Review

Epigenetic mechanisms underlying enhancer modulation of neuronal identity, neuronal activity and neurodegeneration

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\textbf{ABSTRACT}

Neurodegenerative diseases, including Huntington’s disease (HD) and Alzheimer’s disease (AD), are progressive conditions characterized by selective, disease-dependent loss of neuronal regions and/or subpopulations. Neuronal loss is preceded by a long period of neuronal dysfunction, during which glial cells also undergo major changes, including neuroinflammatory response. Those dramatic changes affecting both neuronal and glial cells associate with epigenetic and transcriptional dysregulations, characterized by defined cell-type-specific signatures. Notably, increasing studies support the view that altered regulation of transcriptional enhancers, which are distal regulatory regions of the genome capable of modulating the activity of promoters through chromatin looping, play a critical role in transcriptional dysregulation in HD and AD. We review current knowledge on enhancers in HD and AD, and highlight challenging issues to better decipher the epigenetic code of neurodegenerative diseases.

1. Neuronal-specific enhancers: neuronal identity vs neuronal activity

1.1. Epigenetic regulations

Epigenetic mechanisms, including DNA methylation, some non-coding RNAs and various histone post-translational modifications acting through combinatorial rules defined by the so-called histone code, modulate the chromatin, which can be relaxed, a feature generally associated with transcriptionally active chromatin (e.g. euchromatin), or in a compacted state (e.g. heterochromatin) usually associated with transcriptional repression (Jenuwein and Allis, 2001). While the continuous discovery of new histone post-translational modifications reflects complexity of histone code and epigenetic regulation, unifying rules have been uncovered. Particularly, histone acetylation, through the action of histone acetyltransferases (HAT), a family of chromatin-remodeling enzymes, has always been implicated in chromatin relaxation. Histone acetylation at promoters and distal regulatory regions – enhancers-, is a prerequisite to target gene activation. Particularly, H3K27 acetylation (H3K27ac) by the HAT CBP/P300 is a mark of transcriptionally active enhancers and promoters (Tie et al., 2014). Additional histone post-translational modifications, including methylation on specific histone residues, contribute to histone code of relaxed chromatin. For instance, trimethylated H3K4 (H3K4me3) is strongly enriched at transcriptionally active promoters, whereas monomethylated H3K4 (H3K4me1) is specifically enriched at enhancers. Histone methylation can also be associated with transcriptionally silent heterochromatin state. Well-characterized heterochromatin marks include H3K9 trimethylation (H3K9m3), a mark of constitutive heterochromatin, and H3K27 trimethylation (e.g. H3K27me3), enriched at facultative heterochromatin, which has the potential to convert to euchromatin (Trojer and Reinberg, 2007).

1.2. Transcriptional enhancers

Enhancers are critical regulatory DNA elements enabling cell-type-specific and dynamic regulations of gene expression. They are enriched in docking sites for transcription factors (TF) in sequence-specific manner. Combinatorial binding of TFs determines the nature and extent of enhancer-mediated transcription (Inukai et al., 2017). Thus, cell-type-specific differences in TF expression contribute to cell-type-specific activity of different enhancer elements. However, most sequence-predicted TF binding sites are not occupied, even when cognate TF are expressed (Hombach et al., 2016). This is because...
enhancer accessibility and ability to interact with promoters are determined by epigenetic mechanisms, which are also regulated in a cell-type-dependent manner. For instance, during cellular differentiation, H3K27ac undergoes massive changes and is deposited at specific gene loci. Lineage-determining TFs, expressed in developmental- and cell-type-dependent manners, provide specificity to the mechanism, recruiting chromatin-remodeling enzymes (e.g. HATs) and structural proteins such as the mediator, CTCF and cohesin, in addition to transcriptional cofactors and RNA polymerase II (RNAPII) (Heinz et al., 2015). Chromatin-remodeling enzymes and structural proteins are implicated in chromatin loop formation, facilitating spatial interaction between distal enhancers and promoters, thereby increasing transcriptional activation of RNAPII complex (Kuras et al., 2003; Ren et al., 2017; de Laat and Duboule, 2013) (Fig. 1).

1.3. Super-enhancers and cellular identity genes

Remarkably, enhancers regulating cellular identity genes show specific epigenetic profile, defined as super-enhancer. This category of enhancers correspond to broad genomic regions highly enriched in H3K27ac and cofactors, such as CBP and the mediator, and encompass complex array of regulatory elements containing binding motifs for cell-type-specific master TFs (Wbyte et al., 2013; Hnisz et al., 2013; Heinz et al., 2015) (Fig. 1). Importantly, chromatin architecture at super-enhancers displays extensive chromatin looping, enabling multiple enhancer/promoter interactions, thereby concentrating transcriptional factors and cofactors and ensuring elevated and sustained expression of cellular identity genes, a feature essential to cellular identity acquisition and maintenance (Nord and West, 2020; Yap and Greenberg, 2018). Recent data indicate that hyper-active regulatory domains defined by super-enhancers induce locally specific biophysics properties, favoring phase-separated condensates of regulatory proteins, including master TFs, coactivators and RNAPII, enabling high-density assembly and elevated expression levels (Sabari et al., 2018; Wang et al., 2019; Zamudio et al., 2019) (Fig. 1).

1.4. Neuronal activity-regulated enhancers

Enhancers also display a highly dynamic regulation since they respond to cellular stimulation, thereby integrating environmental signals and triggering adaptive genomic response. Dynamic regulation of enhancers is especially critical to neuronal function. In response to environmental stimuli, it drives transcriptional reprogramming promoting synaptic plasticity and adaptive behavior, including learning and memory (Campbell and Wood, 2019; Graff and Tsai, 2013; Kim et al., 2010; Lopez-Atalaya and Barco, 2014; Yap and Greenberg, 2018). In response to stimulation, signaling cascades (e.g. cAMP- and Ras/ MAPK-dependent pathways) are activated in neuronal tissues, which leads to the recruitment and/or activation of TFs and HATs (e.g. CREB and CBP) to enhancers and promoters of early response genes (ERGs), notably the transcription factor Fos. This first, rapid response leads to increased H3K27ac, enhancer RNA (eRNA) transcription, strengthening of enhancer/promoter interaction and up-regulation of ERGs, thereby inducing a second regulatory wave, leading to activation of cell-type-specific late response genes (LRGs), which depends on the specific function of the cell within a neural circuit (Yap and Greenberg, 2018). In brain tissues, LRGs are effector genes promoting synaptic plasticity. In response to neuronal stimulation, H3K27ac is increased at LRGs enhancers (Fig. 2). LRGs are induced in time and cell-type-specific controlled manners thanks to the cooperation between AP-1 proteins, especially FOS, cell-type-specific pioneer transcription factors and factors regulating nucleosome eviction (Vierbuchen et al., 2017). It is noteworthy that, in contrast to activity-regulated enhancers, cellular identity enhancers did not show increased H3K27ac in response to cellular stimulation (Vierbuchen et al., 2017).

Thus, neuronal enhancers (and H3K27ac regulation) are critical for the acquisition and maintenance of stable neuronal identity, but also for the dynamic regulation of neuronal activity. While genome wide association studies (GWAS) provide increasing evidence that cell-type-specific enhancers, especially super-enhancers, are hotspots for risk variants modulating susceptibility to neurological diseases, fewer epigenomic studies have addressed the role of enhancers in brain diseases (Heinz et al., 2015; Nord and West, 2020; Nott et al., 2019). However, the advent of genome-wide scale approaches to investigate the brain epigenome has made it possible to identify defined epigenetic signatures in neurological diseases, including neurodegenerative diseases such as HD and AD. Whereas genetic mouse models of these diseases have led to pioneered and critical exploratory studies, increasing data are currently being produced using human brain samples. Here we focus on epigenomic data generated using brain tissues from HD and AD mouse models, as well as post-mortem brain samples from patients. Remarkably, the data indicate that, in both HD and AD brains, neuronal- and glial-specific enhancers show distinct epigenetic signatures, which might stimulate the development of common innovative therapeutic strategies.

2. Epigenetic dysregulation and enhancer regulation in HD

2.1. Etiology and neuropathology of HD

HD is a progressive neurodegenerative disease, usually characterized by adult onset, though there are also juvenile forms of the disease, showing severer clinical presentation and faster progression when compared to the adult form. This is a purely genetic disease caused by an unstable CAG triplet repeat expansion in the first exon of the HTT gene. The number of CAG repeats at HTT is polymorphic in the normal population and does not exceed 36–39 CAGs. Above this threshold, the CAG repeat is pathogenic, resulting in the production of toxic mutated HTT proteins with polyglutamine (polyQ) expansion highly prone to aggregation. Since longer repeats are more toxic, there is an inverse correlation between the number of repeats and age of disease onset (Bates et al., 2015). Moreover, the HD mutation is unstable in the germline and in somatic tissues, which results in increasing numbers of CAG repeats in successive generations and in somatic tissues with age (Lopez Castel et al., 2010). GWAS showed that genetic modifiers in HD, which modulate the age-at-onset, predominantly target DNA repair genes implicated in CAG repeat instability, including FAN1 and the mismatch repair genes MLH1 and MSH3 (Genetic Modifiers of Huntington’s Disease (GeM-HD) Consortium, 2019, 2015; Jones et al., 2017). Despite ubiquitous expression of the HTT gene, polyQ-HTT is predominantly toxic to specific neurons of the striatum, e.g. medium spiny neurons (MSNs). However, as disease progresses, additional brain regions are affected, including cortical regions. Microglias and astrocytes also contribute to the pathogenic process through astrogliosis and inflammatory response, as observed in several neurodegenerative diseases. Neurodegeneration results from a long period of brain cell dysfunction, characterized by multiple cellular defects, resulting from both gain- and loss-of function mechanisms (Bates et al., 2015; Saudou and Humbert, 2016). Particularly, the HD mutation induces large-scale transcriptional and epigenetic dysregulations in the HD brain (Francelle et al., 2017).

2.2. HD transcriptomic signatures

A number of transcriptomic studies were performed using brain tissues of HD mice and post-mortem brain tissues (Francelle et al., 2017; Hodges et al., 2006; Kuhn et al., 2007; Labadorf and Myers, 2015; Luthi-Carter et al., 2000; Seredenina and Luthi-Carter, 2012). Specifically, comprehensive transcriptomic profiling using HD knockin mice expressing mutated Htt with different CAG repeat lengths indicated that transcriptional dysregulation in HD is CAG length-, age- and tissue-dependent, being most extensive in the striatum, and thus correlated with disease progression (Langfelder et al., 2016). Dysregulated genes in
Fig. 1. Regulation of brain cell-identity through super-enhancers. a, schematic representations of conventional enhancer-promoter chromatin looping (left) and chromatin looping at a super-enhancer-regulated gene (right). Super-enhancers are highly enriched in H3K27ac (yellow shadow), RNAPII and transcription factors (TF), including the mediator and cell type-specific TFs, leading to the generation of phase-separated condensates (phase-separation, blue circle). Super-enhancers regulate genes that define cell-type-specific identity and function, and that are generally highly expressed in their specific tissue/cell type. In contrast, conventional enhancers display more discrete features.

b, schematic representation of cell-type-specific epigenetic signature of neuronal striatal super enhancers. The striatum comprises different cell types, including neurons (purple) and glial cells (green), expressing cellular identity genes regulated by super-enhancers. Identity genes may be neuronal-specific or glial-specific. The picture is even more complex since different subpopulations of neurons and glial cells are present in the mammalian striatum, expressing each specific subsets of cellular identity genes, controlled by specific super-enhancers (for example D1 and D2 MSNs as compared to interneurons, and astrocytes, oligodendrocytes or microglia glial cells). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
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HD striatal tissue display characteristic signature that is conserved across mouse models, including knockin and transgenic mice, and also in post mortem brain tissues from HD patients (Achour et al., 2015; Kuhn et al., 2007; Langfelder et al., 2016; Luthi-Carter et al., 2000; Vashishtha et al., 2013). Specifically, down-regulated genes in HD striatum are enriched in neuronal function genes, particularly in genes that specify striatal identity (Achour et al., 2015; Hervás-Corpión et al., 2018; Langfelder et al., 2016; Vashishtha et al., 2013). These genes include typical markers of mature MSNs, including dopamine D1 receptor (D1R), dopamine D2 receptor (D2R), RGS9, DARPP32..., and the data indicate that gene down-regulation in HD striatal tissue is not just the consequence of neuronal death (Francelle et al., 2017; Kuhn et al., 2007). Furthermore, mouse data generated at different time points, including pre-symptomatic age, suggest that gene down-regulation in HD is an early process (Langfelder et al., 2016). Remarkably, up-regulated genes in HD brain tissue display a distinct functional signature since they are enriched in immune and developmental genes (Achour et al., 2015; Kuhn et al., 2007; Labadorf and Myers, 2015; Langfelder et al., 2016).

2.3. HD epigenomic signatures

Several epigenomic studies have been generated using brain tissues of HD mice and HD patients (Achour et al., 2015; Bai et al., 2015; Dong et al., 2015; Horvath et al., 2016; McFarland et al., 2012; Merienne et al., 2019; Ng et al., 2013; Valor et al., 2013; Vashishtha et al., 2013) (Table 1). Histone acetylation, including H3K27ac, H3K9,14 ac, H4K12ac and H2Aac, was a major focus in those studies. ChIP-seq analyses indicated that changes in H3K9,14 ac and H4K12ac were limited in the hippocampus and cerebellum of the HD transgenic mouse N171-82Q, and did not particularly correlated with transcriptional changes (Valor et al., 2013). In contrast, extensive changes in H3K27ac were
| Experimental approach | Biological specimen | Key findings | Bibliographic reference |
|-----------------------|---------------------|--------------|-------------------------|
| Co-immunoprecipitation, H3K27m3 and Htt ChIP-PCR | WT, Htt null and HdhQ111 embryoid bodies | Htt involvement in PRC2 complex activity and chromatin binding at heterochromatin domains enriched in H3K27me3 | Seong et al., 2010 |
| H3K9/K14ac (H3ac) ChIP-ChIP | R6/2 mice striatum | Genome-wide decrease in H3K9/K14ac but low correlation with differential gene expression | McFarland et al., 2012 |
| Reduced representation bisulfite sequencing (RRBS) and FRA-2, JUND, and SOX2 ChIP-seq | Cells carrying polyglutamine-expanded HTT (STHdhQ111/Q111) and wild-type cells (STHdhQ7/Q7) | DNA methylation changes at genes presenting expanded Htt-mediated transcriptional alterations and AP-1/Sox2 binding sites | Ng et al., 2013 |
| H3K9/14 ac and H4K12ac ChIP-seq | N171-82Q mice hippocampus | Few overlap of H3K9,14 and H4K12 ac and transcriptionally dysregulated genes. Small subset of genes with H3K9,14 and transcriptional dysregulation co-occurrence | Valor et al., 2013 |
| H3K27ac and RNA Polymerase II ChIP-seq | R6/1 HD mice striatum | H3K27ac hypo-acetylation and decreased RNA Polymerase II binding at neuronal super-enhancers associated with genes showing decreased transcriptional levels | Achour et al., 2015 |
| H3K4me3 ChIP-PCR and ChIP-seq | Human cortex from control and HD patients and R6/2 HD mice cortex and striatum | Decreased and increased H3K4me3 at the TSS of genes involved in neuronal function and gene expression regulation, respectively, accompanied by transcriptional dysregulation | Vashishtha et al., 2013 |
| H3K4me3 ChIP-seq | Neuronal (NeuN+) human cortical nuclei | H3K4me3 differentially enriched regions at genes implicated in neuronal development and neurodegeneration | Bai et al., 2015 |
| H3K27me3, H3K4me3 and H3K36me3 ChIP-seq | Isogenic WT, Htt null and heterozygous Htt CAG knock-in ESCs and NPCs | Htt involvement in ESCs for H3K27me3 deposition at “bivalent” loci and in their maintenance and removal in NPCs. CAG size, while slightly affecting H3K27me3, primarily impact H3K4me3 at “active” loci | Biagioli et al., 2015 |
| H3K4me3 ChIP-seq | Neuronal (NeuN+) human cortical nuclei | Low correlation of H3K4me3 differentially enriched regions and differentially expressed genes in HD human neurons | Dong et al., 2015 |
| Western Blot, Immunohistochemistry, H3ac and H3K4me3 ChIP-PCR | R6/1 and YAC128 HD mice brain, mHtt-electroporated mice brain cells, mHtt-infected neurons and PC12-TetOn-HD23/72Q | Absence of bulk chromatin changes but histone deacetylation at the TSS of particular genes involved in neuronal functions, accompanied in some cases with transcriptional dysregulation and defective H3K4me3 | Guiretti et al., 2016 |
| DNA-methylation by bisulfite sequencing | Human brain tissues from controls and HD patients | HD brain regions present a significant epigenetic age acceleration by an average of 3.2 years in specific brain regions (frontal lobe, parietal lobe, and cingulate gyrus) in a CAG-dependent manner | Horvath et al., 2016 |
| H3K4me3, H3K27ac and H3K36me3 ChIP-seq | Neural cell cultures from differentiated control and HD iPSCs | Genome-wide alterations affecting genes involved in cell lineage determination | IPSC-HD consortium, 2017 |
### Table 1 (continued)

| Experimental approach | Biological specimen | Key findings | Bibliographic reference |
|-----------------------|---------------------|--------------|-------------------------|
| H3K9me3 ChIP-on-ChIP  | R6/2 mice striatum | H3K9me3 increase in genes involved in cellular protein metabolic processes and intracellular signal transduction and decrease in genes associated with sensory perception and neurological system processes | Lee et al., 2017 |
| eRNA transcriptomic analysis | R6/1 HD mice striatum | Decreased eRNA of striatal neuronal identity genes associated to decreased RNA Polymerase II binding | Le Gras et al., 2017 |
| Transcriptomic meta-analysis | R6/1 and N171-82Q mice striatum, cortex, hippocampus and cerebellum | Significant transcriptional signatures overlap of HD mice models and mouse deficient for epigenetic regulatory genes | Hervás-Corpión et al., 2018 |
| Total H3 and H3K27me3 ChIP-PCR | Drosophila melanogaster HD model | H3K27me3 is not altered in flies expressing mutant HTT | Song et al., 2018 |
| H3K27ac ChIP-seq | Human caudate and cerebellum | H3K27ac hipo-acetylation at neuronal super-enhancer regulated genes showing decreased transcriptional levels | Merienne et al., 2019 |
| H3K4me3 ChIP-seq and ATAC-seq | Neuronal cell cultures from differentiated control and HD iPSCs | H3K4me3 alterations near TSS of genes involved in cell-cycle, highly overlapping with transcriptional upregulation for genes with increased H3K4me3 and binding of TFs involved cell-cycle regulation | Smith-Geater et al., 2020 |
| DNA-methylation by bisulfite sequencing | Human blood, lymphoblasts, and fibroblasts tissue from controls and HD patients; Q20 and Q175 HD KI mouse tissue; control and HD sheep blood | Conserved DNA methylation changes in blood samples at 33 CpG sites, including HTT gene associated with motor progression in manifest HD cases at three particular loci (PEX14, GRK4 and COX412) | Lu et al., 2020 |

**Fig. 3.** Cell type-specific dysregulation of super-enhancers in HD. Scheme illustrating epigenetic signatures in the HD striatum. Super-enhancers regulating neuronal identity genes (purple) and glial identity genes (green) are differentially impaired in HD. In control striatum (top panels), both neuronal and glial super-enhancer-regulated genes are highly enriched in H3K27ac (green circles), leading to extensive promoter-enhancer interactions and high transcriptional rates. In the HD striatum (bottom panels), neuronal super-enhancers (bottom left panel) are depleted in H3K27ac, correlating with down-regulation of neuronal identity genes. In contrast, glial super-enhancers in HD (bottom right panel) show increased H3K27ac, associated with increased transcription. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
observed in the striatum of HD R6/1 transgenic mice (Auchour et al., 2015; Le Gras et al., 2017). Similar results were found analyzing H3K27ac ChIP-seq data generated using post mortem striatal tissue of HD patients at early symptomatic stage (Merienne et al., 2019). Although bulk striatal tissue was used in these studies, integrated analysis with cell type-specific transcriptomic striatal database allowed specifying the contribution of neurons and glial cells to H3K27ac changes. H3K27ac was depleted at neuronal super-enhancers in HD vs controls, which correlated with down-regulation of neuronal super-enhancer-regulated genes (Auchour et al., 2015; Merienne et al., 2019) (Fig. 3). Remarkably, this associated with depletion in RNAPII throughout neuronal super-enhancers, and reduced eRNAs (Auchour et al., 2015; Le Gras et al., 2017; Sabari et al., 2018). In contrast, H3K27ac and transcription were increased at glial-specific enhancers (Merienne et al., 2019). Whether maintenance or acquisition of striatal cell identity is compromised in HD is an intriguing possibility that could underlie the mechanism.

HD promoter features were also investigated targeting H3K4me3, which is enriched at active promoters (Bai et al., 2015; Dong et al., 2015; Guiretti et al., 2016; Vashishtha et al., 2013) (Table 1). ChIP-seq data generated using the striatum and cortex of HD R6/2 transgenic mice indicated that H3K4me3 was widely depleted at neuronal identity gene promoters, which displayed broad H3K4me3 profiles, while genes showing increased H3K4me3 showed a developmental signature (Vashishtha et al., 2013). H3K4me3 was also investigated using post mortem prefrontal cortex from HD patients, a region however showing mild neuropathological involvement in HD (Bai et al., 2015; Dong et al., 2015). These studies specifically analyzed cortical neurons after nuclei sorting using fluorescently activated nuclei sorting (FANS), and identified hundreds of regions differentially enriched in H3K4me3 in HD vs control samples, which were preferentially depleted in H3K4me3. Although the connection between increased H3K4me3 and transcription in HD brain remains elusive, depleted H3K4me3 in HD vs control samples correlated with reduced transcription (Dong et al., 2015).

Collectively, H3K4me3 and H3K27ac epigenomic data indicate that the HD mutation induces loss of activity of neuronal-specific enhancers and promoters implicated in the control of neuronal identity genes. Whether the HD mutation also affects activity-driven epigenetic regulation of neuronal-specific genes implicated in neuronal plasticity is yet unknown, since none of above epigenomic studies described were performed using behavioral paradigms challenging the brain.

2.4. Abnormal epigenetic aging vs development

On the one hand, HD is an age-related disease that is progressive in nature and generally characterized by adult onset, which might suggest that epigenetic aging is altered in HD. DNA methylation can be used to estimate biological age, which better reflects the aging process than gene expression or more directly related markers (Horvath, 2013). Using this reference as an epigenetic biomarker of aging, the authors showed significant acceleration of biological age (Horvath, 2013). Using this reference as an epigenetic biomarker of aging, the authors showed significant acceleration of biological age (Horvath et al., 2016) (Table 1). Specifically, persistent expression of developmental genes, including OCT4, was observed during striatal neuron differentiation in HD iPSCs, together with abnormal H3K27ac and H3K4me3 profiles, which reflected more immature neuronal state than that observed in controls (HD iPSC Consortium, 2017; Smith-Geater et al., 2020).

Thus, abnormal epigenetic regulation during neurodevelopment might compromise proper acquisition of cellular identity of HD terminally differentiated neurons. It is possible, however, that HD-mediated epigenetic alterations during development render neurons more vulnerable to environmental stressors, which may be compensated during early life, but not at later stage, due to cellular aging. Thus, HD epigenetic neurodevelopmental and aging-associated components may be related.

2.5. Dysregulation of epigenetic regulators by mutated HTT

A number of studies have provided evidence for dysregulation of specific chromatin regulators in HD, which may contribute to disruption of the HD epigenetic landscape. It was found in early studies that the HAT CBP is recruited in polyQ-HTT aggregates in HD neurons (Nucifora et al., 2001; Seredenina and Luthi-Carter, 2012; Steffan et al., 2001). Since H3K27ac is a bona-fide target of CBP (Tie et al., 2014), titration of CBP by polyQ-HTT aggregates could lead to neuronal-specific depletion of H3K27ac. Noticeably however, mutant HTT aggregate formation is a rather late event with respect to HD pathogenesis. Thus, sequestration of CBP in polyQ-HTT aggregates is unlikely to explain epigenetic dysregulation occurring during neuronal differentiation. Nonetheless, a numbers of studies indicate that targeting histone acetylation in HD is beneficial, at least in animal models (Butler and Bates, 2006; Francelle et al., 2017). Specifically, several histone deacetylase inhibitors (HDACi) have been used to treat HD mice and drosophila models, which led to partial recovery of HD-like phenotypes (Ferrante et al., 2003; Gardian et al., 2005; Hockly et al., 2003; Jia et al., 2016; Naia et al., 2017; Siebzehnrübl et al., 2018; Steffan et al., 2001; Suelves et al., 2017; Thomas et al., 2008). Interestingly enough, the HDACi LBH589 improved HD neuronal differentiation (Siebzehnrübl et al., 2007; Siebzehnrübl et al., 2018). However, since no epigenomic data have been generated on HDACi treated animals, it is unclear whether histone acetylation is restored at neuronal super enhancers upon treatment. Moreover, the few transcriptomic data do not support complete rescue of neuronal identity gene transcription, and rather suggest that HDACi modulate metabolic genes (Naia et al., 2017). Yet, in mature neurons, histone acetylation is critical to activity-driven transcription, i.e. to the dynamic regulation of plasticity genes in response to neural stimulation (Malik et al., 2014). Thus, it would be interesting to test whether compounds that target histone acetylation affect activity-driven genes in the context of HD.

Additional pieces of evidence indicate that protein complexes and/or enzymes facilitating a repressive chromatin state are modulated by polyQ-HTT, which could impair the balance between euchromatin and heterochromatin. For example, the activity of polycomb repressive complex 2 (PRC2) was enhanced by mutant HTT, and during neuronal differentiation, HTT was required for proper regulation of H3K27me3, a PRC2 target enriched in facultative heterochromatin (Biagioli et al., 2015; Seong et al., 2010; Song et al., 2018) (Table 1). However, the effect of mutant HTT on H3K27me3 in mature neurons remains elusive. Other studies showed that the histone H3K9 methylase ESET/SETDB1
### Table 2

**Summary of HD epigenomic studies.**

| Experimental approach | Biological specimen | Key findings | Bibliographic reference |
|-----------------------|---------------------|--------------|-------------------------|
| HDAC1, HDAC2, HDAC3, acetyl H2BK5, acetyl H3K14, acetyl H4K5, acetyl H4K12, phospho-GR1 (S211) and phospho-RNA Pol II ChIP-PCR | Hippocampal tissue from control and CK-p25 mice | HDAC2, but not HDAC1 and HDAC3, is increased at promoter of genes involved in memory and synaptic plasticity in the AD mouse CK-p25, with a concomitant reduction of several histone acetylation marks, RNA Pol II recruitment and gene transcription | Graff et al., 2012 |
| H3K27ac ChIP-seq | Human cell and tissue samples | SNPs associated to AD are over-represented in brain super-enhancers as compared to other tissues | Hinz et al., 2013 |
| DNA-methylation by bisulfite sequencing | Human prefrontal cortex of control and AD patients | AD associated CpG methylation regions are significantly enriched in weak enhancers | De Jager et al., 2014 |
| H4K12ac ChIP-seq | Hippocampal CA-1 neuronal an non-neuronal cells from control and APP/PS1-21 mice | Global decrease of H4K12ac in both, neuronal and non-neuronal cell populations | Benito et al., 2015 |
| H3K4me1, H3K4me3, H3K9me3, H3K27me3, H3K27ac, H3K36me3 and and H4K20me1 ChIP-seq | Hippocampus from control and CK-p25 AD mice | CK-p25 increased-level enhancer and promoters showed functional enrichment in immune and stimulus-response functions, while decreased-level enhancer and promoters were enriched in synapse and learning-associated functions, matching transcriptional alterations | Gjonoska et al., 2015 |
| H3K4me1 and H3K6me3 ChIP-seq | Hippocampal neuronal nuclei from control, Kmt2a cKO and Kmt2b cKO mice | Significant overlap between H3K4me3 hipo-methylated promoters in the AD mice CK-p25 and the lysine methyltransferase cKO Kmt2a, but not Kmt2b, affecting genes involved in memory- and synaptic-plasticity-related processes | Kerimoglu et al., 2017 |
| H2BK12/K15ac, H2BK5ac and H3K27ac ChIP-seq | Dorsal hippocampus from control and THY-Tau22 transgenic mice | Significant decrease of H2B and not H3K27 acetylation levels in tauopathic mice hippocampus affecting genes involved in neuronal functions | Chatterjee et al., 2018 |
| H3K27ac ChIP-seq | Human entorhinal cortex from control and AD patients | Genome-wide acetylic alterations at regulatory regions affecting genes | Marrs et al., 2018 |

| Experimental approach | Biological specimen | Key findings | Bibliographic reference |
|-----------------------|---------------------|--------------|-------------------------|
| H4K16ac ChIP-seq | Lateral temporal lobe of young, old cognitively normal, and AD individuals | H4K16ac changes define functionally distinct subsets of age-regulated (changed by aging in physiological and AD conditions), age-dysregulated (changed by aging but not in AD) and disease-specific (only changed in AD) high percentage (30%) of non-coding AD SNPs localize at enhancer regions within topologically associated domains shared with their eQTL genes, suggesting a major role of chromatin high-order three-dimensional structures in AD disease | Nativio et al., 2018 |
| ATAC-seq, ChIP-seq, PLAC-seq | Neurons, astrocytes, oligodendrocytes and microglia isolated from human brain cortex | neurons of enhancers in AD at intergenic and exonic regions associated with genes involved in neurogenesis and neurodevelopment characterize as an AD-risk associated haploype via an enhancer-promoter chromatin loop | Sanchez-Mut et al., 2018 |

was increased in the striatum of HD transgenic mice, a feature correlating with dysregulation of H3K9me3, a marker of constitutive heterochromatin (Lee et al., 2017; Ryu et al., 2006). Underlying mechanism might involve impaired interaction between mutated HTT and ATP7P-ESET/SETDB1 complex (Irmak et al., 2018). Finally, using a genetic screen in a drosophila model system indicated that HTT physiological
function includes chromatin re-organization through regulation of H3 methylation at heterochromatin-euchromatin boundaries (Dietz et al., 2015). While these studies support the notion that HTT might act as an epigenetic regulator contributing to reprogramming of facultative and/or constitutive heterochromatin during neurodevelopment, the direct effect of mutant HTT on repressive histone marks in mature neurons and their impact on transcriptional regulation remains unclear.

3. Epigenetic dysregulation and enhancer regulation in AD

3.1. Etiology and neuropathology of AD

AD is an aging-related neurodegenerative disease characterized by the accumulation of amyloid beta peptides (Aβ) and neurofibrillary tangles, which are composed of abnormally phosphorylated Tau protein. AD leads to progressive synaptic and neuronal loss, most particularly in the prefrontal cortex and hippocampus, thereby resulting in memory decline (Serrano-Pozo et al., 2011). Neuroinflammatory response is also a major hallmark of AD. A minority of cases, usually characterized by early onset (i.e. <65 years), is caused by mutations in genes implicated in Aβ processing, including APP and presinilins. However, the vast majority of cases are sporadic (>95%) and late onset, and result from more complex etiology implicating both environmental and genetic risk factors. While aging is the strongest environmental risk factor, GWAS studies revealed several genetic risk variants, including variants associated with APOE and BIN1 (Bellenguez et al., 2019; Jansen et al., 2019).

3.2. Brain enhancers, hotspots for AD-risk variants

Consistent with AD pathogenesis, genes associated to AD-risk variants are enriched in 4 major functions, including Aβ formation, tau, lipid metabolism and immune response (Jansen et al., 2019). Thus, it is believed that risk variants play causal role, modulating transcription of associated genes (Grubman et al., 2019; Jansen et al., 2019; Klein et al., 2016; Nott et al., 2019). However, the interpretation of risk variants remains elusive in many instances, since they are often located in non-coding regions of the genome that may be distant to the gene(s) they modulate (Maurano et al., 2012; Nott et al., 2019). Analysis of GWAS catalog database showed that nearly 30% of non-coding AD SNPs are located in enhancers, with 95% of the AD SNPs located in enhancers co-localizing with their expressed quantitative trait locus (eQTL) genes in topologically associated domains (Kikuchi et al., 2019). Epigenome-wide studies using post mortem brain tissues of AD patients further point to a critical role for enhancers in AD-risk variants, since differential DNA methylation patterns between AD and control individuals were enriched at enhancers (De Jager et al., 2014; Li et al., 2019; Lunnon et al., 2014) (Table 2). The role of enhancers and DNA methylation in mediating the effect of risk factors in AD was supported by a study showing that an AD-risk associated haplotype in enhancer-like regulatory region associates to hypermethylation of PM20D1 promoter, which alters the regulation of this stress-responsive gene (Sanchez-Mut et al., 2018) (Table 2). The authors proposed that AD-risk associated haplotype impairs CTCF-mediated chromatin loop implicating PM20D1 promoter and enhancer (Fig. 4).

The heterogeneity of cerebral tissues represents another limitation to the interpretation of risk variants, especially since increasing evidence
indicates that functional consequences of risk variants are cell-type-specific (Yeh et al., 2017; Tansey et al., 2018; Nott et al., 2019). Network analysis of bulk AD brain transcriptome indicated gain of microglial gene connectivity and loss of neuronal connectivity, suggesting cell-type-specific effects of AD-risk variants, notably up-regulation of microglial-specific genes and down-regulation of neuronal-specific genes (Zhang et al., 2013). Studies using single-nucleus/cell RNA sequencing on AD and control cortices provided additional insights, showing that APOE is upregulated in an AD-specific microglial subpopulation (Grubman et al., 2019; Mathys et al., 2019). To interpret the effects of AD risk variants in a cell-type-specific manner, Nott and collaborators performed epigenomic analysis using human resected cortical brain tissues and found that microglia-specific enhancers were more particularly enriched in AD risk variants (Nott et al., 2019). Using proximity ligation assisted ChiP-seq (PLAC-seq) to establish cell-type-specific enhancer-promoter interactome maps and CRISPR/Cas9 technology, they further showed that risk variant rs6733839, the second highest AD-risk variant, is located in microglia enhancer controlling microglia-specific transcription of BIN1 (Nott et al., 2019). Thus, increasing evidence indicates that brain-specific enhancers, most particularly microglial-specific enhancers, are hotspots for genetic and/or epigenetic variations in AD, thereby contributing to AD pathogenesis in a cell-type-specific manner (De Jager et al., 2014; Jansen et al., 2019; Kikuchi et al., 2019; Nott et al., 2019). Finally, AD-associated risk variants are enriched in super-enhancers, suggesting critical role for super-enhancers in AD etiology (Hnisz et al., 2013; Nott et al., 2019).

3.3. Genome-wide scale enhancer dysregulation in AD

In addition to locus-specific effects on enhancers due to disease-associated genetic variants, several studies indicate more global transcriptional dysregulation of enhancers in AD brain tissue, correlating with transcriptional alterations (Benito et al., 2015; Chatterjee et al., 2018; Gjoneska et al., 2015; Klein et al., 2016; Li et al., 2019; Marzi et al., 2018) (Table 2). First evidence came from studies using AD mouse models (Benito et al., 2015; Gjoneska et al., 2015). Transcriptomic and epigenomic profiling using the hippocampus of CK-p25 mouse model, showing amnyloid and tau pathologies, revealed coordinated down-regulation of synaptic plasticity genes and associated enhancers and promoters and, in contrast, upregulation of immune response genes and regulatory regions, including genes and regulatory regions specifically active in microglia (Gjoneska et al., 2015). H3K27ac and H3K4me3 were reduced at neuronal-specific enhancers and promoters, respectively, which correlated with down-regulation of their target genes, whereas the direction of epigenetic and transcriptional changes at glial-specific regulatory regions genese was opposite (Gjoneska et al., 2015). Consistently, decreased and increased-level regulatory regions were enriched in distinct DNA motifs, recognized by neuronal- and glial-specific transcriptional regulators, respectively (Gjoneska et al., 2015). H3K27ac profiling of AD post-mortem entorhinal cortex samples supported mouse data, showing that enhancer dysregulation is a major hallmark of AD brain (Marzi et al., 2018). Comparing samples of AD patients vs control individuals, thousands of genes were identified that associated with hyper- or hypo-acetylated peaks, and the direction of change in acetylation positively correlated with some of the transcriptional changes (Marzi et al., 2018). Gene ontology analysis further indicated that genes nearby increased H3K27ac in AD samples were enriched in metabolic functions, possibly including glial response, while neuronal processes associated with regions depleted in H3K27ac (Marzi et al., 2018). This might suggest that AD, similar to HD, leads to opposite H3K27ac changes at neuronal- and glial-specific enhancers. Although super-enhancers and identity genes have not been specifically investigated in AD studies, one cannot exclude that comparable genome-wide scale reprogramming of neuronal and glial cell identities operates in AD and HD brains.

Comprehensive fine-mapping of DNA methylation further suggests a crucial role for enhancer dysregulation in AD neuronal pathogenesis, since thousands of differentially methylated enhancers were identified in neurons isolated from prefrontal cortex of AD patients vs control individuals (Li et al., 2019). Surprisingly however, most of these regions were hypomethylated non-CpG sites (e.g. CpH sites), a result that correlated with increased transcriptional activity of closest genes (Li et al., 2019). Methylation at CpH is a major feature of mature neurons, rising during development and correlating with synaptogenesis (Lister et al., 2013). While the role of these non-canonical methylation sites in AD is yet to be uncovered, the results by Li and collaborators indicate that hypomethylation at CpH sites essentially targets genes linked to neurogenesis, including genes promoting neuronal proliferation and migration (Li et al., 2019). Thus, pathological re-activation of neurodevelopmental genes mediated by loss of CpH methylation in enhancers of neurons might be feature of AD.

Finally, changes in additional histone modifications, particularly histone acetylation, including H3K9ac, H3K14ac, H4K5ac, H4K12ac, H4K16ac and H2Bac were also observed in brain tissues of AD mouse models and/or post-mortem AD brain cells. While it is not clear whether those acetylation changes were enriched in specific regulatory regions, these results indicate a degree of complexity of AD epigenetic signature (Benito et al., 2015; Chatterjee et al., 2018; Graff et al., 2012; Klein et al., 2019; Nativio et al., 2018) (Table 2). Collectively, epigenomic data show that AD leads to significant cell-type-specific epigenetic dysregulation of brain enhancers. While histone acetylation remains a major focus in AD epigenomic studies, H3K4me3 was found dysregulated in AD mice, indicating that epigenetic regulation of promoters is likely impaired in AD (Gjoneska et al., 2015; Kerimoğlu et al., 2017).

3.4. Epigenetic control of activity-regulated genes in AD

The dynamic epigenetic control of gene program regulating neuronal plasticity is critical to memory formation and maintenance, and histone acetylation plays a central role in this mechanism (Yap and Greenberg, 2018). Several studies suggest that altered regulation of histone acetylation contributes to memory decline in AD (Fischer, 2014a). Early study revealed that histone deacetylase 2 (HDAC2) was increased at neural plasticity genes, both in brain tissues of AD mice and in post-mortem brains from AD patients (Graff et al., 2012). Consequently, AD mice were treated with HDAC inhibitors (HDACi), which generally improved memory function and, when tested, also ameliorated synaptic plasticity (Fischer, 2014b; Graff et al., 2012). More specifically, epigenomic and transcriptomic analyses showed that, in APP/PS1-21 CE mice, treatment with SAHA specifically restored H4K12ac at synaptic plasticity genes in CA1 hippocampal neurons, which correlated with partial transcriptional normalization (Benito et al., 2015). Interestingly enough, memory function and synaptic plasticity were also restored in tauopathic mice treated with an activator of the HAT CBP/P300, the compound CSP-TTK21 (Chatterjee et al., 2018; Chatterjee et al., 2013). Epigenomic and transcriptomic analyses using the dorsal hippocampus of tauopathic mice further showed that the functional amelioration observed (rescue of long-term spatial memory, LTD and learning-induced CA1 dendritic spines) associated with transcriptional rescue of activity-regulated genes and increased H2B acetylation at CBP-regulated enhancers, while H3K27ac remained unchanged at this age (Chatterjee et al., 2018). In addition, CBP levels were decreased in the hippocampus of tauopathic mice as well as in postmortem prefrontal cortices of AD patients (Bar-tolotti et al., 2016; Schueller et al., 2020), suggesting a role for CBP in the dysregulation of these genes (Chatterjee et al., 2018), an hypothesis supported by an earlier study showing that gene transfer delivery of CBP in the hippocampus of AD mice improves memory processes (Caccamo et al., 2010).
Altered epigenetic aging may be another mechanism driving epigenetic defects in the AD brain. Whether epigenetic aging is accelerated and/or dysregulated was recently addressed through epigenomic studies using post mortem brain tissues of AD patients (Li et al., 2019; Nativio et al., 2018). Investigating H4K16ac, a promoter mark linked to DNA damage repair and increased in senescent cells (Dang et al., 2009; Kozak et al., 2010), Nativio and collaborators identified 3 types of changes in the lateral lobe of AD patients (Nativio et al., 2018). A first category of changes corresponded to disease-specific changes and were observed comparing AD patients to age-matched individuals. A second category of age-dysregulated changes defined changes found in aged vs young individuals but not in AD vs young individuals. The last category of changes comprised age-regulated changes, observed in both aged control and AD, vs young individuals. Interestingly, disease-specific changes affected genes were enriched in neuronal functions, while age-dysregulated changes implicated immunity and stress response genes, reflecting glial responses. Age-dysregulated changes were predominantly characterized by age-dependent increase in H4K16ac in control individuals, but age-dependent H4K16ac depletion in AD individuals, suggesting AD leads to dysregulated aging and is not simply accelerated aging (Nativio et al., 2018). However, cell type-specific epigenomic analysis focusing on H4K12ac indicated aging-related acceleration of decreased H4K12ac in hippocampal neurons of AD mice modeling amyloid pathology, and the mechanism correlated with down-regulation of target genes, which were enriched in neuronal plasticity genes (Benito et al., 2015). Also, using the epigenetic clock on enhancer CpG sites from healthy individuals, Li and collaborators found that neurons of advanced AD cases show significant acceleration of epigenetic aging (Li et al., 2019). Thus, current studies provide a rather complex picture of the interplay between AD and epigenetic aging. Undoubtedly, investigating the impact of aging on additional epigenetic marks, including H3K27ac, and at cell type-specific resolution should help refine the conclusions and specify the role of epigenetic aging in AD. It is noteworthy that H3K27ac was found to be a key predictor of age-related transcriptional changes in various mammalian tissues (Benayoun et al., 2019). Finally, recent evidence suggests that tau-related alteration induces widespread reorganization of chromatin architecture, which could contribute to aging-related mechanisms (Klein et al., 2019). Remarkably, neurons appear to be more specifically affected by the mechanism (Klein et al., 2019). Altered maintenance and regulation of heterochromatin due to pathologically phosphorylated tau would be the driving force, through impairment of nuclear lamina organization (Chang et al., 2010; Klein et al., 2019; Mansuroglu et al., 2016).

Several mechanisms might contribute to large-scale dysregulation of epigenetic landscape in AD. Yet, it is unclear whether enhancer dysregulation is a primary defect driving other epigenetic changes or is secondary to earlier mechanisms.

4. Conclusions and perspectives

Epigenomic and transcriptomic data generated on animal models and tissues from HD and AD patients revealed epigenetic changes in affected brain tissues, for both diseases. Remarkably, despite different etiologies between HD and AD, current data indicate that HD and AD pathogenesis associate with large-scale dysregulation of enhancers and promoters, which positively correlates with transcriptional alterations. Although additional studies are required to specify the nature, temporal dynamics, spatial chromatin re-organization and cell type-specificity of changes at HD/AD enhancers and promoters, a picture emerges from current data. Neuronal- and glial-specific regulatory regions and their associated genes show lower and increased activities, respectively, in disease vs control brains, which might contribute to loss of neuronal function and inflammatory responses, two major pathological hallmarks.

More specifically, HD data show that neuronal super-enhancers are particularly vulnerable in the HD striatum, suggesting loss of striatal identity. The role of glial cells in this mechanism needs to be better deciphered, but it is noteworthy that glial-specific genes are increased in the HD striatum, which might support the idea of pathological epigenetic reprogramming. The timing of such defects needs to be investigated, but data generated on stem cell-based models suggest that it could start earlier than anticipated, perhaps during neuronal differentiation. Epigenomic analysis on additional affected brain tissues in HD should also tell whether loss of tissue identity is specific to the striatum, or whether it just develops earlier in this tissue, the primary target of the disease. While the mechanism underlying super-enhancer signature in HD striatum remains unclear, it would be of interest to investigate additional components of enhancers that are particularly enriched in super-enhancers, including CBP, the mediator and master transcriptional factors of tissue-specific identity. Also, it is possible that specific chromatin architecture and/or biophysics properties, promoting phase separation at super-enhancers, are disrupted, thereby contributing to transcriptional effects and cellular reprogramming.

While the role of neuronal super-enhancers in AD remains to be specified, it is noteworthy that glial (particularly microglial) super-enhancers are enriched in AD-associated risk variants, which suggests critical role for super-enhancers in AD etiology. Large-scale remodeling of neuronal and glial epigenetic landscape in AD neuronal tissues might support more global implication of super-enhancers in AD pathology, but this remains to be investigated.

Also remarkably, re-activation and/or persistent activation of neurendendevolopmental genes are features observed in both HD and AD models. Whether these events reflect epigenetic reprogramming of HD/AD neural tissues and contribute to loss of tissue identity, is an intriguing possibility. During neuronal differentiation, neurodevelopmental genes undergo PRC-dependent silencing implicating H3K27me3, notably inducing bivalent chromatin state at associated promoters and enhancers, which ensures transcriptional repression while keeping permissive transcriptional state (Rada-Iglesias et al., 2011; Taberlay et al., 2011). In mature neurons, PRC maintains repressive chromatin state at developmental genes, which prevents neurodegeneration as well as down-regulation of mature neuron identity genes (von Schimmelmann et al., 2016). It is tempting to speculate that this mechanism is impaired in HD/AD neurons. If so, would it result from continuous process starting from early neuronal life (e.g. during development and neuronal differentiation) or would it be the consequence of the aging process?

Finally, the regulation of activity-driven regulatory regions and their associated genes is impaired in AD brain tissues, supporting the notion that dynamic regulation of neuronal activity is altered in AD. Whether similar mechanism is at play in HD remains to be investigated.

A unifying mechanism that would underlie epigenetic defects in HD or AD remains to be uncovered. The fact that common chromatin regulators (e.g. CBP) are impaired in both diseases might suggest a degree of overlap. Understanding the mechanism(s) driving epigenetic dysregulation is a current challenge, with potentially major therapeutic implications. Major limitations to take up the challenge include the brain complexity and the difficulty to address causal relationships between epigenetic changes and functional consequences. However, the current development of innovative deep sequencing methods, together with new genome editing tools and behavioral paradigms allowing to characterize and manipulate epigenetic and transcriptomic signatures of particular neural cell populations in specific activation states and at single cell resolution will undoubtedly overcome these issues (Grubman et al., 2019; Liu and Jaenisch, 2019). Also, advanced methods (e.g. Hi-C) to establish 3D maps of enhancer-promoter interactions in vivo at genome-wide and cell-type-specific levels will be critical to decipher causal roles of enhancers in neurodegenerative diseases (Nott et al., 2019). Finally, the generation of multi-omics atlas and databases using diseased brains together with the development of bioinformatics methods will also be
essential to provide comprehensive picture and build accurate models in disease stages, including pre-symptomatic and prodromal stages, represents a limitation to assess early temporal dynamics of epigenetic and transcriptional changes. In this context, mouse models will remain instrumental.

Declaration of Competing Interest

None.

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