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Review

Epigenetic Mechanisms Involved in Huntington's Disease Pathogenesis

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Abstract. Transcriptional dysregulation is an early event and may be an important pathological mechanism in Huntington's disease (HD). However, the exact process that leads to alterations in gene expression in HD is not clear. One potential mechanism underlying transcriptional abnormalities in HD may be epigenetic alterations which regulate gene expression without changing the DNA sequence. Previous work has demonstrated that epigenetic marks, such as DNA methylation and post-translational modifications of histone proteins, are significantly altered in HD cellular and animal models as well as HD patients. Furthermore, studies have shown a therapeutic role for histone deacetylase (HDAC) inhibitors in numerous HD models. Here, we review a range of studies describing epigenetic changes in HD as well as several potential therapeutics that target aberrant epigenetic alterations in HD.

Keywords: Epigenetics, Huntington's disease, DNA methylation, histone modifications, huntingtin, transcription

INTRODUCTION

Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurological disease that typically begins in young adult life and is invariably fatal [1]. Patients with HD initially demonstrate personality changes and small involuntary movements. As the disease progresses, the movement disorder is more pronounced, and cognitive issues and psychiatric disturbances occur [2]. Weight loss is also a common feature in HD, highlighting the existence of a generalized metabolic deficit in patients [3]. Pathologically, HD is characterized by cerebral atrophy. Although HD affects a number of brain regions such as the cortex, thalamus, and subthalamic nucleus, the striatum is the most severely affected region [4, 5].

HD is caused by a mutation in the huntingtin gene located on chromosome 4 that encodes the protein huntingtin (Htt) [6]. This mutation is an expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeat within exon 1, which is translated into a polyglutamine (polyQ) moiety in the Htt protein. While normal individuals have 7–34 CAG repeats, in HD patients the repeat length is expanded. Typically, repeat lengths of >40 glutamines lead to HD, and repeat lengths of >100 glutamines cause juvenile onset disease [7].

Even though the genetic mutation was discovered in 1993, the mechanism by which mutant Htt causes neuronal dysfunction is not yet unclear. However, a number of pathogenic mechanisms including transcriptional dysregulation [8–11], excitotoxicity [12], mitochondrial dysfunction [13–15], caspase activation and apoptotic cell death [16–19], and autophagy, among others, have been implicated in HD pathogenesis.

Transcriptional dysregulation

One key mechanism underlying HD pathogenesis is transcriptional dysregulation [8–11]. Aberrant transcriptional alterations occur early in HD and have been demonstrated in patients as well as multiple cellular and animal models of HD [8, 20, 21]. Specifically, HD patients as well as transgenic and knockin mouse

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models exhibit alterations in specific genes at the level of mRNA expression [8, 9, 22–24]. Previous studies in mouse models have shown changes in neurotransmitter receptor mRNA and protein levels that occur before the phenotypical disease onset [9, 21, 23, 25, 26]. These findings are consistent with positron emission tomography (PET) studies showing a decrease in dopamine D1 and D2 receptors in gene-positive but clinically asymptomatic HD patients [22, 27]. Thus, neuronal dysfunction appears to precede neurological symptoms in HD. Microarray studies using brain tissue samples from the R6/2 transgenic mouse model [21, 25] illustrated that mRNA levels are altered for genes involved in neurotransmitter signaling, calcium metabolism, and transcriptional processes [28–31]. Most of these transcripts were decreased and a larger number of genes were decreased in symptomatic mice compared to presymptomatic mice, suggesting a progressive effect. Following these initial studies, microarray analyses demonstrated mRNA changes in several other mouse and cellular HD models [8, 24]. Overall these findings agree with genome-wide studies from human brain tissue samples [32] and to a lesser degree with studies analyzing human blood samples [33]. These findings show that a large number of genes are altered in symptomatic HD patients and these results are recapitulated in HD animal models. Taken together, these findings suggest that transcriptional dysregulation is an important process in HD pathogenesis. However, the mechanisms that lead to selective alterations in gene expression are not yet clear.

Mutant Htt (mHtt), containing a polyQ expansion, interacts with numerous transcription factors such as CREB-binding protein (CBP) [10, 34], TATA-binding protein (TBP) [35], p53 [36], Sp1 [37] and nuclear factor κ light-chain-enhancer of activated B cells (NF-κB) [38]. These results led to the initial hypothesis that mHtt nuclear aggregates may cause transcriptional dysregulation by sequestering transcription factors. However, our previous findings in the R6/2 model demonstrated that there was no difference in transcript levels between neurons containing intranuclear inclusions and those lacking inclusions [39]. In addition to its interaction with transcription factors, Htt is cleaved by caspases yielding fragments that enter the nucleus and form nuclear aggregates, thereby potentially disrupting transcription [40]. Loss of wildtype Htt expression also promotes nuclear translocation of the repressor element-1 silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF), which is proposed to alter transcription of selective gene targets [41]. Furthermore, expanded polyQ repeats in the amino terminus of the Htt protein produce structural similarities to known transcription factors [42, 43] that may enhance its interactions with other nuclear proteins. Finally, Htt itself may directly bind to DNA [44] thus altering transcription. While these are all viable processes whereby mHtt can alter transcription, the exact mechanisms that lead to changes in gene expression in HD are not fully understood.

Epigenetics

Recent pioneering work in the field provides strong evidence that epigenetic mechanisms contribute to transcriptional dysregulation in HD. Epigenetics includes heritable and stable alterations in gene expression that occur without changing the DNA sequence [45–47]. The epigenetic mechanisms involved in regulating gene expression are complex and numerous. These modifications include alterations in the 3D structure of chromatin, chemical modifications of DNA (methylation and hydroxymethylation), post-translational modification of histones (acetylation, methylation, ubiquitylation, phosphorylation, SUMOylation, ADP ribosylation, etc.), and interactions of non-coding RNAs with chromatin [48, 49]. Alterations in the epigenome are relevant for neuronal loss and dysfunction. Therefore, novel treatment strategies for neurodegenerative diseases are focused on targeting the epigenome. In this review we will discuss the epigenetic alterations to DNA and histones that occur in patients as well as in cellular and animal models of HD.

Altered epigenetics in Huntington's disease

DNA methylation

DNA methylation occurs via the action of DNA methyltransferases (DNMTs) that add methyl groups to the C5 position of cytosine which predominantly resides in cytosine-guanine dinucleotide (CpG) regions in the genome [50]. This process creates 5-methylcytosines (5mCs) and can be followed by an additional step of 5mC oxidization to yield hydroxymethylcytosines (5hmCs) [51]. To simplify, within promoter regions, 5mC is associated with transcriptional repression, whereas 5hmC is associated with transcriptional activation [52, 53]. Methylation of CpG islands hinders transcription factor binding to DNA sequences via the recruitment of co-repressor complexes [54]. These methylated DNA regions are bound by methyl-binding domain-containing proteins,

such as methyl CpG-binding protein 2 (MeCP2), which recruit co-repressors like histone deacetylases (HDACs) and methyltransferases to gene promoters. CpG methylation was originally thought to cause gene repression, however, it is now understood to be a dynamic process that can either promote or inhibit gene expression [50]. DNA methylation is critical for imprinting, X chromosome inactivation, and cell differentiation. In addition, it can be modified at specific loci in germ cells through exposure to environmental factors [55, 56].

For years it was believed that DNA methylation was a stable epigenetic mark involved in development. However, it has recently become clear that DNA methylation may be influenced by neuronal activity [57–59] and selectively altered in disease states [60, 61]. Thus, CpG methylation in HD was examined for brain derived neurotrophic factor (BDNF; *Bdnf*) and adenosine A2A receptor (A_2A; *Adora2a*), two genes with decreased expression in patients and several HD models [62]. While examination of single CpG dinucleotides of the *Bdnf* gene revealed little effect of mHtt expression in the R6/1 hippocampus [63], 5hmC levels were decreased at the 5'-end of the *Adora2a* gene in both human and murine striata [64]. Together these findings demonstrate that alterations in the *Bdnf* and *Adora2a* genes are not due to changes in 5mC alone.

While the analysis of DNA methylation at the single gene level has not revealed significant alterations, genome-wide studies have been more informative. Modified bisulfite sequencing with single base pair resolution was employed to measure DNA methylation in the ST*Hdh* cellular model of HD [65]. The results from this study demonstrated that there was a bias towards hypomethylation associated with CpG-poor regions in the mHtt expressing ST$Hdh^{111/111}$ compared to control ST$Hdh^{7/7}$ cells. However, changes at CpG-rich regions, typically associated with transcription start sites, were inversely related to alterations in transcription. Further analysis of the CpG-poor regions demonstrated a negative correlation between transcription factor binding and DNA methylation in ST$Hdh^{111/111}$ relative to ST$Hdh^{7/7}$ cells [65]. In another study, global levels of 5hmC were reduced in the striatum and cortex of presymptomatic YAC128 mice [66]. Importantly, the genomic distribution of 5hmC levels confirmed hypomethylation at several key loci, although hypermethylation was also detected to a lesser extent. Despite a positive correlation between the presence of differential 5hmC regions and gene expression, the subset of genes examined was too small to define the precise contribution of 5hmC deficits in HD. Therefore more extensive analysis is still required in order to better understand the role of 5hmC in HD. Another study demonstrated that 7-methylguanine (7mG), a newly discovered DNA modification, was reduced in nuclear protein fractions from HD mouse models and in motor cortex from HD patients [67], suggesting that 7mG modifications may also be relevant to HD pathology. Though these findings demonstrate that DNA methylation changes may be directly linked to changes in gene expression in HD, further comprehensive and genome-wide analyses are required to unveil their precise role in HD pathogenesis.

Despite these findings, caution should generally be employed when interpreting DNA methylation studies in neurons since most reports regarding DNA methylation have focused on proliferative cells. While DNA methylation studies typically concentrate on CpG methylation, non-CpG methylation is prominent in neuronal tissue [53, 68, 69]. In addition, the brain has the highest 5hmC levels in the body [70–72]. Therefore, while the parallel reductions in gene expression in HD may be due to decreases in 5hmC, this could also be due to increased 5mC levels under baseline conditions. Finally, as new DNA modifications such as 7mG are identified, deciphering the role of each alteration in the pathophysiology of disease becomes more complicated.

The effects of mHtt are not limited to alterations in DNA methylation or DNMTs since changes in MeCP2 interactions might also contribute to pathogenesis. A recent study by our group demonstrated that Htt directly interacts with MeCP2 in mouse and cellular models of HD [73] (Fig. 1). Our results also demonstrated that Htt-MeCP2 interactions were enhanced in the presence of the expanded polyglutamine (polyQ) tract and were stronger in the nucleus compared to the cytoplasm [73]. In addition, MeCP2 binding to the promoter of the *Bdnf* gene was increased and siRNA-mediated reduction of MeCP2 levels rescued this effect and normalized *Bdnf* expression [73]. These findings suggest that aberrant interactions between Htt and MeCP2 are an additional mechanism that contributes to transcriptional dysregulation in HD.

Histone post-translational modifications

Chromatin consists of nucleosomes that contain 147 base pairs of DNA wrapped around an octomer of histone proteins comprised of two H2A, H2B, H3 and H4 histones. When the interaction between DNA and the octomer of histones is tight, resulting

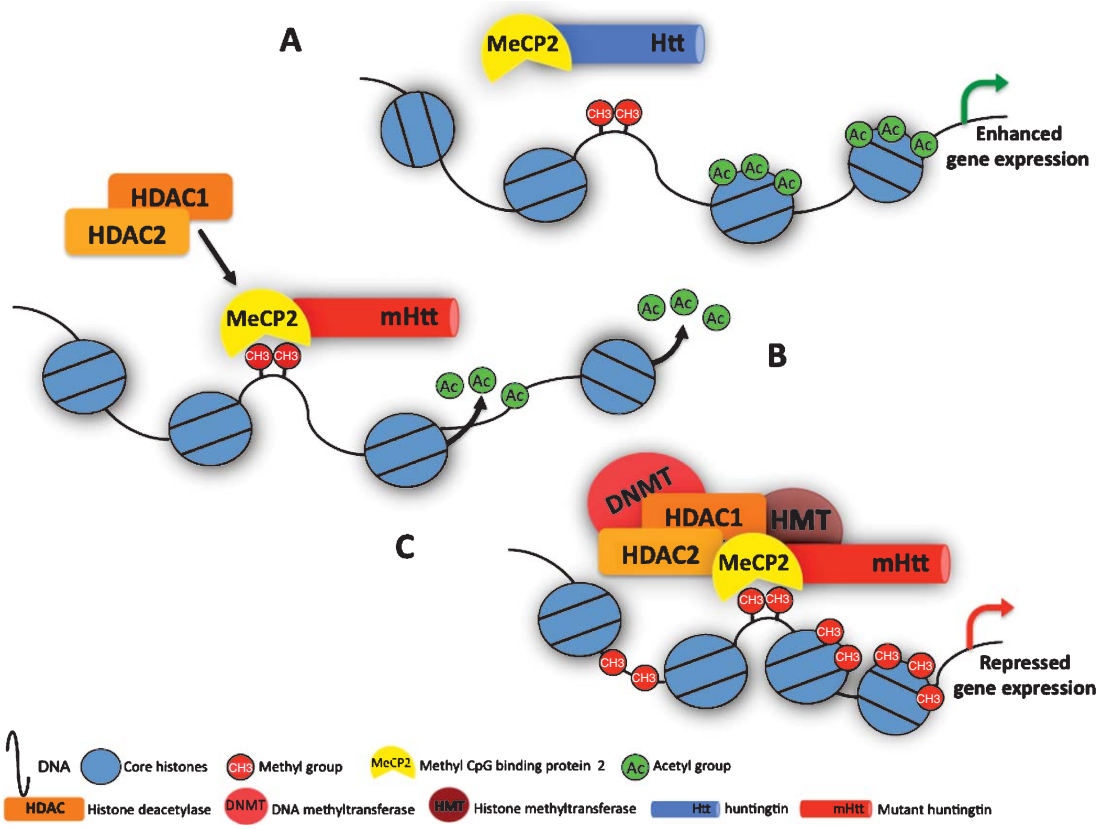

Fig. 1. Schematic of Htt-MeCP2 interactions A) Wildtype Htt and MeCP2 interact B) There is an increase in the interaction between mHtt and MeCP2 leading to an increase in the recruitment of MeCP2 to promoter regions. MeCP2 binding to methyl CpGs recruits HDAC1 and HDAC2 leading to deacetylation of histones C) MeCP2/HDAC complex recruits methyltransferases (DNMTs), which add methyl groups (CH_3) to the C5 position of cytosine in the genome, as well as histone methyl transferases (HMT), which also add methyl groups to histones. Methylation of cytosines in CpG islands together with methylation of histones inhibits transcription.

in a compact nucleosome, this structure is referred to as heterochromatin. Conversely, a less constrained interaction between DNA and the histone octomer is known as euchromatin. Due to the compact structure of heterochromatin, DNA is less accessible to the transcriptional machinery thus facilitating transcriptional suppression. In contrast, the more relaxed structure of euchromatin is easily accessible and allows for enhanced gene expression. Combinations of post-translational histone modifications alter the affinity of DNA for histone proteins, thereby positively or negatively affecting gene transcription [74]. The N-terminal tails of histones contain amino acid residues that are sites for post-translational modifications, including acetylation, phosphorylation, methylation, ubiquitylation, SUMOylation, and ADP ribosylation, among others [75]. The addition or removal of these modifications occurs via specific enzymes, demonstrating the reversible nature of histone marks [75]. In HD, alterations in histone modifications have been studied extensively (Fig. 2) and the next section focuses on these studies.

Histone acetylation

Histone acetylation, the most studied epigenetic mark, leads to a change in chromatin structure from heterochromatin to euchromatin thus enhancing gene expression. Acetylation of lysine (K) residues on histone tails decreases the electrostatic interactions between histones and DNA [75] promoting a relaxed chromatin conformation that allows for the recruitment of transcription factors and the basal machinery to regulatory DNA sequences. Although this is a simplified description, hyperacetylation of histones at promoter regions is correlated with increased gene expression and hypoacetylation is associated with decreased gene expression [76]. In HD, several studies have reported a global reduction of acetylated histone levels [77–84]. However, other groups did not find these alterations in the same mouse models [85–89]. Specifically, studies

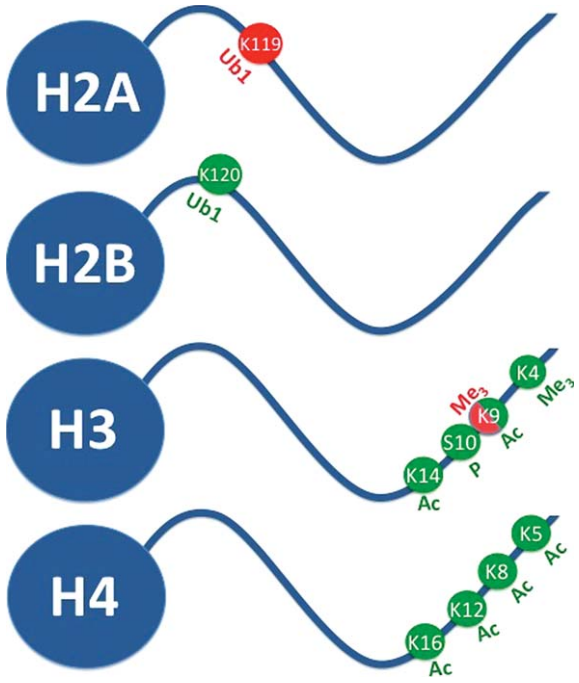

Fig. 2. Post-translational modifications of histones described in HD. Lysine (K) residues on the N-terminal tail of histones undergo modifications such as acetylation, methylation, or ubiquitylation, whereas serine (S) residues can be phosphorylated. Schematic representation of known histone modifications in HD that include: H2AK119ub1, H2BK120ub1, H3K4me3, H3K9me3, H3K9ac, H3S10p, H3K14ac, H3K9K14ac2, H4K5K8K12K16ac4. Green modifications represent facilitatory marks while red modifications represent inhibitory marks.

from our group and others demonstrated that histone acetylation was only decreased when associated with selective downregulated genes [88–90]. In addition, a number of hyperacetylation events were also revealed using genome-wide studies in HD mouse models [89, 91]. The extent of histone acetylation is regulated by the action of two opposing enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs) [92], the role of which in HD will be reviewed in the following sections.

Histone acetyltransferases (HATs)

Dysregulation of histone acetylation in HD has been linked to CREB-binding protein (CBP), which functions as a HAT and is associated with several neurodegenerative diseases [92]. Specifically, CBP was located in intracellular inclusions *in vitro*, in brain tissue from animal models and in postmortem human HD patients [10, 34, 93]. Together these studies suggested that depletion of soluble CBP might affect transcription of genes relevant for neuronal survival. In agreement, a fifty percent reduction in CBP levels exacerbated neurodegeneration in a *C. elegans* HD model [94] and diminished the median life expectancy in the N171-82Q HD mouse model of HD [86]. Conversely, overexpression of CBP rescued the deficits in CBP/CREB-dependent transcription, histone hypoacetylation, and mHtt-induced toxicity in polyglutamine disease models [10, 34, 80, 95, 96]. These results have been confirmed in a wide array of HD models by independent research groups and more recently in neuronal populations from HD patients [97]. In addition, *in vitro* mHtt expression inhibited the HAT activity of CBP suggesting a more direct link between mHtt and CBP [98].

Despite the proposed association between altered CBP activity and mHtt-induced toxicity, the link between these cellular processes is not yet clear. Inclusions containing mHtt failed to significantly colocalize with or alter the nuclear distribution of CBP and other transcription factors in several HD mouse models [99–101]. In agreement, CBP exhibited a weak interaction with mHtt aggregates in a later stage of polyQ expression, whereas soluble mHtt exhibited a stronger interaction with CBP and inhibited HAT activity prior to the formation of inclusions in PC12 cells [102]. Soluble expanded polyQ fragments also demonstrated enhanced interaction with CBP and toxicity relative

to the aggregated polyQ version [103]. These results agree with the observations from our group and others that altered gene expression is not necessarily connected with nuclear Htt aggregate formation in HD mice [37] and can occur in its absence [104, 105]. Thus, soluble mHtt could interact with transcription factors and chromatin-remodeling proteins to facilitate early pathological changes prior to the formation of nuclear inclusions. The conflicting findings linking CBP activity to soluble or aggregate forms of mHtt might be due to experimental confounds caused by *in vitro* overexpression of proteins that could force co-aggregation or variable mHtt expression levels [80, 86, 106]. Finally, *Hdh*$^{Q7/Q111}$ knockin mice exhibit impairments in spatial and recognition memory along with decreased levels of CBP and acetylated histone H3 [82], suggesting that CBP may be important for the cognitive impairments seen in HD patients. It should be noted that despite the high degree of similarity to CBP, p300, another HAT, is absent from intracellular mHtt inclusions and is not degraded in the presence of mHtt [102]. More importantly, p300 does not rescue cell toxicity in overexpression assays [34]. These findings suggest that CBP may play a unique role, amongst HATs, in HD pathogenesis.

Histone deacetylases (HDACs)

In addition to HAT activity, HDAC activity is also altered in HD. The HDAC enzymes are divided into four classes: class I (HDACs 1, 2, 3 and 8), II (HDACs 4, 5, 6, 7, 9 and 10), III (NAD±sirtuin family) and IV (HDAC11). The first study measuring HDAC levels in HD demonstrated that there was an increase in the nuclear expression of HDAC5 without an overall change in transcript levels in human striatum and cortex [107]. In contrast, a recent study in R6/2 mice demonstrated that there was an increase in HDAC1 protein levels and a concomitant decrease in class II HDACs (particularly HDAC6) [108]. However, class I and II HDAC levels were not changed in cortical tissue from CAG140 knock-in mice or postmortem HD brain [108]. In agreement with the reported increase of HDAC1 expression in HD mice [108] decreasing HDAC1 via lithium promoted mHtt degradation in a HD cellular model [109]. However this relationship does not appear to extend to all class I HDACs since overexpression of wild-type Htt decreased HDAC3 activity, due to physical interactions between the two proteins [110].

Over the past several years a number of groups have assessed the role of HDACs in HD models via genetic knockout or knockdown approaches. The first report demonstrated that decreasing the HDAC3 ortholog in the *C. elegans* HD model suppressed mHtt-induced degeneration of sensory neurons but reducing any other orthologs of class I, II or III HDACs enhanced neurodegeneration [111]. In line with this study, decreasing Rpd3 (ortholog to HDAC1/2/8) or Sir2 (Sirt1) was neuroprotective but did not improve survival in a *Drosophila* HD model [112]. Interestingly, Bates and colleagues have demonstrated that decreasing HDACs (3, 6, 7 and Sirt2) in the R6/2 mouse via genetic crosses did not ameliorate the pathological phenotype associated with HD or reverse transcriptional deficits [113–116]. In contrast, a recent study from their group showed that reduction of HDAC4 delayed cytoplasmic mHtt aggregates, improved behavioral outcomes, and extended lifespan in R6/2 mice [117]. However, these effects appeared to be independent from the traditional role of HDACs in modifying gene transcription [117]. Finally, in HD cell lines challenged with cytotoxic insults, overexpression of HDAC7 was neuroprotective, though independent of its HDAC activity [118]. These studies demonstrate alterations in the activity of specific HAT and HDAC enzymes, however, it is not yet clear if these changes play a causal role in HD pathogenesis.

Histone methylation

While the effects of histone acetylation on gene expression are clear, the implications of histone methylation are not as straightforward since methylation causes both gene expression and silencing events. Histone methylation occurs via the addition of methyl groups to lysine (K) or arginine (R) residues on histone tails. This modification is relatively stable compared to histone acetylation, which does not alter the charge of the targeted amino acid residues [119]. Histone methylation can occur in mono-(me), di-(me2), or tri-methylated (me3) forms, with each methylation event yielding distinct and sometimes opposite effects on gene transcription [119]. Histone methylation at gene promoters can either enhance or repress transcription depending on the target amino acid [120]. For example, di- and tri-methylation of histone H3 on K residues 9 (H3K9me2/3) and 27 (H3K27me2/3) decrease gene transcription [119]. Conversely, tri-methylation of histone H3 on K residues 4 (H3K4me3) and 36 (H3K36me3) increases gene expression [119]. The extent of histone methylation is regulated at a locus by the action of histone methyltransferases (HMTs) and histone demethylases (HDMs) [120].

In both R6/2 mice and HD patients, H3K4me3, a marker of active gene expression [121–123], is reduced at promoters of selective downregulated genes in cortical and striatal regions [124]. These results were confirmed using a genome-wide analysis in the R6/2 mouse. Specifically, this study demonstrated a widespread change in H3K4me3 occupancy that was strongly associated with decreased transcription [124]. In addition, there were unusual patterns of H3K4me3 occupancy downstream of the transcription start site suggesting that there might be selective regulatory control of Htt target genes that drive transcriptional alterations in HD [124]. H3K4me3 hypomethylation was hypothesized to be due to upregulation of the histone demethylase, lysine-specific demethylase 5C (KDM5C). Supporting this idea, knockdown of KDM5C increased the transcript levels of specific downregulated genes and attenuated toxicity in an HD fly model [124].

In contrast with H3K4 methylation, H3K9 methylation is a mark of gene repression. Histone H3K9 di-methylation (H3K9me2) and tri-methylation (H3K9me3) are increased in brain tissue from R6/2 and N171-82Q mice as well as in HD patients [78, 84, 125, 126]. This H3K9 hypermethylation originated from upregulation of upstream chromatin factors [126]. Specifically, there was a concurrent increase in the levels of H3K9me3 and its specific histone-lysine N-methyltransferase SET domain bifurcated 1 (SETDB1). This transcriptional upregulation of SETDB1 was proposed to be due to the GC-box-binding transcription factors Sp1 and Sp3. While this finding agrees with the reported increase in Sp1 activity in HD [127], it contradicts with previous reports by our group and others demonstrating reduced function of Sp1 in HD models [37, 128, 129]. These conflicting results may be due in part to variation between different expression systems or HD models used in each study. In addition, the DNA-dependent ATPase/helicase alpha-thalassemia/mental retardation syndrome X-linked (ATRX) [130, 131] protein is increased in models of HD. ATRX is known to colocalize with H3K9me3 and heterochromatin-binding protein 1 alpha (HP1α) [132]. Consistent with ATRX's role in heterochromatin condensation, there was an increase in pericentromeric heterochromatin clusters that was linked to enhanced expression of the transcription factor caudal type homeobox 2 (Cdx2) and its binding occupancy at the ATRX promoter in R6/2 striatum [132]. These findings suggest a causal role between ATRX expression and the formation of heterochromatin clusters. Together these studies demonstrate that both hypo- and hypermethylation play important roles in regulating gene transcription in HD.

Histone phosphorylation

Histone phosphorylation is another post-translational modification associated with increased gene transcription [120]. Phosphorylation of serine 10 on histone H3 promotes HAT activity, phospho-acetylation of neighboring amino acid residues, and inhibits repressive methylation marks on H3 [75]. Yazawa and colleagues were the first group to report aberrant phosphorylation of histone H3 in polyQ diseases [133]. Later it was demonstrated that histone H3 phosphorylation (H3S10p) and expression of its downstream target gene c-Fos were decreased in striatal neurons transfected with expanded Htt [134]. The phosphorylation level of H3S10p is extremely low under basal conditions, but it is significantly upregulated following neuronal activation in a rapid and transient manner [135–137]. Thus, it has been proposed that impaired H3S10p induction is due to downregulation of the upstream kinase mitogen- and stress-activated protein kinase-1 (MSK-1). In agreement with this hypothesis, overexpression of MSK-1 restored full induction of H3S10p and c-Fos expression and prevented striatal death *in vitro* and *in vivo* [134, 138] via cooperative action with transcription factors, such as CREB, to activate pro-survival factors.

Another instance of histone phosphorylation occurs with the 'universal' histone variant H2A.X, which differs from canonical H2A in C-terminal phosphorylation and in a few amino acids in the primary sequence. H2A.X is phosphorylated at S139 by ataxia telangiectasia mutated kinase (ATM) generating γH2A.X in a cellular model as well as in R6/2 mice due to DNA damage [139, 140]. γH2A.X and breast cancer-associated 1 (BRCA1), another ATM substrate, are uncoupled in the presence of mHtt, leading to increased DNA breaks in neurons [141]. Moreover, activation of γH2A.X facilitates DNA repair [142]. However, attenuating the elevated ATM signaling seen in HD leads to decreased mHtt-induced cell death in various HD animal models and in pluripotent stem cells from human HD patients [143]. These findings suggest that levels of γH2A.X and ATM must be tightly controlled in HD in order to protect neurons from damage without inducing deleterious, apoptotic effects.

Histone monoubiquitylation

Histone monoubiquitylation occurs through the covalent attachment of the ubiquitin protein to K

residues using an E3 ubiquitin ligase. Histone H2A is monoubiquitylated (H2Aub1) at K119 by the Polycomb repressor complex PRC1. H2Aub1 is associated with silencing of developmental genes, pericentromeric regions, and the inactive X-chromosome [144]. Prior H3K27 methylation by the Polycomb complex PRC2 is generally required for H2A monoubiquitylation. While H2A ubiquitylation leads to transcriptional repression, histone H2B monoubiquitylated (H2Bub1) at K120 is typically associated with active genes. H2Bub1 is a prerequisite step to histone H3 methylation at K4 and K79, and more importantly, H2Bub1 regulates general chromatin structure by ensuring integrity of histone positioning.

Previous studies from our group and others demonstrated that overall levels of H2Aub1 were increased, independent of the ubiquitin-proteasome system [145–147], whereas H2Bub1 levels were reduced in the R6/2 mouse brain [146]. Furthermore, manipulation of E3 ubiquitin ligase ring finger proteins in the mutant ST*Hdh* cell lines demonstrated that the ring finger protein 2 (Rnf2 or Ring2) regulates H2Aub1 and downstream methylation of H3K9. Conversely, Rnf20 (homolog to yeast Bre1) regulates H2Bub1 and downstream methylation of H3K4 [146]. Although global elevation of H2Aub1 has been demonstrated in HD mice, conflicting evidence exists regarding the link between transcriptional activity and ubiquitylation of promoters for individual genes [146, 147]. Together these findings point to the potential involvement of the Polycomb Repressive Complexes (PRC) in HD, although their link to transcriptional activity was unclear until recently. A new study recently demonstrated that expanding the polyQ tract in mHtt enhances its ability to facilitate PRC2 and thereby alter the chromatin landscape in pluripotent and lineage restricted progenitor cells [148]. Specifically, Htt was necessary for the proper deposition, maintenance, and removal of H3K27me3, a histone mark that is deposited by PRC2 [148]. Although further studies are required to fully understand the nature of Htt's interaction with PRC as well as with other epigenetic regulators, these findings demonstrate that mHtt can regulate the broader epigenetic machinery in order to orchestrate alterations in higher order chromatin states [148].

Epigenetic-based therapies for the treatment of HD

HDAC inhibitors

Given the role of histone modifying enzymes in regulating gene expression, the use of HDAC inhibitors as novel therapeutic approaches for the treatment of HD has gained considerable attention. The potential role for HDAC inhibitors (HDACi) in HD was first described in two influential papers which demonstrated that administration of broad-spectrum HDACi (sodium butyrate (NaB), suberoylanilide hydroxamic acid (SAHA), and trichostatin A (TSA)) rescued cell death and degeneration in models of polyQ disorders [98, 149]. Following those studies, the beneficial effects of HDACi have been described in numerous cellular and animal models of HD [150]. It has been proposed that HDACi administration yields therapeutic effects by increasing histone acetylation associated with gene promoters and thereby reversing deficits in gene expression. However, HDACi may also exert their effects by altering other marks, such as reducing the repressive H3K9me2 and H2Aub1 marks, due to the cross-talk between different histone modifications [78, 88]. In addition, a recent study demonstrated that HDAC1/3 inhibition, via HDAC4b treatment, produced widespread changes in DNA methylation, including CpG methylation at the genomic locus for the lysine-specific methylase 5D (KDM5D), in fibroblasts from human HD patients [151]. These alterations in other epigenetic marks may assist HDACi in restoring normal gene expression. Additionally, HDACi treatment could provide therapeutic benefit by directly altering the expression of HDAC enzymes. For example, SAHA treatment altered the expression of HDAC2 and 4 protein levels, and HDAC7 and 11 RNA levels [113, 117].

Despite promising pre-clinical data with HDACi, broad spectrum HDAC inhibition may have unintended effects in human HD patients. Therefore, recent efforts have focused on the development of more selective HDACi [152, 153]. An important issue for the development of HDACi as therapeutics is the identification of the HDAC enzymes critical for the disease process. There are now 18 known human HDAC enzymes [154] each of which have distinct roles in the body. HDAC1 and HDAC3 have been implicated in neurotoxicity and the pathological mechanisms related to polyQ disease [153]. Moreover, HDACi selective for HDAC1/3 ameliorated pathological processes in cellular and animal models of HD [90, 155, 156]. Recent studies by our collaborators along with our group demonstrate that the HDACi 4b and related compounds exhibit more specificity for HDAC1 and HDAC3 while still producing significant improvements in polyQ-induced deficits in HD models [90, 156]. Interesting, HDACi 4b treatment has also been shown to have transgenerational effects, improving HD phenotypic behaviors

in untreated F1 male offspring [151]. Despite these promising findings, recent concerns with oral administration of HDACi 4b may limit future use of this compound [157]. Additional selective HDACi are currently under development for the treatment of HD and other neurodegenerative diseases [158]. It will be important to assess whether these novel compounds yield similar pre-clinical therapeutic benefits to broad spectrum HDACi.

It should be noted that there are several concerns in regards to the genomic effects of HDACi treatment. Acute treatment with the HDAC TSA preferentially hyperacetylated active loci already premarked with H3K4me3 and H3K9K14ac at the transcription start site [159]. This finding suggests that HDAC inhibition may favor transcriptionally permissive states. Another puzzling result is the fact that microarray studies revealed a relatively limited number of corrected genes following HDACi treatment in HD models [77, 78, 84]. Therefore, there is a possibility that HDACi exert their beneficial effects by altering other cellular processes besides transcriptional regulation.

In addition to histones, hundreds of proteins can be acetylated [160] and therefore altered in response to HDACi treatment [161]. Thus, HDACi could produce beneficial outcomes via combinatorial effects on histones and non-histone substrates, including cytoskeletal and mitochondrial proteins as well as transcription factors. Importantly, acetylation K444 on Htt can promote its clearance via the autophagic-lysosomal system [162]. Similarly, AcK9/pS13/pS16 are also linked to autophagic degradation and can be altered by the HDACi 4b [156, 163]. HDACi treatment also increased tubulin acetylation at K40 and rescued *in vitro* microtubule-dependent transport deficits, including trafficking of BDNF-containing vesicles [164]. Since this trafficking is disrupted in HD [165], HDACi treatment may also ameliorate HD symptomatology through restoring normal BDNF levels in the striatum.

Methylation inhibiting drugs

Methyltransferase inhibitors have been tested in various neurological disorders. However, to date they have not been utilized in HD. Despite this, histone methylation can be indirectly altered by GC-binding anthracyclines, such as mithramycin A and chromomycin [166]. Anthracyclines are bacterial compounds with antibiotic and anticancer properties that interact with the minor groove of DNA and inhibit binding of GC-rich-binding transcription factors like Sp1 family members. In 82Q HD mice, mithramycin or chromomycin treatment reversed the hypoacetylation of histones H3 and H4 and hypermethylation of histone H3, extended survival, improved motor phenotypes and increased brain volume [84]. Similarly, mithramycin treatment attenuated hypermethylation of histone H4, extended survival and improved motor phenotypes in R6/2 mice [125]. Mithramycin treatment also restored the expression of the methyltransferase SETDB1, a key enzyme that regulates histone methylation [126]. Given these findings, future pre-clinical studies will be important to further determine if anthracycline treatment could be a potential treatment for HD.

CONCLUSIONS

As reviewed above, alterations in gene expression and the epigenome are important and early mechanisms underlying HD pathology. Importantly, Htt protein itself interacts with a number of transcription factors as well as epigenetic regulators. Therefore, it was hypothesized that reversal of epigenetic marks associated with HD may restore, at least partially, the normal transcriptional program and ameliorate the pathological phenotype. However, it remains to be determined to what extent changes in the epigenome play a causal role in transcriptional dysregulation. Genome-wide studies have demonstrated that the relationship between alterations in the epigenome and gene expression changes is complicated. Up to this point, only a few epigenetic marks have been analyzed using genome-wide approaches [65, 91, 92, 124, 147]. These findings demonstrate that alterations in the epigenome in HD are more complex than previously appreciated and highlight the importance of targeting epigenetic "signatures" as opposed to individual epigenetic marks for the treatment of HD. In addition, these studies challenge our current view regarding the method by which epigenetic mechanisms regulate gene expression given that co-occurrence of changes in gene expression and epigenetic modifications does not necessarily involve a causal relationship. This puzzling result could be due to several issues including our incomplete understanding of the role of epigenetics in the CNS under normal conditions. Moreover, a number of additional epigenetic marks remain to be examined in HD. It is conceivable that combinations of epigenetic marks converging on selective loci are responsible for enhancing or attenuating transcription. Therefore, more in depth and comprehensive approaches employing novel genome- and epigenome-wide methods of analysis will help to assess and identify the sets of

genes and epigenetic mechanisms that are involved in these processes. Finally, a more extensive and complete understanding of chromatin states and 3D chromatin structure is critical as these structural changes could also alter transcription.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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