat and the insecticide dieldrin, which have both been associated with the development of PD, were found to affect histone acetylation, with exposure to paraquat increasing H3 acetylation and hampering overall HDAC activity, and exposure to dieldrin increasing H3 and H4 acetylation, in N27 dopaminergic cells (Song et al., 2010, 2011a). Dieldrin induces apoptosis in neurons and is thought to enhance histone acetylation through its inhibitory interaction with the proteasome system, leading to the build-up of CREBBP, an important KAT. Administration of the KAT inhibitor anacardic acid in a mouse model exposed to dieldrin, decreased histone acetylation and apoptosis, suggesting that the neurotoxic effect of

dieldrin leading to apoptosis might be the result of detrimental histone acetylation (Song et al., 2010). See Table 8 for an overview of the aberrant chromatin remodeling seen in PD.

5.3. Chromatin remodeling in Huntington's disease

In general, HD is associated with hypoacetylated and hyper-methylated histones (Ferrante et al., 2004; Jenuwein and Allis, 2001; Suzuki and Bird, 2008; Table 9). The mechanism underlying histone hypoacetylation has been fairly well characterized and is thought to center around the deleterious interaction between CREBBP and mutant HTT (Alarcón et al., 2004; Korzus et al., 2004). The polyglutamine section of mutant HTT is thought to physically interact and sequester CREBBP, hampering its KAT activity (Lee et al., 2013a). Besides its KAT activity, CREBBP has additional integral functions in the regulation of transcription, interacting with various transcription factors and the RNAPII complex. Sequestration of CREBBP by mutant HTT thus disrupts transcription at multiple levels (Ferrante et al., 2004; Gardian et al., 2005; McFarland et al., 2012; Ryu et al., 2006; Sadri-Vakili et al., 2007). Interestingly, a study using transgenic mice expressing a form of CREBBP without KAT activity found that this modification specifically affected the consolidation of short-term memory into long-term memory, leaving short-term memory unaffected (Korzus et al., 2004). A similar study with inactive EP300, a homolog of CREBBP, found long-term recognition and contextual fear memory to be impaired (Oliveira et al., 2007).

It has been proposed that disruption of CREBBP functioning by mutant HTT is also indirectly responsible for the induction of histone hypermethylation and the subsequent formation of large abnormal heterochromatin domains (Lee et al., 2008). CREBBP is normally thought to repress the expression of *Drosophila* Su(var)3–9 and enhancer of zeste proteins (SET) domain, bifurcated 1 (*SETDB1*), a gene encoding the HKMT SETDB1 that methylates H3K9. Due to the shutdown of CREBBP by mutant HTT, the repression of *SETDB1* is released and SETDB1 levels increase, subsequently resulting in H3K9 hypermethylation. This mechanism is corroborated by observations of increased levels of SETDB1 and H3K9me3 in striatal neurons of both transgenic HD mice and HD cases (Ryu et al., 2006). Additionally, H3K9me3 induced chromatin remodeling has been directly associated with altered gene expression profiles in HD (Lee et al., 2008, 2013b; Stack et al., 2007). Among the genes thought to be affected by this aberrant chromatin condensation is cholinergic receptor, muscarinic 1 (*CHRM1*) (Lee et al., 2013b). Decreased expression of CHRM1 has been proposed to induce synaptic dysfunction and CHRM1 levels are indeed lowered in the HD striatum (Calabresi et al., 2000; Cha et al., 1998). Deregulation of striatal cholinergic signaling has been identified as a pivotal factor in the pathophysiology of HD, especially affecting medium spiny neurons (Wang et al., 2006).

6. Non-coding RNAs in neurodegeneration

6.1. Non-coding RNAs and Alzheimer's disease

In addition to DNA methylation and chromatin remodeling, ncRNAs, and especially miRNAs, have more recently been identified as possible contributors to AD pathology (Sonntag, 2010; Table 10). Interestingly, miRNA profiling studies have found several

miRNAs to be upregulated in peripheral blood mononuclear cells of AD patients (Schipper et al., 2007). Apart from the blood, many brain region-specific imbalances in miRNA expression have been identified in relation to AD (for review see van den Hove et al., 2014), including those with candidate binding sites in the 3' UTRs of BACE, PS1 and APP. More specifically, miR-16, −17, −20a, - 101, −106a, −106b, −107, −124, −137, −147, −153, −195, −323–3p, - 520c, −644, −655 and let-7 are thought to regulate APP metabolism and Ab production (Bicchiet al., 2013; Delay et al., 2011; Fanet al., 2010; Hebert et al., 2009; Liang et al., 2012; Liu et al., 2012b; Long and Lahiri, 2011; Niwa et al., 2008; Patel et al., 2008). MiR-16 overexpression was found to reduce APP levels in SAMP8 mice (Liu et al., 2012b). In human neurons, miR-106a, −153 and −520c were found to target APP mRNA, downregulating APP and Ab levels (Long et al., 2012; Patel et al., 2008). Others, however, could not corroborate the involvement of miR-106a and miR-520c in the regulation of APP expression (Delay et al., 2011; Hebert et al., 2009). Inhibiting miR-101 in hippocampal neurons proved to decrease APP expression and Aβ load, indicating a possible detrimental role of the miRNA in AD (Long and Lahiri, 2011). Conversely, miR-124, a miRNA involved in adult neuronal differentiation (Cheng et al., 2009), is reported to be down-regulated in some AD patients (Smith et al., 2011a). MiR-124 is thought to, together with polypyrimidine tract binding protein 1 (PTBP1), modulate the alternative splicing of APP exons 7 and 8. Additionally, miR-124, but also miR-9, −29a/b-1, −29c, −107, - 195, −298, −328 and −485–5p, affect Aβ indirectly by modulating BACE1 translation (Fang et al., 2012; Hebert and De Strooper, 2009; Hebert et al., 2008; Zhu et al., 2012). In addition, in SAMP8 mice miR-195 expression was found to be decreased, whereas BACE1 levels were heightened (Zhu et al., 2012). The involvement of all these miRNAs in AD might, however, not be a general phenomenon. For instance, the miR-29a/b-1 cluster was found to be lowered in the anterior temporal cortex of sAD patients, coupled with high BACE1 protein levels, but only in approximately 30% of the examined cases (Hebert et al., 2008). In a transgenic AD mouse model miR-29c was observed to be highly expressed and was found to hamper BACE1 expression (Zong et al., 2011). Levels of miR-107 were found to be lowered in the temporal cortex of AD cases, which was suggested to facilitate AD progression as a result of diminished BACE1 repression (Wang et al., 2008c, 2011, 2010c). MiR-195, −298, and −328 also reduce Ab production by inhibiting BACE1 translation (Boissonneault et al., 2009; Zhu et al., 2012). Interestingly, while most of the miRNAs affecting BACE1 expression repress translation by binding to the 3' UTR of its mRNA, miR-485–5p represses BACE1 by binding to the open reading frame in exon 6 (Faghihi et al., 2010). The involvement of post-transcriptional regulation of BACE1 is further supported by the observation that in AD brains BACE1 protein levels are increased, whereas mRNA levels remain unchanged (Hebert and De Strooper, 2009). Serine palmitoyltransferase (SPT) is an enzyme crucial for ceramide synthesis, which is thought to facilitate Aβ production. MiR-9, −29a/b-1, −137 and −181c negatively modulate SPT production and their levels were lowered in the frontal cortex of AD patients (Geekiyanage and Chan, 2011). MiR-137 is known to additionally promote proliferation of neural stem cells through the inhibition of differentiation and dendrite formation (Smrt et al., 2010; Szulwach et al., 2010).

MiRNAs can thus affect Aβ production, but Aβ can also affect the expression of some miRNAs *in vitro,* for example inducing miR- 106b expression (Wang et al., 2010b) but

repressing miR-9 and miR-181c (Schonrock et al., 2012). Curiously, Hebert et al. (2009) found miR-106b to be downregulated in the anterior temporal cortex of AD brains. Furthermore, miR-106 was reported to not only directly bind to and inhibit the translation of APP, but also affect APP trafficking and Aβ clearance. Additionally, by regulating the ATP-binding cassette, sub-family A (ABC1), member 1 (ABCA1), which transports cholesterol, it is thought to influence BACE and γ-secretase functioning. ABCA1 expression in the hippocampus has been positively correlated with cognitive impairments in AD (Akram et al., 2010). Normally, miR-106b is thought to promote neurogenesis through its regulation of the insulin-like growth factor 1 (IGF1) pathway (Brett et al., 2011). MiR-9 has been reported to be a pivotal player in the differentiation and migration of neural stem cells (Delaloy et al., 2010; Zhao et al., 2009).

Furthermore, while there are generally no AD-associated mutations in tau, miR-15, −16, −132, and −497 are thought to regulate tau expression and might play a role in AD. In example, a decrease in miR-132 is suggested to mediate the alternative splicing of tau exon 10, through a lowered repression of polypyrimidine tract-binding protein 2 (PTBP2), which hampers physiological phosphorylation of tau (Hebert et al., 2012; Smith et al., 2011b). Alternative splicing of tau influences whether it contains 3 or 4 microtubule-binding repeats (3R-tau and 4R-tau, respectively) (Liu and Gong, 2008). Furthermore, changes in the 3R:4R tau ratio are thought to be related to neurodegeneration (Caffrey et al., 2006). Apart from miR-132, miR-9, −124 and −137 have also been reported to affect the 3R:4R tau ratio. MiR-212 and miR-454 have also been implicated in NFT pathology in AD (Cogswell et al., 2008; Wang et al., 2011). Note that dysregulated miRNA expression in relation to tau is probably not unique for AD and likely also occurs in other tauopathies. For instance, miR-132 was found to be downregulated in progressive supranuclear palsy and frontotemporal lobar degeneration (Hebert et al., 2013; Smith et al., 2011b).

Phosphorylation of tau is performed by extracellular signal-regulated kinase 1 (ERK1), which in turn is regulated by members of the miR-16 family (miR-15, −16, −195 and −495), of which miR- 15 was found to be downregulated in AD (Hebert et al., 2012). Tau can also be phosphorylated by glycogen synthase kinase 3 beta (GSK-3β), which has been implication in Aβ and NFT formation, and has been reported to be negatively regulated by miR-26a, a miRNA that is dysregulated in AD (Cogswell et al., 2008; Mohamed et al., 2010). As stated above, SIRTI negatively regulates tau expression, while miR-9, −34c and −181c, however, have been shown to (in their turn) inhibit S1RT1 production, thereby enhancing tau production in AD (Schonrock et al., 2012; Zovoilis et al., 2011). MiR-128 has been suggested to affect tau clearance, through its regulation of cochaperone B-cell chronic lymphocytic leukemia (CLL)/lymphoma 2 (BCL2)-associated athanogene 2 (BAG2), and has been reported to be altered in AD (Carrettiero et al., 2009; Lukiw, 2007). There is additional indirect evidence for the involvement of miRNAs in the regulation of tau metabolism, as studies knocking out Dicer, which is crucial for miRNA processing, observed increased hyperphosphorylation of tau, alternate splicing of tau and neurodegeneration (Bilen et al., 2006; Hebert et al., 2010).

Next to miRNAs impacting on Aβ and tau metabolism, various miRNAs that were found to be dysregulated in AD also affect other pathological hallmarks of AD. MiR-146a, is for

instance a regulator of inflammatory processes through its interaction with interleukin-1 receptor-associated kinase 1 (1RAK1) that is upregulated in AD brains (Cui et al., 2010; Taganov et al., 2006). In addition to 1RAK1, miR-146a was reported to bind to the 3' UTR of complement factor H, a suppressor of inflammation which is downregulated in AD (Lukiw et al., 2008). Another regulator of inflammation is miR- 101, which normally inhibits COX-2, but its levels were shown to be lowered in AD, whereas levels of COX-2 were increased (Long and Lahiri, 2011). MiR-132 and miR-125b have been linked to synaptic plasticity, and miR-132 was lower in the hippocampus, cerebellum and medial frontal gyrus of AD patients, whereas miR- 125b levels were higher in these areas (Sethi and Lukiw, 2009). Brain cytoplasmic RNA 200 (BC200) was initially reported to be decreased in the temporal neocortex of AD cases (Lukiw et al., 1992), but later studies reported increased BC200 levels in the hippocampus and superior frontal gyrus, but erroneously located in the neuronal soma (Mus et al., 2007). BC200 is thought to enhance long-term synaptic plasticity by interacting with protein synthesis in postsynaptic microdomains. In transgenic mice overexpressing a combination of APPswe and human APP with the V717F Indiana mutation (APPind; Tg19959 mice) miR-103 and miR-107 were found to be decreased, which was linked to increased cofilin expression (Yao et al., 2010). Cofilin is a pivotal player in cytoskeletal integrity and is thought to influence microtubule stability, neuronal transport and synaptic functioning (Minamide et al., 2000).

Compared to miRNAs, evidence for the involvement of other ncRNAs in AD pathology is sparse. RNA polymerase 111 (RNAP111)-dependent ncRNA neuroblastoma differentiation marker 29 (NDM29) was found to facilitate the production and secretion of Ab by influencing APP processing (Massone et al., 2012), whereas the lncRNA BACE1-antisense (BACE1-AS) positively affects BACE1 expression (Hebert and De Strooper, 2009). BACE1-AS has a length of about 2 kb and is transcribed from the DNA strand complementary to the BACE1 gene (Faghihi et al., 2008). 1t is thought to enhance the stability of BACE1 mRNA, facilitating BACE1 protein production. Interestingly, BACE1-AS transcription is enhanced in response to Ab exposure, initiating a vicious cycle, as its positive effects on BACE1 expression in turn enhances Ab production. In both AD patients and Tg19959 mice, BACE1-AS was indeed found to be overexpressed. Although only confirmed for the nonconventional miR-485–5p, evidence suggests that the binding of BACE1-AS to BACE1 mRNA enhances mRNA stability by competing with miRNA binding (Faghihi et al., 2010). The ncRNA 17a has been observed to promote Ab secretion and accumulation and is elevated in the cerebral cortex of AD cases, which is thought to be the result of inflammatory factors (Massone et al., 2011).

6.2. Non-coding RNAs and Parkinson's disease

Apart from epigenetic transcriptional regulation of *SNCA,* some miRNAs have been identified that regulate its function on a translational level. One of these is miR-7, which negatively regulates α-synuclein expression through binding to the 3' UTR of α-synuclein mRNA and is mainly expressed in neurons (Junn et al., 2009). Through its suppression of α-synuclein, including cytotoxic mutant forms, it is thought to have a neuroprotective role in PD. Interestingly, miR-7 levels were shown to be decreased *in vitro* and in animal models after exposure to the toxic metabolite of MPTP, 1-methyl-4-phenyl-pyridinium ion (MPP+),

increasing α-synuclein expression. Downregulation of miR-7 might thus, at least in part, explain how MPTP induces PD-like pathology.

Another miRNA, miR-153, represses α-synuclein production both at a mRNA and protein level (Doxakis, 2010). Indirectly, miR-433 has also been implicated in *SNCA* expression, via its regulation of the fibroblast growth factor 20 (FGF20). FGF20 expression has been positively correlated with α-synuclein expression, and a 3' UTR SNP (rs1270208) has been linked to an increased risk to develop PD. This SNP interferes with miR-433 binding, increasing FGF20 expression (Wang et al., 2008a). Conversely, α-synuclein has been shown to affect the expression levels of certain miRNAs in *in vivo* models were α-synuclein was overexpressed. Levels of various miRNAs were affected in a transgenic mouse model overexpressing human A30P α-synuclein (Gillardon et al., 2008; Table 11). In a transgenic *C. elegans* model expressing human α- synuclein, alterations in levels of 12 miRNAs were found (Asikainen et al., 2010). The significance for the human situation, however, remains to be elucidated as the human orthologs of these miRNA remain to be identified.

In addition to *SNCA*, the expression of *LRRK2,* a gene implicated in both fPD and sPD, is also regulated by miRNAs. MiR-205 targets the 3' UTR of LRRK2 mRNA and was found to be downregulated in sPD cases in which LRRK2 protein levels were increased, whereas miR- 205 was able to mitigate the aberrant neurite growth induced by *LRRK2* mutation R1411G *in vitro* (Cho et al., 2013). Conversely, mutant LRRK2 (I1915T or G2019S) was observed to inhibit the actions of let-7 and miR-184*. These miRNAs regulate E2F transcription factor 1 (E2F1) and differentiation regulated transcription factor protein (DP) levels, transcription factors associated with cell cycle regulation and cell survival. LRRK2 thus induces E2F1 and DP expression, which is associated with reduced dopaminergic neuron numbers and locomotor activity in *Drosophila,* effects that have also been linked to mutant *LRRK2* (Gehrke et al., 2010). Overexpression of let-7 or miR-184* reversed the deleterious effects of mutant LRRK2 expression. Note, however, that let-7b was also found to progressively inhibit neural stem cell proliferation in the subventricular zone with age (Nishino et al., 2008). Interestingly, the disruption of let-7 and miR-184* activity by mutant LRRK2 is thought to be an indirect effect, as the increased activity of mutant LRRK2 increases the phosphorylation of eukaryotic translation initiation factor 4E binding protein (4E-BP). 4E-BP interacts with Argonaute 2, a pivotal constituent of the RISC, which in turn is required for proper let-7 and miR-184* functioning (Imai et al., 2008). The negative regulation of these miRNAs by LRRK2 thus depends on gain of function mutations, such as I1915T and G2019S (Imai et al., 2008; Smith et al., 2006). Indeed, mutant LRRK2 without enzymatic activity does not affect miRNA repression (Gehrke et al., 2010). Additionally, LRRK2 might also affect Dicer, another protein integral to the RNA interference (RNAi) pathway, as knocking down LRRK2 was able to attenuate some of the pathology in the *Drosophila* model related to decreased Dicer activity.

MiRNA profiling of PD brains at different stages of the disease pointed towards a miR-34b/c downregulation, mainly at the early premotor stages (1–3) (Minones-Moyano et al., 2011). MiR-34b/c is thought to modulate mitochondrial functioning via its modulation of DJ-1 and parkin, proteins that have both been associated with fPD. In the blood, comparing healthy individuals with untreated PD patients, miR-1, −22*, and −29 were found to be differentially

expressed, while miR-16–2*, −26a2*, and −30a were differentially expressed comparing treated and untreated PD patients (Margis et al., 2011). Table 11 contains the most important findings regarding ncRNAs associated with PD.

6.3. Non-coding RNAs and Huntingon's disease

In accordance with the widespread dysregulation of gene expression, the expression of miRNAs are also affected in HD (Table 12). In HD models and patients neuronal miRNA expression was found to be decreased in general, resulting in an upregulation of their target mRNAs (Han et al., 2004; Johnson et al., 2008; Lee et al., 2011; Table 12). In addition, it was observed that mutant HTT expression decreased miR-125b and miR-150 expression (Ghose et al., 2011). These miRNAs have P53 among their targets, which is known to repress xsNF-κB and miR-146a expression. Further interactions between P53 and mutant HTT mediate nuclear and mitochondrial damage in HD models and patients (Bae et al., 2005).

7. Epigenetic-based diagnostics and therapies

The available treatment strategies for most progressive neurodegenerative diseases only provide symptomatic relief, stressing the need to develop innovative, realistic therapeutic approaches that can effectively modulate the disease process. The factor common to all of the conditions discussed in this review is their neurodegenerative nature. Treatments providing a general neuroprotective effect could thus potentially be beneficial for any of them. Among such treatments HDAC and DNMT inhibitors represent interesting options to act upon the epigenetic machinery. These are already used in the treatment of other disorders such as epilepsy and cancer (Xu et al., 2012). The versatile and reversible nature of epigenetic changes makes epigenetic mechanisms ideal targets for the development of efficient, novel treatment strategies (Coppede, 2014). The adverse role of HDAC2 in memory facilitation has, for instance, led to the investigation of HDACIs as a potential treatment for memory impairment, for example in AD (Guan et al., 2009).

7.1. Strategies targeting DNA methylation

Neurodegenerative disorders may involve a dysregulated SAM metabolism, resulting in global DNA hypomethylation, as well as the hypermethylation of some crucial genes. It is thus not surprising that strategies aiming to increase or decrease DNA methylation have been investigated. Enhancing DNA methylation can be achieved by boosting SAM metabolism, for example through the administration of SAM itself, and by vitamin B_{12} and folate supplementation that was shown to be effective (Durga et al., 2007; Haan et al., 2007; Scarpa et al., 2003). Reducing the levels of methylated DNA can be accomplished with DNA demethylating agents, such as DAC (Wang et al., 2013). However, these treatment options are highly unspecific, which may, especially in the case of DNA demethylating compounds, result in considerable adverse effects. Apart from therapies targeting DNA methylation, it has also been suggested that differential genomic and mtDNA methylation patterns may serve as diagnostic biomarkers (Devall et al., 2014; How Kit et al., 2012).

7.1.1. Alzheimer's disease—Scarpa et al. (2003) argued that the Hcy accumulation often seen in AD might be an indication for an abnormal SAM metabolism. The resulting decrement in SAM levels could explain a global decrease in DNA methylation, which in turn could lead to an overexpression of multiple genes, including ones involved in AD pathology. lnterestingly, *in vitro* SAM administration led to a repression of PS1 gene expression and Aβ production. Accordingly, folate and vitamin B_{12} supplementation have been found to enhance cognitive functioning and slow the development of dementia (Durga et al., 2007; Haan et al., 2007). There are, however, also other studies that could not detect a positive effect of folate and vitamin B_{12} supplementation (Malouf et al., 2005; McMahon et al., 2006), and it has been reported that folic acid supplementation, in addition to other side-effects, might exacerbate neuropathology in patients with low vitamin B_{12} levels (Campbell, 1996). The observation that some crucial genes are hypermethylated in AD has led to the suggestion that the DNA demethylating agent DAC could be used to restore normal expression levels of these genes. AD, however, is also associated with general hypomethylation and due to the non-specific nature of DAC it might in fact cause more harm than good (Wang et al., 2013).

7.1.2. Parkinson's disease—Similarly to AD, a disturbed SAM metabolism has also been associated with PD, and decreased methylation was linked to cognitive decline (Obeid et al., 2009). A viable option to counteract this decline would be to increase the levels of SAM, through administration of methionine, choline, folates or vitamin B12, among other possibilities (Xu et al., 2012).

7.2. Strategies targeting chromatin modifications

One of the most promising epigenetics-based treatment options in relation to neurodegeneration are HDACls. There are many HDACls, which can be subdivided into four classes, including short-chain fatty acids, hydroxamic acids, epoxyketones and benzamides. Of these, sodium butyrate (SB) has received most of the attention for clinical use. The bioavailability of SB in the central nervous system has been characterized and is well tolerated in animals and in humans due to its low toxicity (Daniel et al., 1989; Egorin et al., 1999; Miller et al., 1987). Chen et al. (2006) investigated the short-chain fatty acid valproate (valproic acid, VPA), a drug used as a mood stabilizer and anti-epileptic that was found to be an HDACl. VPA is thought to enhance H3 acetylation indirectly, possibly through the recruitment of the KAT EP300 (Marinova et al., 2009). This study found that VPA exerts a neurotrophic effect, involving the repression of pro-inflammatory factors released by microglia and a stimulation of neurotropic factor expression, including glial cell line-derived neurotrophic factor (GDNF) and BDNF, by astrocytes. VPA may thus represent a viable treatment option to counteract neurodegeneration. Comparable effects have been attributed to other HDACls, including TSA, suberoylanilide hydroxamic acid (SAHA) and SB, as well as MS-275 and apicidin, which specifically inhibit class l HDACs (Chen et al., 2012; Kidd and Schneider, 2010; Leng et al., 2010; Marinova et al., 2011; 2009; Wu et al., 2008). Some HDACls, such as 4-phenylbutyrate (4PBA), VPA, and urocortin, might also exert some of their neuroprotective effects independent of their effects on HDACs (Huang et al., 2011; Roy et al., 2012; Zhou et al., 2011).

The use of HDACIs in the treatment of neurodegenerative diseases is thus promising and deserves much attention. However, several issues, especially concerning the non-specific action of most tested HDACIs, must be overcome for HDACIs to be ready for clinical use. For example, as some HDACIs are already being used in cancer therapy, it was observed that they induce cell death and cell-cycle arrest, which has also been reported to affect neurons (Brahe et al., 2005; Marks, 2010; Marks and Xu, 2009; Salminen et al., 1998). HDACIs have additionally been observed to disturb the immune system (Kelly-Sell et al., 2012; Rossi et al., 2012). It has thus been found that targeting specific HDACs would be more preferable over the more general HDACIs. Some examples of specific HDACIs are tubacin, a selective HDAC6 inhibitor, and suramin, a selective S1RT1 and S1RT2 inhibitor (Haggarty et al., 2003; Trapp et al., 2007).

7.2.1. Alzheimer's disease—A decrease in BDNF expression, a pivotal player in memory processes (Yamada et al., 2002), has been implicated as an early marker in the development of AD (Walker et al., 2013) and TSA treatment has been shown to enhance BDNF expression *in vitro* significantly, possibly through restoring BDNF promoter histone acetylation levels (lshimaru et al., 2010; Tian et al., 2010). Another HDAC1, VPA, can counter Aβ production in human embryonic kidney 293 (HEK293) cells expressing APPswe isoform 751 and in a transgenic mouse model overexpressing APPind (PDAPP mice) (Su et al., 2004). Using a transgenic mouse model with a 7-fold overexpression of APPswe (APP23 mice), this decrease in Aβ was shown to be due to an inhibition of GSK-3β-mediated γ-secretase cleavage of APP by VPA, which was also found to improve behavioral impairments (Qing et al., 2008). Another HDACl, (4PBA), was shown to reverse learning and memory problems in Tg2576 AD model mice, without affecting Aβ levels, but decreasing tau phosphorylation (Ricobaraza et al., 2009). This was accompanied by increases in GSK-3β, histone acetylation, as well as ionotropic glutamate receptor 1 (GluR1), postsynaptic density protein 95 (PSD95) and microtubule-associated protein 2 (MAP2), the later three being involved in synaptic plasticity (Ricobaraza et al., 2009). A subsequent study using the same mouse model showed that 4PBA elevated intraneuronal Aβ clearance, paired with an increase in plasticity-related proteins and subsequent restoring of dendritic spine densities in the hippocampus (Ricobaraza et al., 2012). Treatment in mice with the HDACl SAHA achieved an increase in H4K12 acetylation levels and accordingly restored expression levels of genes associated with learning (Peleg et al., 2010). VPA and SAHA were also reported to restore CLU expression *in vitro* (Nuutinen et al., 2010). Effective VPA, SB, and SAHA treatment in AD models has additionally been linked to elevating H4 acetylation levels and alleviation of memory deficits (Kilgore et al., 2009). lnterestingly, although VPA, SB, and SAHA by elevating H4 acetylation are likely to generally affect gene expression, the HDACl TSA was found to specifically enhance expression of those genes involved in memory consolidation (Vecsey et al., 2007). Curiously, inhibition of SIRTs, the class Ill HDACs, with nicotinamide was observed to restore cognitive impairments in 3xTg-AD mice, by indirectly promoting microtubule stability, which is affected by hyperphosphorylated tau in AD (Green et al., 2008). Recently, Forum Pharmaceuticals compound 0334 (FRM-0334), a class I HDACI specifically designed to cross the blood-brain barrier (BBB) was developed, addressing the problem of BBB permeability (Arrowsmith et al., 2012). FRM-0334 is one the first HDACI that is

specifically being tested for the treatment of AD, with most others having an approved indication in cancer treatment (Arrowsmith et al., 2012). In relation to specific HDAC inhibition, the selective HDAC6 tubacin has been reported to affect tau phosphorylation *in vitro* (Ding et al., 2008). In addition to HDACIs, KAT agonists are being developed (Chatterjee et al., 2013) and it has also been suggested that targeting HKMTs and HKDMs may prove to be a viable treatment strategy for AD (Fischer, 2014).

7.2.2. Parkinson's disease—As stated above, preventing histone deacetylation may alleviate memory problems, such as those associated with AD (Guan et al., 2009). Similar approaches in PD models suggest that HDAC inhibition could be neuroprotective. In *in vitro* and *Drosophila* models the HDACIs SB and SAHA attenuated α-synuclein-induced toxic effects (Kontopoulos et al., 2006), illustrating the prominent role of disrupted histone acetylation in the neurotoxic effects of α-synuclein, caused by its direct binding to histones. TSA was able to rescue mitochondrial fragmentation and cell death induced by MPP+ in human neuroblastoma cells (Zhu et al., 2014). Similar results were obtained when inhibiting the HDAC SIRT2 with 2-cyano-3-(5-(2,5-dichlorophenyl)-2-furanyl)-N-5-quinolinyl-2-propenamide (AGK2) (Outeiro et al., 2007). Additionally, pretreatment with VPA has been shown to protect midbrain dopaminergic neurons from inflammation and a-synuclein-induced neurotoxicity (Chen etal., 2006,2007; Kidd and Schneider, 2011; Pengetal.,2005).

Currently, one of the main treatments for PD is the dopamine precursor L-DOPA, which provides some symptom alleviation. Although not intended as such, chronic L-DOPA treatment was observed to induce epigenetic alterations. Specifically, the development of L-DOPA-induced dyskinesia presented with decreased H3K4me3 levels, whereas L-DOPA induced hyperkinesia was associated with decreased acetylation levels of H4K5, H4K8, H4K12 and H4K16, in the striatum of animal models (Nicholas et al., 2008). Additionally, it was shown that L-DOPA-induced dyskinesia paralleled H3 phosphoacetylation, suggesting that the inhibition of striatal H3 phosphoacetylation when using L-DOPA might prevent the development of dyskinesia (Darmopil et al., 2009).

7.2.3. Huntington's disease—In HD, reversing the reduced expression of crucial genes due to histone hypoacetylation has been attempted through the application of HDACIs, showing promising results, both in terms of neuropathology and motor symptoms (Ferrante et al., 2004; Gardian et al., 2005; Igarashi et al., 2003; McFarland et al., 2012; Sadri-Vakili et al., 2007; Steffan et al., 2001; Sugai et al., 2004; Thomas et al., 2008). HDACIs improved memory and behavior in CREBBP deficiency or KAT deletion animal models (Alarcon et al., 2004; Korzus et al., 2004; Wood et al., 2006). Additionally, in an *in vitro* model based on the administration of toxic polyglutamine, a model that also exhibits histone hypoacetylation, HDACIs were able to mitigate the toxic effects of polyglutamine (McCampbell et al., 2001). As in PD, SAHA, and SB also were effective in transgenic HD mice (Hockly et al., 2003). HDAC inhibition, either through SAHA or SB administration, or HDAC2 knock-out, improved memory deficits in mice (Mielcarek et al., 2011). SB-treated transgenic mice overexpressing exon 1 of human *HTT* with an expanded CAG repeat length (R6/2 mice), however showed improved motor performance and decreased neuropathology, and survived significantly longer than non-treated mice (Ferrante et al., 2003). Alternatively,

4PBA may represent a promising candidate treatment for HD, as it is already Food and Drug Administration-approved and data about pharmacokinetics, toxicity, and dosing are available. Although 4PBA itself has no inhibitory effect on HDACs, its metabolite phenylacetate does, in addition to having a high bioavailability in the brain (Dasgupta et al., 2003). As with SB, treatment with 4PBA improved motor symptoms and neuropathology in a transgenic HD mouse model (Gardian et al., 2005). Unfortunately, a multicenter, double-blind, placebo-controlled clinical trial of 4PBA to determine safety and tolerability in HD, patients showed that its efficacy was very low, necessitating the use of high doses (Ebbel et al., 2010; Hogarth et al., 2007). Therefore, although promising in animal models, the use of 4PBA in the treatment of HD is not optimal. A novel HDACI, the pimelic diphenylamide HDACI 4b, has also shown to be effective in R6/2 mice, improving the HD-related transcriptional abnormalities, including H3 acetylation and mRNA levels, and behavioral phenotype (Thomas et al., 2008). Additionally, in a different HD model, that expresses the first 171 amino acids of HTT with 82 CAG repeats at a relatively low steady-state level (N171–82Q mice), HDACI 4b enhanced body weight, motor function and cognitive performance, which may be mediated by modulatory effects of HDACI 4b on post-translational mechanisms, such as protein phosphorylation and ubiquitination (Jia et al., 2012a). Accordingly, activation of inhibitor of kappaB kinase (IKK) by HDACI 4b enhanced phosphorylation and acetylation of HTT, and subsequent clearance effected by the ubiquitin-proteasomal and autophagy systems. The selectivity of HDACI 4b to inhibit class I and class II HDACs, and restore proper gene expression, was also explored in various HD models, including mice, flies, and cells (Jia et al., 2012b). Targeted inhibition of HDAC1 and HDAC3 was observed to mitigate mutant HTT-induced degeneration of the eyes and brain in *Drosophila*, and subdued some of the metabolic defects seen in STHdhQ111 mutant *HTT* knock-in striatal cells. In addition to HDACI 4b, some additional compounds were tested, revealing that one of the, compound 136, could effectively inhibit HDAC3 and restore proper gene expression in HD models. Although the exact targeting mechanisms remain elusive, HDACIs upregulate prosurvival genes selectively, while downregulating pro-death genes (Hu et al., 2011b).

Apart from drugs targeting HDACs, DNA-binding drugs have also received some attention in the context of HD. These efforts are mainly focused on the DNA intercalating anthracyclines, such as mithramycin A and chromomycin A3, which were isolated from *Streptomyces argillaceus* and *Streptomyces griseus,* respectively (Blanco et al., 1996; Chakrabarti et al., 2000; Prado et al., 1999). Mithramycin A and chromomycin A3 inhibit the replication and translation processes in cells, processes that are especially indispensable to tumors. Mithramycin A has already been used to treat Paget’s disease, hypercalcemia in malignancy, and various types of cancer (Ralston, 1994; Ryan, 1977; Kennedy, 1972).These DNA intercalating agents specifically block the binding of transcription activators and repressors that bind to GC-rich regions of gene promoters, thereby affecting gene expression (Ralston, 1994; Hagen et al., 1995; Majello et al., 1995). Their interference with transcription factors SP1 and SP3 are thought to be neuroprotective, as these induce detrimental responses after oxidative stress and DNA damage (Chatterjee et al., 2001). In R6/2 mice, mithramycin A was found to reduce clinical and neuro- pathological symptoms, as well as significantly increase survival rate, probably via the reduction of pericentromeric

heterochromatin condensation through an epigenetic mechanism (Ferrante et al., 2004; Ryu et al., 2006). Mithramycin Acan repress the HKMT SETDB1 and thereby reverse the H3K9 hypermethylation seen in R6/2 mice (Ferrante et al., 2004). The effects of chromomycin A3 have been investigated in both N171–82Qand R6/2 mice, showing that it can beneficially tip the methylation-acetylation balance at H3K9 in favor of acetylation, reactivating the chromatin and improving the HD phenotype (Stack et al., 2007). Despite already being used as chemotherapy in cancer, mithramycin A and chromomycin A3 are not well-suited for chronic use, which would be required for HD treatment, due to their relatively high, dose-dependent, toxicity in humans. Nevertheless, they may serve as a template in the development of less toxic DNA-binding compounds to treat HD.

7.3. Strategies targeting non-coding RNAs

Due to their relatively high specificity, miRNAs have been investigated as potential therapeutic targets for the treatment of neurodegenerative disorders. Alternatively, miRNA mimics, miRNA precursor analogs, and anti-miRNAs could also be employed to restore miRNA homeostasis in such conditions (Junn and Mouradian, 2012). Although these RNA-based strategies are specific, a major obstacle, as with HDACIs, remains access and distribution to the brain. For instance, simple intravenous administration of anti-miRNAs conjugated to cholesterol molecules (“antagomirs”), while showing promise, failed to cross the BBB (Krutzfeldt et al., 2005). Additionally, although cholesterol facilitates cell entry, it might induce undesirable side effects (Junn and Mouradian, 2012). More invasive, direct injections into the ventricles may represent an effective way of circumventing the BBB to enhance the performance of such treatments (Kuhn et al., 2010; Yu et al., 2012). Packaging siRNAs into exosomes has been suggested as a less invasive strategy to pass the BBB (Alvarez-Erviti et al., 2011; Lakhal et al., 2013).

7.3.1. Alzheimer’s disease—Suggested miRNA targets for the treatment of AD include miR-124 and miR-195, which, when increased, could lower the levels of BACE1 and subsequently Aβ (Fang et al.,2012; Zhu et al., 2012). Alternatively, miR-323–3p, which is associated with inflammatory responses, has been proposed as a target for therapy in AD (Xu et al., 2014). Apart from being promising treatment targets, miRNA levels have also been investigated as potential diagnostic and prognostic markers for AD. For instance, Schipperetal. (2007) investigated miRNA expression in blood mononuclear cells of mild sAD patients, finding miR-34a and miR-181b to be upregulated in these patients. Although it remains to be elucidated whether these miRNAs play a significant role in AD pathology, they might serve as valuable prognostic biomarkers, especially as they can be relatively easily measured in the blood. Identifying changes in miRNA expression in very early, non-symptomatic stages of AD will substantially enhance AD diagnostic and treatment efficacy.

7.3.2. Huntington’s disease—Because HD is caused by the expression of mutant HTT, directly targeting its mRNA through RNAi is an attractive treatment strategy (Hu et al., 2009; Lombardi et al., 2009; Zhang and Friedlander, 2011). Due to the cardinal role of normal HTT in neuronal survival and functioning, it is crucial that such a treatment specifically target only mutant HTT. Choosing for adeno-associated virus short hairpin RNA (shRNA)-mediated RNAi, Harper et al. (2005) were able to improve motor function and

neuropathology in transgenic N171–82Q mice. Subsequently, studies using adenovirus-shRNA, lentivirus-shRNA, adeno-associ-ated virus-miRNA, or cholesterol-conjugated siRNA were successful in downregulating mutant HTT, reducing aggregates and improving motor functions and neuropathology (Boudreau et al., 2009; DiFiglia et al., 2007; Drouet et al., 2009; Franich et al., 2008; Huang et al., 2007; Machida et al., 2006; McBride et al., 2008; Rodriguez-Lebron et al., 2005). Interestingly, chemically modified single-stranded siRNAs (ss-siRNAs) with mismatched bases have a 100-times higher mutant HTT targeting efficacy when compared to unmodified RNA, as tested in an HD mouse model expressing one mutant HTT copy with 150 CAG repeats and a normal HTT copy with 7 CAG repeats (*Hdh*$^{Q150/Q7}$ mice) after intraventricular infusion (Yu et al., 2012). This increased potency likely stems from the ability of these ss-siRNAs to distinguish mutant from normal HTT optimally, in collaboration with RISC, in a similar fashion as miRNAs.

8. Discussion and future perspectives

Epigenetic dysregulation currently garners much attention as a potentially pivotal player in aging and age-related neurodegenerative disorders, mediating interactions between genetic and environmental risk factors, or directly interacting with disease-specific pathological factors. Despite the profound differences in the epigenetic aberrancies, some similar patters begin to emerge and key-player molecules arise and build bridges between the seemingly diverse psychopathophysiology of neurodegenerative diseases, such as AD, PD, and HD. For instance, careful consideration of the (de)methylation dysregulations reveals a differential methylation pattern in genes that are accounted for the genetic predisposition of AD and PD; namely *APP, PS1, BACE, APOE* for AD *and SNCA, PARKIN16* for PD. Moreover, there is derailled histone acetylation in all three diseases discussed and more specifically in AD and PD, a genome wide deacetylation of histones is observed. The various modifications on histone 3 are another common factor of these diseases that cannot be overlooked and especially the upregulated tri-methylation of H3K9 in both AD and HD. Finally, the deviant expression of specific ncRNAs in all the three discussed diseases posits their key-player role in their pathophysiology. Briefly, the differential expression of miR-132 and miR-29 is a common observation not only among all three age-related neurodegenerative disorders but also normal aging. MiR-22, miR-26a and miR-125 also present a differential expression pattern that is common in these diseases.

Even though the epigenetic research over more neurodegenerative disorders is expanding, their common points remain rather faint and sporadic, impeding the advancement towards innovative therapeutic strategies targeting neurodegeneration in general, instead of disease-specific processes. This notion stems from the fact that large, empirical and broad studies are rare, with most investigations using only small samples with low statistical power, focusing on very specific tissues, cell types, or genes, and looking only at one or a few epigenetic modifications (Lunnon and Mill, 2013). This substantial heterogeneity in research makes it hard to draw concrete conclusions about the exact involvement of epigenetics in neurodegeneration, stressing the need for studies with larger samples sizes, longitudinal designs with repeated sampling schemes, study designs with tissue and cell-specific analyses-but not just one type at a time-the inclusion of multiple epigenetic markers and levels, and genome-wide approaches. Although epigenome-wide association studies are

performed, it should be noted that the Illumina 450k Methylation Beadchip array, which is the most commonly used platform for such studies, does not cover the complete methylome. Although this array covers most CpG-rich promoters, it may miss important phenotypically relevant variations in the methylome. Recent investigations have stressed the importance of DNA methylation at non-promoter and CpG-poor sites (Davies et al., 2012; Hansen et al., 2011; Lister et al., 2009). On a similar note, microarray- based transcriptome analyses are limited to known exons and transcripts (Guffanti et al., 2014). For a whole transcriptome approach, including known and potentially novel ncRNAs, strategies based on next-generation sequencing should be employed, complemented with proper bioinformatic analyses. When compared to proteins, a much larger proportion of the human genome is transcribed into ncRNAs (Amaral et al., 2008). Nevertheless, due to their codon-bias, open reading frames and strong sequence conservation, protein genes can be detected more reliably than ncRNAs (Raasch et al., 2010) Raasch et al. (2010 have therefore proposed a procedure combining multiple ncRNA identification strategies for increased sensitivity, but which is limited in its use for large genomes due to its high computational requirements.

An additional caveat of many published studies on epigenetics is the specificity of the detection techniques used. In the case of DNA modifications this is partly the result of the discovery of novel modifications. DNA methylation can be detected with techniques such as those based on sodium bisulfite sequencing or methyl-ation-sensitive restriction enzyme cleavage. With the discovery of DNA hydroxymethylation, however, it was found that these methods cannot distinguish between methylated and hydroxy-methylated DNA (Ito et al., 2011). By a method of quantitative subtraction, oxidative bisulfate sequencing can be used to identify DNA methylation and hydroxymethylation in parallel. This procedure involves the oxidation of 5-hmC to 5-fC and subsequently to uracil. 5-fC, however, has recently been observed to play a role in epigenetic priming, and thus has an independent function from 5-mC and 5-hmC (Song et al., 2013). Epigenetic priming of 5-fC occurs mainly at poised enhancer sequences and is thought to activate these sites, possibly through the recruitment of transcriptional coactivator EP300. To specifically detect 5-fC, Song et al. (2013) have described two methods, one of which has a single-base resolution and is also based on bisulfite sequencing. To detect 5-fC, this chemically assisted bisulfite sequencing method uses hydroxylamine protection of 5-fC to prevent it from bisulfite-mediated deamination and reduction to 5-hmC. The genomic location of 5-fC can then be determined by comparing hydroxylamine-treated bisulfite sequencing with traditional bisulfite sequencing. Sequencing of one of the various epigenetic DNA modifications should thus not be done without taking into account the other, functionally different, DNA modifications.

Although epigenomic profiling provides valuable gene-specific information, the input material for profiling studies often consists of tissue homogenates. Investigations into the regional and cellular specific effects of diseases illustrate that certain regions and cell types are often differentially affected and using homogenates may thus prevent the proper detection of potentially crucial epigenetic changes that only occur in a limited number of cells (Blalock et al., 2011). Indeed, in the healthy brain region-specific differentially methylated regions can be distinguished (Davies et al., 2012; Ladd-Acosta et al., 2007). Even when using a homogenate of a specific brain region of interest, different cell types could still give interfering read-outs, for instance when considering the widely different

levels of 5-mC and 5-hmC between cerebellar Purkinje and granule cells (Kriaucionis and Heintz, 2009). Although attempts are being made to investigate cell-specific epigenetic profiles these studies are few and are mostly limited to DNA methylation (Guo et al., 2013). Interestingly, Guintivano et al. (2013) have developed a model to correct DNA methylation patterns for cellular heterogeneity in the brain. Additionally, various methods to isolate cells of interest are nowadays available, including density gradients (Whittemore et al., 1993), laser capture microdissection (Suarez-Quian et al., 1999), fluorescence-activated cell sorting (Uchida et al., 2000) and magnetic affinity cell sorting (Yu et al., 2004). These methods have only been sparingly used for epigenetic studies and need to be validated for this purpose. 1t has been suggested that the isolation processes themselves could already influence gene expression (Lunnon and Mill, 2013).

When looking at the potentially high variability of epigenetic markers across different tissue and cell types it may thus be worth investing in novel techniques such as CLARITY (Chung et al., 2013) and fluorescent *in situ* RNA sequencing (Lee et al., 2014) to determine the regional distribution of epigenetic markers and how this may result in regional differences in RNA and protein expression. To complicate matters further, there is increasing evidence that mitochondrial gene expression is also epigenetically regulated, the investigation of which presents a whole new set of challenges (Devall et al., 2014).

For molecular studies of the human brain most investigations depend on post-mortem tissue donated by patients. Apart from possible influences of cell isolation techniques on epigenetics markers, various peri- and post-mortem factors, such as postmortem interval, are known to affect tissue components, including RNA, and which could thus potentially affect epigenetic analyses (Barton et al., 1993; Stan et al., 2006). Such factors are thus most likely to influence ncRNA quality, but are in addition likely to compromise chromatin structure and possibly some DNA modifications. DNA methylation, however, is thought to be relatively stable and thereby represents one of the more reliable epigenetic markers when analyzing post-mortem tissue (Pidsley and Mill, 2011).

Although many epigenetic changes are associated with aging and neurodegeneration, it remains unclear whether they are integral to the aging and neurodegenerative processes, or are an epiphenome-non; the result of other factors such as increased oxidative stress. Investigating causality with respect to epigenetic alterations is challenging in epidemiological studies and especially in studies relying on post-mortem human tissue (Mill and Heijmans, 2013; Pidsley and Mill, 2011). Epigenetic alterations identified through the comparison of epigenetic profiles of post-mortem tissue between disease states and controls could be a combination of disease instigating alterations, but also epigenetic changes that are secondary to disease pathology (Relton and Davey Smith, 2012) as well as changes that are an effect of medication (Boks et al., 2012). Thus, when disease related epigenetic alterations are identified in epigenome-wide association studies, a major issue is to determine whether such changes actually played a role in the etiopathogenesis of the disease. An approach to overcome this hurdle would be to compare post-mortem brain samples of subjects with varying stages of disease severity and including samples from preclinical, possibly prodromal stages of the disease (Lunnon and Mill, 2013). Control samples should be very carefully selected, as for example amyloid plaques, a pathological hallmark of AD, also

occur in subjects without any overt symptoms of the disease. Additionally, comparisons between familial and sporadic cases could help in the identification of causal epigenetic alternations and those that might be the secondary result of genetic mutations. Disease-specific epigenetic changes could in addition be identified by comparing patients with the target disease, with patients with similar diseases, such as frontotemporal lobar degeneration, and dementia with Lewy bodies when looking at AD, PD, and HD.

Alternatively, determining the exact role of epigenetic alterations in progressive, age-related neurodegenerative diseases could be achieved through the longitudinal assessment of the epigenome, starting with individuals in a preclinical stage of the disease. However, assessing the epigenome of living individuals is only achievable in easily accessible tissues, such as peripheral blood. Although robust disease associated epigenetic markers in the blood have great potential as diagnostic and prognostic markers, thorough comparisons between such markers in the blood and brain should be made before their relevance to the disease process can be established. Although many tissue-specific differentially methylated regions related to tissue-specific gene expression can be identified, an important study by Davies et al. (2012) indicates that at least some inter-individual methylomic variation is represented in both brain and blood. Blood sampling could be used to investigate epigenetic markers in the brain in such cases. In addition to DNA methylation, chromatin status and ncRNAs in peripheral mononuclear cells have been identified as potential diagnostic markers for brain-related conditions (Pasinetti et al., 2012; Sharma, 2012). Currently, for AD, PD, and HD, it is largely unknown whether epigenetic alterations relevant to the disease process are present in the blood. Nevertheless, in the case of AD, some changes in the blood transcriptome reflect disease-related changes in the brain (Lunnon et al., 2012).

Animal models could potentially be used to determine the relationships between disease-associated epigenetic markers in the brain and those in blood. Additionally, the epigenetic effects of specific environmental factors, such as medication, can be investigated in isolation from other possible confounding factors (Lunnon and Mill, 2013). Presently, the most used models are transgenic mouse models that express mutated human genes associated with familial disease forms (German and Eisch, 2004). Overexpressing human mutant APP in mice may, however, result in unwanted side-effects as these models will likely also have elevated levels of APP-related products such as C-terminal fragment-β/α and amyloid precursor protein intracellular domain (Saito et al., 2014). As Aβ plays an important role in AD, the increased presence of these additional APP-related products and APP itself may limited the usefulness of such models. Saito et al. (2014) have recently circumvented these problems of APP overexpression by directly manipulating the mouse *App* gene, inducing fAD-related mutations that selectively enhance Aβ production and the Aβ42 to Aβ40 ratio, without affecting APP expression. Nevertheless, there are so far only few animal models of the more common late-onset sporadic forms of AD and PD. Some examples of sAD models are those based on *APOE* (Raber et al., 1998), or specific environmental/pharmacological interventions such as colchicine (Kumar et al., 2007), cholesterol (Sparks et al., 1994), or inhibition of the neuronal insulin receptor (Hoyer et al., 2000). In case of sPD, models based on toxins are mainly used, such as those using the MPTP neurotoxin, which induces a permanent PD-like syndrome (Przedborski and Vila, 2003).

Using rodents to model diseases that occur mainly at the end of the life-span is attractive as they age relatively quickly. Rodent physiology, however, might prove to be too different to allow for the generation of a true model of sporadic late-onset neurodegenerative diseases. Moreover, as there are no natural counterparts of most of these diseases in rodents the successful generation of a true model depends on the available knowledge about the disease, which is in the case of sporadic late-onset neurodegenerative diseases very limited. Therefore, other model organisms may be more suitable, including non-human primates, which can naturally develop limited AD-like pathology (Podlisny et al., 1991), and *in vitro* models. Especially human primary cultures and induced pluripotent stem cells (iPSCs) represent highly promising alternatives to animal models (lsrael et al., 2012; Wojda and Kuznicki, 2013). A number of methods have been described to generate iPSCs from easily accessible fibroblasts that can be differentiated into neurons, or induce neural progenitor-like cells (iNPCs) directly (Qiang et al., 2011; Takahashi et al., 2007; Tian et al., 2013; Verma and Verma, 2011). However, these methods have not been fully optimized yet and involve procedures that induce widespread epigenetic alterations (Kim et al., 2010a).

To map the sequence of events leading to the development of complex diseases fully, epigenomic data should not be investigated in isolation, but should be complemented with other modalities, including genomic, transcriptomic and proteomic data (Meaburn et al., 2010). As such, through the integration of genetic and epigenetic approaches (Mill, 2011), non-coding genetic variation might be found to influence gene expression through epigenetic mechanisms. Such integrated data may also help in determining where in the etiopathogenesis of complex neurodegenerative conditions epigenetic players start to play a role. lntegrated knowledge may additionally help to reveal whether therapeutic strategies targeting epigenetic mechanisms should have a general mode of action, aiming at, for example, DNA methylation at large (Szyf, 2014), or a more targeted approach, for example changing the DNA methylation status of a specific DNA sequence (de Groote et al., 2012).

Concluding, although it is clear that various levels of epigenetic regulation, including DNA and chromatin modifications, and ncRNAs, are affected during aging, AD, PD, and HD, it remains to be elucidated exactly how these epigenetic processes fit into the etiopathogenesis of these disorders and whether they play a causal role. Such knowledge is crucial for the exploration of novel therapeutic avenues, which are sorely needed to combat the devastating neurodegenerative diseases.

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Abbreviations:

3-mA	3-methyladenine
3R-tau	tau with 3 microtubule-binding repeats

3xTg-AD	triple transgenic mouse model of AD
4PBA	4-phenylbutyrate
4E-BP	eukaryotic translation initiation factor 4E-binding protein
4R-tau	tau with 4 microtubule-binding repeats
5-caC	5-carboxylcytosine
5-fC	5-formylcytosine
5-hmC	5- hydroxymethylcytosine
5-hmU	5-hydroxymethyluracil
5-mC	5-methylcytosine
7-mG	7-methylguanine
A	adenosine
Aβ	amyloid β protein
ABCA1	ATP-binding cassette, subfamily A (ABC1), member 1
ABCA7	ATP-binding cassette, subfamily A (ABC1), member 7
ac	acetylation (as in H3K9ac)
AD	Alzheimer's disease
ADAM10	a disintegrin and metalloproteases domain 10
ADAR	adenosine deaminases that act on RNA
ADAT	adenosine deaminases that act on tRNAs
ADP	adenosine diphosphate
AGK2	2-cyano-3-(5-(2,5-dichlorophenyl)-2-furanyl)-N-5-quinolinyl-2-propenamide
AICDA	activation-induced cytidine deaminase
ALKBH5	AlkBalkylation repair homolog 5 (*E. coli*)
Alu	*Arthrobacter luteus* elements
ANK1	ankyrin 1
antagomirs	anti-miRNAs conjugated to cholesterol molecules
APOBEC	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like protein
APOE	apolipoprotein E

APP	amyloid β precursor protein
APP23 mice	transgenic mouse model with a 7-fold overexpression of APPswe
APP/PS1–21 mice	transgenic mice overexpressing APPswe and human PS1 with the L166P mutation, line 21
APPind	human APP with the V717F Indiana mutation
APPswe	human APP isoform 695 with the double KM670/671NL Swedish mutation
ATP	adenosine triphosphate
ATP13A2	ATPase type 13A2
BACE	β-secretase
BACE1-AS	BACE1-antisense
BAF	Brg1/hBrm associated factor
BAG2	B-cell chronic lymphocytic leukemia (CLL)/lymphoma 2 (BCL2)-associated athanogene 2
BBB	blood–brain barrier
BC200	brain cytoplasmic RNA 200
BDNF	brain-derived neurotrophic factor
BLCAP	bladder cancer associated protein
C	cytosine
C57BL/6 mice	C57 black 6 inbred mouse strain
CA	cornu ammonis
CAG	cytosine-adenine-guanine
cAMP	cyclic adenosine monophosphate
caspase	cysteine-dependent aspartate-directed protease
CBP	cAMP response element-binding protein binding protein
CD2AP	cluster of differentiation 2-associated protein
CD33	cluster of differentiation 33
CDK2AP	cyclin-dependent kinase 2 associated protein
C. elegans	*Caenorhabditis elegans*

CHD	chromodomain, helicase, DNA binding
CHRM1	muscarinic acetylcholine receptor 1
CLU	clusterin
COG3	golgi complex subunit 3
COX-2	cyclooxygenase-2
CpG	cytosine-phosphate-guanine
CR1	complement component receptor 1
CREB	cAMP response element-binding protein
CREBBP	CREB binding protein
CYFIP2	cytoplasmic FMR1-interacting protein 2
DAC	5-aza-2$^{'}$-deoxycytidine (decitabine)
DAF-16/FOXO	dauer 16/forkhead box O
DG	dentate gyrus
DNMT	DNA methyltransferase
DNMT3L	DNMT3-like
DP	differentiation regulated transcription factor protein
dsRNA	small double-stranded RNA
E1A	adenovirus early region 1A
E2F1	E2F transcription factor 1
EC	entorhinal cortex
EDARADD	ectodysplasin-A receptor-associated death domain
EID1	EP300 interacting inhibitor of differentiation 1
EP300	E1A-binding protein P300
ERK1	extracellular signal-regulated kinase 1
eRNA	enhancer RNA
EZH	enhancer of zeste homolog (*Drosophila*)
f6A	N6-formyladenosine
fAD	familial AD
FANCC	Fanconi anemia, complementation group C

FGF20	fibroblast growth factor 20
FLNA	filamin1
fPD	familial PD
FRM-0334	Forum Pharmaceuticals compound 0334
FTO	fat mass and obesity-associated protein
GABRA2	gamma-aminobutyric acid receptor subunit alpha 2
GAD-3	gastrulation defective 3
GADD45	growth arrest and DNA damage 45
GCF	granulocyte chemotactic factor
GCN	general control of amino acid synthesis
GDNF	glial cell line-derived neurotrophic factor
GFAP	glial fibrillary acidic protein
GluR	glutamate receptor
GPNMB	glycoprotein (transmembrane) nmb
GR1	glucocorticoid receptor 1
GSK-3β	glycogen synthase kinase 3β
His	histidine
H	histone protein, always followed by a number (for example, H3 in H3K4)
H2AX	histone protein H2A member X
HAT	histone acetyltransferase
Hcy	homocysteine
HD	Huntington's disease
HDAC	histone deacetylase
HDACI	HDAC inhibitor
***Hdh*$^{Q150/Q7}$ mice**	transgenic mouse model expressing one mutant HTT copy with 150 CAG repeats and a normal HTT copy with 7 CAG repeats
HEK293	human embryonic kidney 293
HKDM	histone lysine demethylase

HKMT	histone lysine methyltransferase
hm6A	N6-hydroxymethyladenosine
HRDM	histone arginine demethylase
HSP90	heat shock protein 90
HTT	Huntingtin
HuR	human antigen R
I	inosine
IBA1	ionized calcium-binding adapter molecule 1
IGF1	insulin-like growth factor 1
IKK	inhibitor of kappaB kinase
INO	inositol requiring 80
iNPC	induced neural progenitor-like cell
iPSC	induced pluripotent stem cell
IRAK1	interleukin-1 receptor-associated kinase 1
ISWI	imitation SWI
JMJD	jumonji domain containing
K	lysine (as in H3K9ac)
KAT	lysine acetyltransferase
Kcnal	potassium channel gene
L-DOPA	L-3,4-dihydroxy-phenylalanine
lincRNA	large intergenic non-coding RNA
LINE-1	long interspersed element 1
lncRNA	long ncRNA
LRRK2	leucine-rich repeat kinase 2
m1A	N1-methyladenosin
m1G	N1-methylguanine
m6A	N6-methyladenosine
MALAT	metastasis associated lung adenocarcinoma transcript 1
MAP2	microtubule-associated protein 2

MAPK	mitogen-activated protein kinase
MAPT	microtubule-associated protein tau
MAT	methionine adenosyltransferase
MBD	methyl-CpG-binding domain protein
me	methylation (as in H3K4me3)
MeCP	methyl CpG-binding protein
MetH	methionine synthase
METTL	methyltransferase-like protein
miR	microRNA
miRNA	microRNA
MPP+	1-methyl-4-phenyl-pyridinium ion
MPTP	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
mRNA	messenger RNA
MS4A4E	membrane-spanning 4-domains, subfamily A, member 4E
MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A
MSK	mitogen- and stress-activated protein kinase
mtDNA	mitochondrial DNA
mtDNMT1	mitochondrial DNMT1
MTHF	methylenetetrahydrofolate
MTHFR	MTHF reductase
N171–82Q mice	transgenic mouse model expressing the first 171 amino acids of HTT with 82 CAG repeats at a relatively low steady-state level
N2a	Neuro-2a
NAD	nicotine adenine dinucleotide
NAT	natural antisense transcript
ncRNA	non-coding RNA
NDM29	neuroblastoma differentiation marker 29
NEAT	nuclear paraspleckle assembly transcript
NeuN	Neuronal nuclei

NF-κB	nuclear transcription factor kappa B
NFT	neurofibrillary tangle
NMDA	*N*-methyl-D-aspartic acid
NPTX	neuronal pentraxin
NuRD	nucleosome remodeling and histone deacetylase
p	phosphorylation (as in H3S10p)
P300	E1A-binding protein P300
PAR	promoter-associated RNA
PARK16	Parkinson disease 16
PASR	promoter-associated short RNAs
P-bodies	processing bodies
PCAF	P300/CBP-associated factor
PcG	Polycomb-group
PD	Parkinson's disease
PDAPP mice	transgenic mice overexpressing APPind
PGC1-α	peroxisome proliferator receptor gamma coactivator-1 alpha
PICALM	phosphatidylinositol binding clathrin assembly protein
piRNA	piwi-interacting RNA
PKCδ	protein kinase Cδ
PP2A	protein phosphatase 2A
PPT	protein phosphatase
PRC1	polycomb repressive complex member Bmi1
PRC2	polycomb repressive complex member EZH2
pre-miRNA	precursor miRNA
PRMT	protein arginine methyltransferase
PROMPTS	promoter upstream transcripts
PS	presenilin
PS1ΔE9	human PS1 deleted in exon 9 mutation

PSD95	postsynaptic density protein 95
PTBP2	polypyrimidine tract binding protein 2
Psid-ps1	phosphatidylserine decarboxylase- pseudogene 1
R	arginine (as in H3R2me)
R6/2 mice	transgenic mice overexpressing exon 1 of human *HTT* with an expanded CAG repeat length
RAN	rat sarcoma (Ras)-related nuclear protein
rasiRNA	repeat-associated small interfering RNA
RISC	RNA-induced silencing complex
RNAi	RNA interference
RNAPII	RNA polymerase II
RNAPIII	RNA polymerase III
ROS	reactive oxygen species
rRNA	ribosomal RNA
S	serine (as inH3S10p)
S100A2	S100 calcium-binding protein A2
sAD	sporadic AD
SAH	S-adenosylhomocysteine
SAHA	suberoylanilide hydroxamic acid
SAHF	senescence-associated heterochromatin foci
SAHH	SAH hydrolase
SAM	S-adenosylmethionine
SAMP8	senescence-accelerated prone mouse 8
SAT-α	satellite-α
SB	sodium butyrate
scaRNA	small Cajal body-specific RNA
sdRNA	snoRNA-derived small RNA
SETDB1	*Drosophila* Su(var)3–9 and enhancer of zeste proteins (SET) domain, bifurcated 1
SHMT	serine hydroxymethyltransferase

shRNA	short hairpin RNA
siRNA	small interfering RNA
smRNA	small modulatory RNA
SIRT	sirtuin
SNCA	synuclein alpha
sncRNA	small ncRNAs
snRNA	small nuclear RNA
snoRNA	small nucleolar RNA
SNP	single nucleotide polymorphism
SORBS3	sorbin and v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog homology 3 domain containing 3
SP	specificity factor
sPD	sporadic PD
spliRNA	splice junction-associated RNA
SPT	serine palmitoyltransferase
ss-siRNA	single-stranded siRNA
STX1B	syntaxin 1B
SUV39H	suppressor of variegation 3–9 homologue
SWI/SNF	switching defective/sucrose nonfermenting
T	threonine
TACE	TNF-α converting enzyme
TE	transposable element
TET	ten-eleven translocation
Tg19959 mice	transgenic mice overexpressing a combination of APPswe and APPind
Tg2576 mice	transgenic mice overexpressing APPswe
THF	tetrahydrofolate
TIP60	human immunodeficiency virus type 1 transactivating protein interactive protein
tiRNA	transcription initiation RNA

TNF-α	tumor necrosis factor alpha
TNKS2	tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase 2
TOM1L	target of myb1 (chicken)-like
TREM2	triggering receptor expressed on myeloid cells 2
TRF1	telomeric repeat binding factor 1
tRNA	transfer RNA
TSA	trichostatin A
TSSa-RNA	transcription start site-associated RNA
U	uracil
UCHL1	ubiquitin carboxy-terminal hydrolase L1
UTR	untranslated region
VPA	valproate/valproic acid
WTAP	Wilm's tumor-associated protein
Y	tyrosine
YTHDF	YTH domain family

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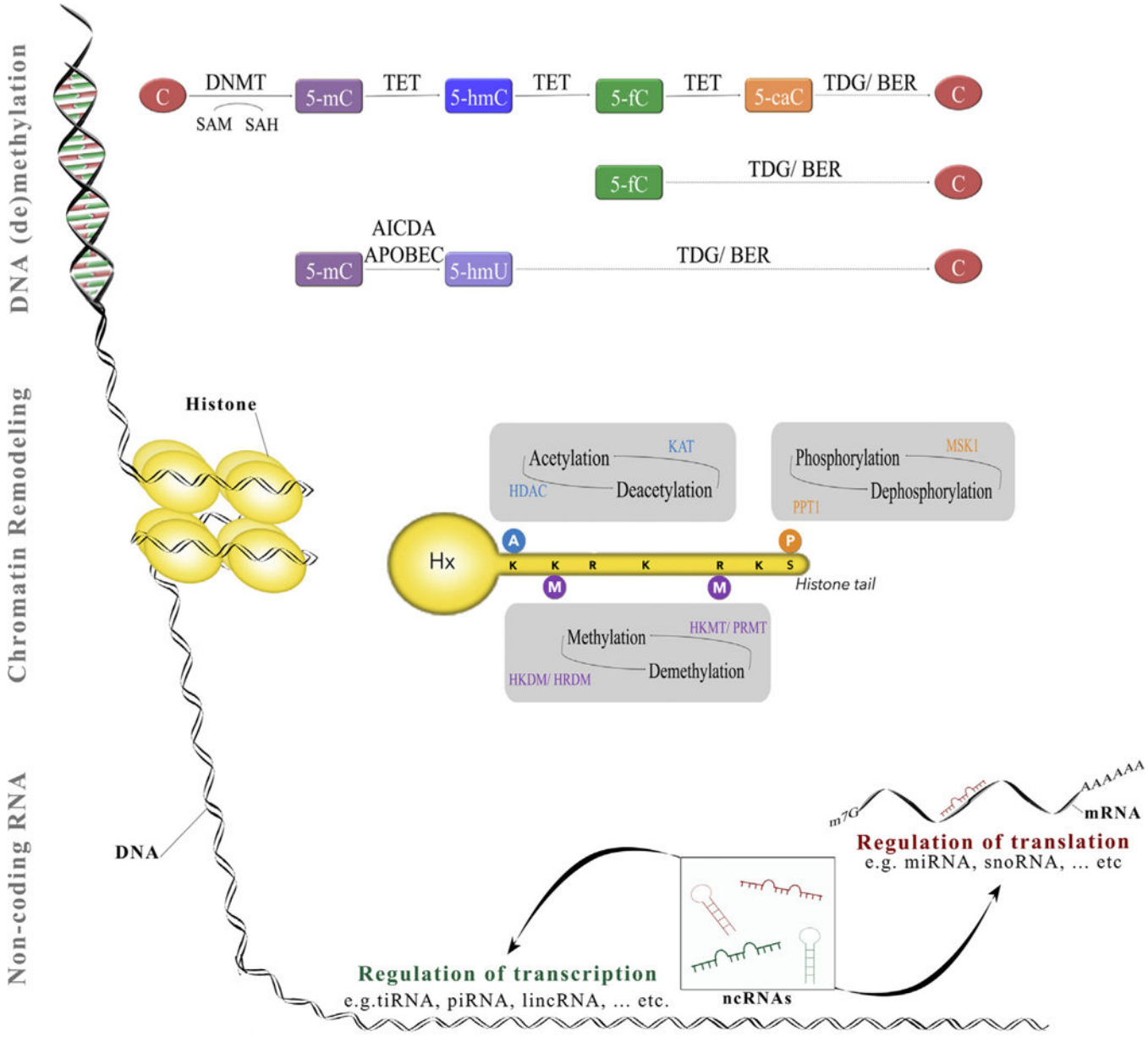

Fig. 1.

The three levels of epigenetic regulation. The upper section summarizes DNA methylation and demethylation processes, the middle section summarizes the most important chromatin remodeling processes, and the bottom section summarizes non-coding RNA regulation. Abbreviations: 5-caC, 5-carboxylcytosine; 5-fC, 5-formylcytosine; 5-hmC, 5-hydroxymethylcytosine; 5-hmU, 5-hydroxymethyluracil; 5-mC, 5-methylcytosine; A, acetyl modification; AICDA, activation-induced cytidine deaminase; APOBEC, apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like protein; BER, base excision repair; C, cytosine; DNMT, DNA methyltransferase; H, histone; HDAC, histone deacetylase; HKDM, histone lysine demethylase; HKMT, histone lysine methyltransferase; HRDM, histone arginine demethylase; K, lysine; KAT, lysine acetyltransferase; lincRNA, large intergenic

non-coding RNA; M, methyl modification; miRNA, micro RNA; MSK1, mitogen- and stress-activated protein kinase 1; ncRNA, non-coding RNA; P, phosphate modification; piRNA, piwi-interacting RNA; PPT1, protein phosphatase 1; PRMT, protein arginine methyltransferase; R, arginine; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; snoRNA, small nucleolar RNA; TET, ten-eleven translocation; TDG, thymine DNA glycosylase; tiRNA, transcription initiation RNA; tRNA, transfer RNA.

Table 1

Epigenetic dysregulation in aging: DNA (de)methylation.

Gene	Regulation	Epigenetic modification	Observed in	Sample size	Approach	Methods	Reference
GABRA2	↑	Methylation	Human	125	Targeted	BS, Methylight PCR	Siegmund et al., 2007
GAD1	↑	(promoter region)			(50 loci)		
HOXA1	↑						
NEUROD1	↑						
NEUROD2	↑						
PGR	↑						
STK11	↑						
SYK	↑						
IFN-γ	↑↑			784	Targeted (9 loci)	BS	Madrigano et al., 2012
RUNX3	↑↑			26	Targeted (7 loci)	BS, MS-PCR	So et al., 2006
ERß	↑↑			7–10	Targeted (1 locus)	BS, MS-PCR, Pyrosequencing, ChIP	Westberry et al., 2011
APP	↓	Methylation	Human	16	Targeted	BS	Tohgi et al., 1999
GCF	↓	Methylation (binding sites)			(18 loci)		
SP1	↑↑	Methylation (interaction sites)					

Protein/(Hydroxy) Methylated base	Regulation	Modification in	Observed in	Sample size	Methods	Reference
DNMT1	↓	Expression	Fibroblasts (fetal lung)	-	DNMT assay ChIP, RT-PCR	Lopatina et al., 2002; Pan et al., 2013
DNMT3a2	↓		Mice (12 month old)	15	IHC	Oliveira et al., 2012
DNMT3a	↑		Mouse Hippocampus	48	IHC	Chouliaras et al., 2011a
5-mC	↑		(DG, CA1–2 and 3)			Chouliaras et al., 2011b
5-hmC	↑			4	HPLC	Munzel et al., 2010; Song et al., 2011b

↑ indicates increased expression levels and

↓ indicates decreased expression levels.

Abbreviations: 5-hmC, 5-hydroxymethylcytosine; 5-mC, 5-methylcytosine; *APP*, amyloid β precursor protein; CA, cornu ammonis; DG, dentate gyrus; DNMT, DNA methyltransferase; *ER*, estrogen receptor; *GABRA2*, γ-aminobutyric acid receptor subunit alpha-2; *GAD1*, glutamate decarboxylase 1; *GCF*, granulocyte chemotactic factor; *HOXA1*, homeobox protein A1; *IFN-γ*, interferon γ; *NEUROD*, neurogenic differentiation factor; *PGR*, progesterone receptor; *RUNX3*, runt-related transcription factor 3; *SP1*, specificity factor 1; *STK11*, serine/threonine kinase 11; *SYK*, spleen tyrosine kinase; BS, bisulfite sequencing; PCR, polymerase chain reaction; MS-PCR, methylation specific-PCR; RT-PCR, real time-PCR; ChIP; chromatin immunoprecipitation; IHC, immunohistochemistry; HPLC: high-performance liquid chromatography.

Table 2

Epigenetic dysregulation in aging: chromatin remodeling.

Chromatin remodeling target	Regulation	Epigenetic modification	Observed in	Sample size	Methods	Reference
H3	↓	Methylation	Rat cerebral cortex	12–18	WB	Thakur and Kanungo, 1981
H3K9	↓	Acetylation	Rat (liver)	N.S.	WB	Kawakami et al., 2009
H3K27	↑	Methylation	SAMP8 mice	6	Nano-LC, MALDI-TOF/	Wang et al., 2010a
H3K36	↓	Tri-Methylation			TOF MS, WB, IHC	
H3K79	↑	Tri-/Methylation				
H3S10p	↑	Phosphorylation	Rat cerebral cortex	N.S.	WB	Kawakami et al., 2009
H4	↓	Methylation	Rat cerebral cortex	12–18	WB	Thakur and Kanungo, 1981
		Monoacetylation				Pina et al., 1988
H4K12	≠	Acetylation	16-months old mice	12	ChIP Seq-PCR,	Peleg et al., 2010
					HAT/HDAC assay	
H4K16	↑	Acetylation	SIRT-1 transfected cell lines	–	ChiP	Pruitt et al., 2006
H4K20	↓	Methylation	SAMP8 mice	6	Nano-LC, MALDI-TOF/TOF MS, WB, IHC	Wang et al., 2010a
H4K20	↑	Tri-methylation	Rats (Kidney, Liver)	N.S.	HPLC	Sarg et al., 2002

Enzyme	Regulation	Modification in	Observed in	Sample size	Methods	Reference
HDAC2	↑	Expression	SOD mice	48	IHC	Chouliaras et al., 2013b
SIRT1	↓		Rat Brain, Senescent cells	24–45,–	WB, IHC, RT-PCR	Quintas et al., 2012; Sasaki et al.,2006; Sommer et al., 2006
PRC1, PRC2	↑		hAD-MSCs, hUCB-MSCs	–	ICC, WB, RT-PCR	Jung et al., 2010

↑indicates increased expression levels,

↓indicates decreased expression levels, and

≠indicates altered expression, not further specified.

Abbreviations: H, histone; HDAC, histone deacetylase; JMJD3; jumonji domain containing 3, K, lysine; p, phosphate modification; PRC; polycomb repressive complex, S, serine; SAMP, senescence-accelerated prone mouse 8; SIRT, sirtuin; SOD, copper-zinc superoxide dismutase 1; hAD-MSC; human adipose tissue-derived mesenchymal stem cells, hUCB-MSC; human umbilical cord blood-derived MSCs N.S., not specified; WB, Western blot; Nano-LC, nano liquid chromatography; MALDI-TOF, matrix assisted laser desorption/ionization time-of-flight; TOF MS, time-of-flight mass spectrometry; ICC; immunocytochemistry, IHC, immunohistochemistry; ChIP Seq, chromatin immunoprecipitation sequencing; HPLC: high-performance liquid chromatography; RT-PCR, real time-PCR.

Table 3

Epigenetic dysregulation in aging: non-coding RNAs.

Regulation	ncRNA	Observed in	Sample size	Approach	Methods	Reference
≠	miRNA lin-4	*C. elegans*	N.S.	Targeted	RFLP mapping, Southern Blot, Northern Blot	Lee et al., 1993
↑	miR-34	C57BL/6J mice	N.S.	Genome-wide	microRNA microarray	Maes et al., 2008
↑	miR-93					
↑	miR-2l4					
↑	miR-669c					
↑	miR-709					
↓	miR-24	Human (blood)	10-14	Targeted	miRNome miRNA profiling	Noren Hooten
↓	miR-103			(800 miRNAs)		et al., 2010
↓	miR-107					
↓	miR-l28					
↓	miR-130a					
↓	miR-155					
↓	miR-221					
↓	miR-496					
↓	miR-1538					
≠	miR-29	C57BL/6J mice and human	Mice: 4; Human: l09	Genome-wide	microRNA microarray	Boon et al., 2011
	miR-34a	$Sirt1^{+/-}$, $Ku80^{-/-}$ and $miR\text{-}34a^{-/-}$ mice	≥4	Targeted (570 miRNAs)	PCR, lSH	Boon et al., 2013
	miR-l46a	HUVEC	-	Genome-wide	microRNA microarray	Vasa-Nicotera et al., 2011
		HUVEC, HAEC, HCAEC	-	Targeted (367 miRNAs)	microRNA microarray, PCR	Olivieri et al., 2013
	miR-217	HUVEC, HAEC, HCAEC	-	Targeted (10 miRNAs)	microRNA microarray, PCR, Northern Blot	Menghini et al., 2009
↓	miR-17	Human cell lines	-	Targeted (599 miRNAs)	microRNA microarray, PCR	Hackl et al., 2010
↓	miR-l9c					
↓	miR-20a					
↓	miR-106a					
↓	miR-l46a	HUVEC	-	Genome-wide	microRNA microarray	Vasa-Nicotera et al., 2011
↑	miR-26a					

Regulation	ncRNA	Observed in	Sample size	Approach	Methods	Reference
↑	miR-181a					
↑	miR-221					
↑	miR-200b					
↑	miR-200c	Human cell lines	-	Targeted (1 miRNA)	WB	Magenta et al., 2011
↑	miR-144	Human (Cortex and Cerebellum) Chimpanzee Macaque monkey	8 4 5	Genome-wide	microRNA microarray	Persengiev et al., 2011
≠	miR-l6	SAMP8 mouse	N.S.	Targeted (7 miRNAs)	PCR, ISH, IHC	Liu et al., 2012b

↑ indicates increased expression levels,

↓ indicates decreased expression levels, and

≠ indicates altered expression, not further specified.

Abbreviations: C57BL/6J mice, C57 black 6 inbred mouse strain; *C. elegans, Caenorhabditis elegans*; miR, micro RNA; SAMP8 mouse, senescence-accelerated prone mouse 8; HUVEC, human umbilical vein endothelial cells; HAEC, human aortic endothelial cells; HCAEC, human coronary artery endothelial cells; N.S., not specified; RFLP, Restriction fragment length polymorphism; PCR, polymerase chain reaction; ISH: *in situ* hybridization; WB, Western blot; IHC, immunohistochemistry.

Table 4

Epigenetic dysregulation in Alzheimer's disease: DNA (de)methylation.

Gene	Regulation	Epigenetic modification	Observed in	Sample size	Approach	Methods	Reference
APP	↓	Methylation (APP gene promoter region)	AD patients	16 1	Targeted (18 loci) Targeted (1 locus)	BS Southern Blot	Tohgi et al., 1999 West et al., 1995
	≠	Methylation (CpG sites in and close to the promoter region)	AD patients	AD Stages I to II (n=17), AD Stages III to IV (n=15), AD Stages V to VI (n=12)	Targeted (6 loci)	BS	Barrachina and Ferrer, 2009, Fuso et al., 2005
PS	≠	Methylation (CpG sites in and close to the promoter region)	SK-N-SH and SK-N-BE cell lines	-	Targeted (5 loci)	HPLC/Nucleic acid analysis	Fuso et al., 2005
BACE	≠	Methylation (CpG sites in and close to the promoter region)	SK-N-SH and SK-N-BE cell lines	-	Targeted (5 loci)	HPLC/Nucleic acid analysis	
	↓	Expression due to folate deptivation-induced global DNA hypomethylation	SK-N-SH and SK-N-BE cell lines	-	Targeted (5 loci)	HPLC/Nucleic acid analysis	
PS1	≠	Methylation (promoter region)	AD patients	24	Targeted (12 loci)	BS	Wang et al., 2008b
	↑	Expression due to folate deptivation -induced global DNA hypomethylation	SK-N-SH and SK-N-BE cell lines	-	Targeted (5 loci)	HPLC/Nucleic acid analysis	Fuso et al., 2005
APOE	≠	Methylation (promoter region)	AD patients	24	Targeted (12 loci)	BS, MALDI	Wang et al., 2008b
MTHFR	≠	Methylation (promoter region)	AD patients (prefrontal cortex, peripheral lymphocytes)	24	Targeted (12 loci)	BS	
	↑	Methylation					
DNMT1	≠	Methylation (promoter region)	AD patients	24	Targeted (12 loci)	BS	
PP2A	↓	Inhibition of methylation due to increase of Hγ levels	N2a cells, AD mouse model (APP/PS1)	-, N.S.	Targeted (1 locus)	IHC	Zhou et al., 2008
SORBS3 *S100A2*	↑ ↓	Methylation	AD patients	18	Targeted (50 loci)	BS, MS-PCR	Siegmund et al., 2007
NEP	↑	Methylation	CEC cell line exposed to Aβ	-	Targeted (1 locus)	MS-PCR	Chen et al., 2009
SP1	↑	Methylation (activator binding site)	Human (cerebral cortex)	16	Targeted (18 loci)	BS	Tohgi et al., 1999

Gene	Regulation	Epigenetic modification	Observed in	Sample size	Approach	Methods	Reference
GCF	↓	Methylation (repressor binding site)	Human (cerebral cortex)	16	Targeted (18 loci)	BS	Tohgi et al., 1999
APOE	↑	Methylation (CpG island located at the 3' end)	AD patients (postmortem)	24	Targeted (12 loci)	BS	Wang et al., 2008b
COX-2	↓	Methylation (promoter region)	AD patients (frontal cortex)	10	Targeted (8 loci)	Promoter region-specific CpG methylation assay	Rao et al., 2012
NF-kB	↓	Methylation (promoter region)					
BDNF	↑	Methylation (promoter region)					
CREB	↑	Methylation (promoter region)					
LINE-1	↑	Methylation	AD patients (blood)	43	Targeted (3 loci)	BS, PCR, pyrosequencing	Bollati et al., 2011
ANK1	↑↑	Methylation	AD patients (EC, superior temporal cortex, PFC)	62, 122, 144	Genome-wide	450K BeadChip	Lunnon et al., 2014

Protein/(hydroxy) methylated base	Regulation	Modification in	Observed in	Sample size	Methods	Reference
5-hmC	↓	Expression	AD mouse model (APP/PS1; hippocampus)	10	IHC	Chouliaras et al., 2013a
			AD patients (EC, cerebellum)	10	IHC	Chouliaras et al., 2013a
5-mC, 5-hmC	↑		AD patients (MGF, MTG, hippocampus)	7 late-stage AD	IHC	Bradley-Whitman and
				5 preclinical AD		Lovell, 2013
				13 MGF 29 MTG	IHC	Coppieters et al., 2014
5-fC, 5-caC	↓		AD patients (hippocampus)	7 late-stage AD	IHC	Bradley-Whitman and
				5 preclinical AD		Lovell, 2013
DNMT3a	↓		AD mouse model (APP/PS1; hippocampus)	10	IHC	Chouliaras et al., 2013a
			AD patients	10	IHC	Chouliaras et al., 2013a
DNMT3a2	↓		Mice (12 months old)	15	IHC	Oliveira et al., 2012
TET1	↑		AD patients (hippocampus)	7 late-stage AD	IHC	Bradley-Whitman and
				5 preclinical AD		Lovell, 2013

↑ indicates increased expression levels,

↓ indicates decreased expression levels, and

≠ indicates altered expression, not further specified.

Abbreviations: 450K BeadChip, Illumina Infinium HumanMethylation 450K BeadChip; 5-caC, 5-carboxylcytosine; 5-fC, 5-formylcytosine; 5-hmC, 5-hydroxymethylcytosine; 5-mC, 5-methylcytosine; AD, Alzheimer's disease; *APOE,* apolipoprotein E; *APP,* amyloid β precursor protein; *BACE,* β-secretase; *BDNF,* brain-derived neurotrophic factor; CEC, cerebral endothelial cell, *COX-2,* cyclooxygenase-2; CpG, cytosine-phosphate-guanine; *CREB,* cyclic adenosine monophosphate response element-bindingprotein; *DNMT,* DNA methyltransferase; EC, entorhinal cortex; *GCF,* granulocyte chemotactic factor; *LINE-1,*longinterspersed element 1; *ANK1,*ankyrin 1; MALDI, matrix-assisted laserdesorption/ionization; MFG, middle frontal gyrus; MTG, middle temporal gyrus; *MTHFR,* 5,10-methylenetetrahydrofolate reductase; *NEP,* neprilysin; *NF-κB,* nuclear transcription factor kappa B; *PP2A,* protein phosphatase 2A; *PS,* presenilin; *S100A2,* S100 calcium-binding protein A2; *SORBS3,* sorbin and v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog homology 3 domain containing3; SP1, specificity factor 1; TET1, ten-eleven translocation 1; SK-N-SH, SK-N-BE, human neuroblastoma cell lines; N2A, neuro-2a cell line; CEC, circulating endothelial cells; N.S., not specified; BS, bisulfite sequencing; HPLC: high-performance liquid chromatography; IHC, immunohistochemistry; MS-PCR: methylation specific-PCR.

Table 5

Epigenetic dysregulation in Parkinson's disease: DNA (de)methylation.

Gene	Regulation	Epigenetic modification	Observed in	Sample size	Approach	Methods	Reference
SNCA	↓	Methylation	sPD patients (SN, Putamen, Cortex)	6, 14	Targeted (1 locus)	BS	Jowaed et al., 2010
				11	Targeted (1 locus)	BS	Matsumoto et al., 2010
PARK16	≠	Methylation	PD patients	12.386	Genome-wide	methQTL	Plagnol et al., 2011
GPNMB	≠	Methylation	PD patients				
STX1B	≠	Methylation	PD patients				
FANCC	≠	Methylation	PD patients	30	Genome-wide	Infinium	Moore et al., 2014
TNKS2							

↓ indicates decreased expression levels and

≠ indicates altered expression, not further specified.

Abbreviations: FANCC, fanconi anemia group C; *GPNMB,* glycoprotein (transmembrane) nmb; *PARK16,* Parkinson disease 16; (s)PD, (sporadic) Parkinson's disease; SN, substantia nigra; *SNCA,* synuclein alpha; sPD, sporadic PD; *STX1B,* syntaxin 1B; TNKS2, tankyrase 2; BS, bisulfite sequencing; GWA: genome-wide association; methQTL, methylation quantitative trait locusc.

Table 6

Epigenetic dysregulation in Huntington's disease: DNA (de)methylation.

Gene	Regulation	Epigenetic modification	Observed in	Sample size	Approach	Methods	Reference
Ap-1	↑↑	Methylation of	Mouse striatal neurons	-	Targeted	RRBS, MeDIP-Seq,	Ng et al., 2013
Sox2	↑↑	promoter region	overexpressing HTT		(10 loci)	ChIP-Seq Assay	
Pax6	↑↑						
Nes	↑↑						
	≠	7-mG DNA and RNA methylation	HD mouse models (R6/2, CAG140 Kl mice) HD patients	10 N.S.		ECD/HPLC	Thomas et al., 2013

↑ indicates increased expression levels and

≠ indicates altered expression, not further specified.

Abbreviations: 7-mG, 7-methylguanine; *Ap*−1, activator protein 1; CAG140 KI mice, transgenic mouse model overexpressing human *HTT* with 140 cytosine-adenine-guanine repeats; HD, Huntington's disease; HTT, Huntingtin; *Nes*, nestin; *Pax6*, paired box 6; R6/2 mice, transgenic mouse model overexpressing exon 1 of human *HTT* with an expanded cytosine-adenine-guanine repeat length; *Sox2*, sex-determining region Y (SRY)-box 2; UTR, untranslated region; N.S., not specified; RRBS, reduced representation bisulfite sequencing; MeDIP-Seq, methylated DNA immunoprecipitation sequencing; ECD, electrochemical detection; HPLC, high-performance liquid chromatography; ChIP-Seq, chromatin immunoprecipitation sequencing.

Table 7

Epigenetic dysregulation in Alzheimer's disease: chromatin remodeling.

Chromatin Remodelling Target	Regulation	Epigenetic modification	Observed in	Sample size	Methods	Reference
Histones (Globally)	↓	Acetylation	AD patients	5–6	Targeted Proteomics assay	Zhang et al., 2012
H3	↑	Acetylation (BACE1 promoter region)	AD patients	31	FAIRE/ChIP	Marques et al., 2012
		Acetylation	AD mouse model (3xTg-AD mice; 4 months of age)	6	IF	Walker et al., 2013
			AD mouse model (Tg2576 mice; PFC)	N.S.	N.S.	Lithner et al., 2009
	↑	Phosphorylation	AD mouse model (Tg2576 mice; PFC)			
	↓		AD patients (Hippocampus)			
	↑	Methylation	AD mouse model (Tg2576 mice; PFC)			
	↓	Methylation	AD mouse model (Tg2576 mice; Striatum)			
H3K9	↑	Tri-methylation	AD monozygotic twin (temporal cortex and hippocampus)	1	IHC	Ryu et al., 2008
H4	↓	Acetylation	AD mouse model (APP/PS1)	4	WB	Francis et al., 2009
	↑	Acetylation	AD mouse model (3xTg-AD mice; 4 months of age)	6	IF	Walker et al., 2013
	↑	Acetylation	AD mouse model (Tg2576 mice; CA1)	N.S.	N.S.	Lithner et al., 2009
H2AX (S1S9)	↑	Phoshorylation	AD patients (Hippocampus and Astrocytes)	13	ICC	Myung et al., 2008
HDAC2	↑	Expression	AD mouse models (CK-p25, 5xFAD, Cdk5cKO mice; Hippocampus and PFC) AD patients (Hippocampus and EC)	6–9 4–8	IHC, WB, Co-IP, ChIP, PCR	Graff et al., 2012
H2BKS	↓	Acetylation	AD mouse models (CK-p25, 5xFAD, Cdk5cKO mice; Hippocampus and PFC)	6–9		
HSKl4	↓	Acetylation	AD mouse models (CK-p25,	6–9		
H4KS	↓	Acetylation	5xFAD, Cdk5cKO mice; Hippocampus and PFC)			
H4Kl2	↓	Acetylation	Mice (16 month old)	4–5	ChIP, PCR, HAT/HDAC assay	Peleg et al., 2010

Chromatin Remodelling Target	Regulation	Epigenetic modification	Observed in	Sample size	Methods	Reference
SlRT1	↓	Expression	AD patients (parietal cortex)	l9	WB, ISH	Julien et al., 2009
	↑	Expression	AD mouse model (3xTg-AD mice)	N.S.		

↑indicates increased expression levels,

↓indicates decreased expression levels, and

≠indicates altered expression, not further specified.

Abbreviations: 3xTg-AD mice, triple transgenic mouse model of AD; 5xFAD, transgenic mouse model overexpressing mutant human APP (695) with the Swedish (K670N and M671L), Florida (I716V), and London (V717I) mutations, and mutant human presenilin 1 with the M146L and L286V familial AD mutations; AD, Alzheimer's disease; *BACE1*, β-secretase 1; CA, cornu ammonis; Cdk5 KO mice; cyclin-dependent kinase 5 knock-out mouse model; CK-p25 mice, transgenic mouse model overexpressing p25 under control of an inducible calcium/ calmodulin-dependent protein kinase II α promoter; EC, entorhinal cortex; H, histone; HDAC, histone deacetylase; K, lysine; PFC, prefrontal cortex; S, serine; SIRT, sirtuin; Tg2576 mice, transgenic mice overexpressing human APP isoform 695 with the double KM670/671NL Swedish mutation; N.S., not specified; FAIRE, formaldehyde-assisted isolation of regulation; IF: immunofluorescence; ICC, immunocytochemistry; Co-IP, protein complex immunoprecipitation; IHC, immunohistochemistry; ChIP, chromatin immunoprecipitation; PCR, polymerase chain reaction; WB, Western blot; ISH: *in situ* hybridization.

Table 8

Epigenetic dysregulation in Parkinson's disease: chromatin remodeling.

Chromatin remodeling target	Regulation	Epigenetic modification	Observed in	Sample size	Methods	Reference
Histones (Globally)	↑	Deacetylation via binding of α-synuclein to PGC1-α promoter element	PD patients (SN)	16	GWES	Zheng et al., 2010
H3	↓	Acetylation via the interaction of α-synuclein with SIRT1	α-Synuclein-transfected SH-SY5Y cells PD *Drosophila* model	- N.S.	WB WB	Kontopoulos et al., 2006
	↑	Acetylation due to Paraquat and/or Dieldrin exposure	N27 dopaminergic cells	-	WB	Song et al., 2010, 2011a
H3K4	↓	Tri-methylation due to MPTP-induced toxicity	Mice (striatum) Macaque monkeys (striatum)	5 18	WB	Nicholas et al., 2008
H4	↑	Acetylation due to Dieldrin exposure	N27 dopaminergic cells	-	WB	Song et al., 2011a
Heterozygous A53T SNCA mutation	≠	Epigenetically silenced affected allele via histone modifications	fPD patient	1	PCR	Voutsinas et al., 2010

↑ indicates increased expression levels,

↓ indicates decreased expression levels, and

≠ indicates a genetic mutation affecting epigenetic regulation.

Abbreviations: fPD, familial PD; H, histone; K, lysine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; PGC1-α, peroxisome proliferator receptor gamma coactivator-1 alpha; SH-SY5Y cells, human neuroblastoma cell line; SIRT1, sirtuin 1; SN, substantia nigra; *SNCA*, synuclein alpha; N.S., not specified; GWES, genome-wide epistasis studies; WB, Western blot; PCR, polymerase chain reaction.

Table 9

Epigenetic dysregulation in Huntington's disease: chromatin remodeling.

Chromatin remodeling target	Regulation	Epigenetic modification	Observed in	Sample size	Methods	Reference
Histones (Globally)	≠	Acetylation	HD mouse model (R6/2 mouse model)	N.S.	WB	Ferrante et al., 2004
H3K9	↑↑	Tri-Methylation	HD mouse model (R6/2	10	RT-PCR, Histone	Ryu et al., 2006
			HD mice; striatal neurons)		Methylation Assay	
			HD patients (striatum)	6		

↑ indicates increased expression levels and

≠ indicates a genetic mutation affecting epigenetic regulation.

Abbreviations: H, histone; HD, Huntington's disease; K, lysine; R6/2 mice, transgenic mouse model overexpressing exon 1 of human *HTT* with an expanded cytosine-adenine-guanine repeat length; N.S., not specified; WB, Western blot; RT- PCR, real-time PCR.

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Table 10

Epigenetic dysregulation in Alzheimer's disease: non-coding RNAs.

Regulation	ncRNA	Observed in	Sample size	Approach	Methods	Reference
↓	miR-124	AD patients	11	Targeted	WB, RT-PCR	Smith et al., 2011a
↓	miR-195	AD mouse model (SAMP8)	N.S.	Targeted (5 miRNAs)	RT-PCR	Zhu et al., 2012
↓	miR-29a/b-1	sAD patients (anterior temporal cortex)	34	Genome-wide	miRNA microarray	Hebert et al., 2008
↑↑	miR-29c	AD mouse model (APPswe/PSΔE9)	6	Targeted	RT-PCR	Zong et al., 2011
↓	miR-107	AD patients	7, 10	Genome-wide	miRNA microarray, ma22 algorithm	Wang et al., 2008c, 2011
		AD mouse model (Tg19959 mice)	7	Targeted	RT-PCR	Yao et al., 2000
↓	miR-106b	AD patients (anterior temporal cortex)	19	Targeted (200 miRNAs)	miRNA microarray, Northern blot	Hebert et al., 2009
↓	miR-9, miR-181c	AD patients	15 (Brain) 10 (cSF)	Targeted (48 miRNAs)	PCR	Cogswell et al., 2008
↓	miR-132	AD patients (hippocampus, cerebellum, medial frontal gyrus)	6	Targeted (15 miRNAs)	Northern Blot	Sethi and Lukiw, 2009
↓	miR-15	Dicer cKO mice	8–10	Targeted (200 miRNAs)	miRNA microarray	Hebert et al., 2010
≠	miR-26a	AD patients	15 (Brain) 10 (csf)	Targeted (48 miRNAs)	PCR	Cogswell et al., 2008
↓	miR-101	HeLa, HEK293T, U373, SK-N-SH, PC12 cells	-	Targeted (1 miRNA)	PCR	Long and Lahiri, 2011
↑	miR-125b	AD patients (hippocampus, cerebellum, medial frontal gyrus)	6	Targeted (15 miRNAs)	Northern Blot	Sethi and Lukiw, 2009
↑	BC200	AD patients (hippocampus, superior frontal gyrus)	12	Targeted (2 miRNAs)	Northern Blot, ISH	Mus et al., 2007
↓	BC200	AD patients (temporal neocortex)	12	Targeted (2 miRNAs)	Northern Blot, ISH	Mus et al., 2007
↓	miR-103	AD mouse model (Tg19959 mice)	7	Targeted (2 miRNAs)	RT-PCR	Yao et al., 2000
↑	BACE1-AS	AD patients	2	Targeted (48 probes)	High-throughput sequencing, ECA	Faghihi et al., 2010
↑	ncRNA 17a	AD patients	11	Targeted (5 probes)	RT-PCR	Massone et al., 2011

↑indicates increased expression levels,

↓ indicates decreased expression levels, and

≠ indicates altered expression, not further specified.

Abbreviations: AD, Alzheimer's disease; BACE1-AS, β-secretase 1-antisense; BC200, brain cytoplasmic RNA 200; Dicer cKO mice, conditional Dicer1 knock-out mouse model; HeLa cells, immortalized cell line established from cervical cancer cells of Henrietta Lacks; miR, micro RNA; miR-29c transgenic mice, transgenic mouse model overexpressing miR-29c; ncRNA, non-coding RNA; sAD, sporadic AD; SAMP8 mouse, senescence-accelerated prone mouse 8; Tg19959 mice, transgenic mouse model overexpressing mutant human APP with the double KM670/671NL Swedish and V717F Indiana mutations; N.S., not specified; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RT-PCR, real time-PCR; WB, Western blot; ISH, *in situ* hybridization; ECA, enzyme complementation assay.

Table 11

Epigenetic dysregulation in Parkinson's disease: non-coding RNAs.

Regulation	ncRNA	Observed in	Sample size	Approach	Methods	Reference
↓	miR-7	HEK293T, SH-SY5Y, NS20Y cell lines	-	Targeted (2 miRNAs)	PCR	Junn et al., 2009
≠	miR-10a	Mouse model	3	Targeted	miRNA expression profiling	Gillardon et al., 2008
≠	miR-10b	(overexpressing		(266 miRNAs)	(microfluidic chips)	
≠	miR-132	A30P α-synuclein)				
≠	miR-212					
≠	miR-495					
↓	miR-205	sPD patients	8	Targeted (1 miRNA)	PCR	Cho et al., 2013
≠	miR-1	Healthy individuals and	8	Targeted	PCR	Margis et al., 2011
≠	miR-22*	untreated PD patients		(85 miRNAs)		
≠	miR-29					
≠	miR-16–2*	Treated and untreated	7 treated			
≠	miR-26a2*	PD patients	8 untreated			
≠	miR-30a					

↓ indicates decreased expression levels and

≠ indicates altered expression, not further specified.

Abbreviations: (s)PD, (sporadic) Parkinson's disease; HEK293T cells, human embryonic kidney cell line; miR, micro RNA; NS20Y, mouse cholinergic neuroblastoma cell line; PD, Parkinson's disease; SH-SY5Y cells, human neuroblastoma cell line; PCR, polymerase chain reaction.

Table 12

Epigenetic dysregulation in Huntington's disease: non-coding RNAs.

Regulation	ncRNA	Observed in	Sample size	Approach	Methods	Reference
↓	miR-22	HD murine models [YAC12	12 (mouse model)	Targeted	miRNA microassay	Lee et al., 2011
↓	miR-29c	and R6/2 mouse model,	18 (rat model)	(567 miRNAs)		
↓	miR-125b	3NP-induced rat model; Striatum]				
↓	miR-128					
↓	miR-132					
↓	miR-139					
↑	miR-146a					
↓	miR-150					
↓	miR-218					
↓	miR-222					
↓	miR-344					
↓	miR-674					
↓	Drosha					

↑indicates increased expression levels and

↓indicates decreased expression levels.

Abbreviations: FVB-Tg(YAC128)53Hay/J mice, transgenic mouse model generated with a yeast artificial chromosome (YAC) containing the human Huntingtin gene with 128 cytosine-adenine-guanine repeats; HD, Huntington's disease; miR(NA), micro RNA.