Epigenetic Mechanism and Therapeutic Approaches in Huntington's Disease

Kangchia Luo *

Dulwich College Shanghai Pudong, Shanghai, 201206, China

* Corresponding Author Email: charles.luo26@stu.dulwich.org

Abstract. Huntington's Disease (HD) is a severe neurodegenerative disorder in which epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, play pivotal roles in its pathogenesis and progression. Abnormal DNA methylation patterns in HD may silence or dysregulate critical genes in the human brain, leading to neuronal dysfunction. Histone acetylation is disrupted by the impairment of CREB-binding protein (CBP), thus altering chromatin structure and impacting essential expression pathways that support neuronal survival. Non-Coding RNAs are yet another prolific branch of epigenetics, exhibiting a variety of duties and properties; in HD, microRNAs, long non-coding RNAs, and other ncRNAs can calibrate or undermine neuronal gene expression, making an impression in the HD scene. Accordingly, a myriad of therapeutic strategies either target or utilize the epigenetic mechanisms in HD. From CRISPR/dCas9 tools that can precisely modify DNA methylation at specific loci, to histone de-acetylase inhibitors that restore histone acetylation balance, to emerging ncRNA-targeted or ncRNA-participating therapies, these strategies develop divergently, with a range of success throughout these different approaches. Although many of these advances face challenges in delivery and specificity, epigenetic therapeutics show great potential in combating HD.

Keywords: Huntington's Disease, mechanism, treatment.

1. Introduction

Huntington's disease (HD) is a fatal neurodegenerative condition that induces conditions such as chorea or spontaneous, uncontrollable movement; cognitive and psychiatric disorders, such as changes in personality or difficulty in problem solving; and loss of coordination, most observed in the inability to maintain balance while walking [1]. The mutation which causes HD entails the abnormal expansion of CAG repeats on human chromosome 4, coding for the Huntingtin (htt) protein . The irregularity of htt proteins will result in neuronal death in the brain by contributing a plethora of factors, which then manifests in the symptoms of HD; notably, htt influences epigenetic processes such as neuronal histone acetylation, apprehension of CBP function, and DNA methylation which entails accelerated neuronal aging [2]. HD and epigenetic mechanisms are inseparable. Investigating HD with epigenetic lenses may yield fruitful perspectives and approaches, expediting efforts towards the cure of this disease. Targeting epigenetic facets of HD in therapeutics can provide insight to potential remedies. This paper aims to provide a brief overview on the development of epigenetics as a research field in biology, followed by a discussion of current epigenetic approaches to HD.

2. Proposed Epigenetic Mechanisms of Huntington's Disease

2.1 DNA Methylation in HD

Methylation in HD has been studied on various scopes, yet a convincing and encompassing pattern still eludes researchers. In preliminary study, it is established that HD will disrupt DNA methylation levels and accelerate the epigenetic aging of neurons - thus paints the background of methylation in HD [3].

A study observed a global loss of DNA hydroxymethylation (5hmc) in YAC128 HD mouse brain tissues, particularly in striatum and cortex regions, compared to controls [4]. However, some transgenic mice species do not conform to this trend, indicating divergent disease epigenome

regulation across species [5]. Expansively, another team, using Epigenome-wide association study (EWAS), showed strong correlation between HD and methylation levels at specific loci -PEX14, GRIK4, COX412- in three mammalian species respectively [6].

Hence, although global methylation changes occur, they may be subtle, tissue-specific, or influenced by uncontrolled variables. Interestingly, Huntington patients' striatum exhibit a significantly decreased expression of MBD2 methylation readers, which may suggest potential disruptions in the interpretation of methylation patterns present [7]. Concretely, more standardized and comprehensive studies are needed before a definitive DNA methylation profile specific to HD can be identified. Newer technologies and techniques auspice different perspectives on methylation patterns. Induced pluripotent stem cell (iPSC) derived neurons can simulate epigenetic alternations, modelling region-specific methylation changes regarding genes involved in synaptic function and neuron survival [8]. Alternatively, NGS methods have facilitated single-cell resolution analysis of epigenetic changes, allowing researchers to identify more subtle changes in methylation patterns [9]. In essence, future research requires data with more detail and accuracy, with analytical methods and algorithms more sensitive to small changes in methylation patterns.

2.2 CBP in HD

As aforementioned, HD arises from a toxic expansion of CAG repeats on the HTT gene, leading to the expression of mutant Huntington (mHtt) protein with a poly-glutamine (polyQ) domain. The mHtt proteins form harmful aggregates which disrupt cellular functions; one of its proposed victims is CBP. Some models show that mHtt can sequester CBP into its aggregates, inhibiting CBP's normal acetyltransferase activity [10]. The regions which are hypoacetylated have not been indicated. Interestingly, despite the CBP impairment, p300 turnover rates remain unfazed; whether p300 is affected mechanistically by mHtt aggregates remains opaque [11]. Depletion of CBP levels correlates with cellular toxicity and transcriptional dysregulation. The N-terminal fragment (exon 1) of mHtt binds and inhibits CBP, p300, and P/CAF acetyltransferase activity, reducing global H3 and H4 acetylation levels. HD impairs both motor and cognitive functions: reduced CBP expression and histone acetylation over the hippocampus locale correlate with diminished expression of genes involved in memory function [12]. Disruption of CBP function, implying interference with histone acetylation, is central to the pathogenesis of HD. The scope of epigenetic inquiries into HD should coincide with genetic factors to offer a holistic view of the molecular mechanisms of HD.

2.3 ncRNA in Huntington

Non-coding RNAs (ncRNAs), including miRNAs and lncRNAs, actively participate in the epigenetic regulation of HD. miRNAs are key modulators of gene networks disrupted in HD. For example, miR-124, crucial for neuronal differentiation and synaptic function, is significantly downregulated in HD [13]. This loss leads to dysregulated transcription of neuroprotective genes, contributing to neuronal dysfunction. In contrast, miR-146a is upregulated in HD brains, particularly in glial cells, where it promotes neuroinflammation by targeting pathways involved in innate immune responses [14].Additionally, miR-128a, another downregulated miRNA in HD, affects genes involved in chromatin structure and mitochondrial function, both of which are disrupted in HD pathogenesis [15].These miRNAs directly interact with epigenetic agents, including DNA methyltransferases (e.g., DNMT1) and HDACs, to alter chromatin states and repress gene expression. lncRNAs also play a pivotal role in HD-related epigenetic changes. The antisense lncRNA HTT-AS1, which overlaps with the HTT locus, regulates HTT gene expression. lncRNAs recruit the polycomb repressive complex 2 (PRC2), a chromatin-modifying complex, to specific gene loci. This interaction induces histone methylation (H3K27me3), leading to transcriptional repression of genes essential for neuronal survival [16]. HD brains also display accelerated epigenetic aging, characterized by altered DNA methylation patterns; ncRNAs guide DNMTs to specific loci, exacerbating transcriptional silencing and contributing to the progression of HD pathology [17]. In summary, dysregulated

miRNAs and lncRNAs mediate complex epigenetic modifications in HD, including DNA methylation, histone changes, and transcriptional repression, amplifying neurodegenerative processes.

3. Therapeutic Solutions

3.1 DNA Methylation Targeted Therapeutics

Epigenetic therapeutic methods targeting DNA methylation in HD aim to correct transcriptional dysregulation by correcting problematic methylation patterns. Problematically, attempts of this token tend to silence genes which are critical for neuronal survival yet irrelevant to HD pathogenesis. Currently, CRISPR/dCas9-based tools have demonstrated the most efficacy in HD targeted testing: with modified, nuclease-inactive dead Cas9 (dCas9) fused to DNA methyltransferases or demethylases, this model guides the epigenetic editing factors to specific, disease-relavent loci while allowing great flexibility for customization [18,19]. Remarkably, dCas9-based tools that edit on the epigenetic level do not risk mutagenesis from repairing double strand breaks. In the HD context, CRISPR/dCas-based systems have been used to selectively reduce hypermethylation at the gene promoter of BDNF (a crucial neurotrophic factor involved in HD pathogenesis), restoring its expression; revitalizing this gene can expedite synaptic activity, preventing death of neurons. This allele- or locus-specific editing minimizes global epigenetic disruptions, offering a more robust and safer alternative to traditional methods.

Small-molecule DNMT inhibitors such as 5-azacytidine and decitabine have also shown promise in preclinical models [20]. These compounds globally reduce DNA methylation levels, potentially alleviating transcriptional repression associated with HD pathology. Nevertheless, their lack of selectivity raises concerns about off-target effects and long-term toxicity, limiting their clinical utility. In response, researchers are developing advanced delivery mechanisms, including adeno-associated virus (AAV) vectors, lipid nanoparticles, and engineered exosomes, are being developed; these systems project to evade the blood-brain barrier (BBB), which prevents most molecules from entering the CNS, and achieve neuron-specific targeting.

Moreover, combining DNA methylation-targeting approaches with other epigenetic therapies, such as histone acetylation activators or RNA-based interventions, offers a multi-layered strategy to address HD's complex pathology. Such combinatory methods could synergistically improve transcriptional reactivation and neuronal protection, creating more comprehensive therapeutic effects.

Despite these advances, challenges remain, including ensuring long-term stability of edits in post-mitotic neurons and mitigating immune responses to the delivery vectors or editing proteins, not to mention ethical concerns revolving in vivo editing in humans. The diversity of HD haplotypes evinces the difficulty of a universal model for CRISPR-based methods; instead, personalized therapeutics, relying on access to genetic and epigenetic databases, present a feasible and accessible direction in HD therapy [21].

3.2 CBP and Histone Acetylation Targeted Therapeutics

Therapeutic approaches targeting CBP aim to restore histone acetylation and transcriptional homeostasis. Multiple studies note that overexpression of CBP or p300 in HD correlate with efficacy in rescuing histone acetylation levels, reducing mHTT toxicity, and improving motor and cognitive functions. Small-molecule HAT activators, such as CBP/p300 bromodomain inhibitors, enhance CBP function and reverse histone hypoacetylation in HD neurons [22].

Histone deacetylase inhibitors (HDACIs), particularly isoform-specific ones like HDAC3 inhibitors, complement CBP-based therapies by preventing the removal of acetyl groups, thereby maintaining an euchromatin structure conducive to transcription [23]. HDAC inhibition has demonstrated improved motor function (improved outcomes in ANOVA assessed rotarod tests) and increased histone acetylation in preclinical HD models. Notably, selective HDAC3 inhibitors demonstrate reduced toxicity and increased efficacy in alleviating transcriptional repression when compared to general HDACIs [24]. Combinatory approaches, leveraging both HAT activators and

HDACIs, offer a promising avenue for restoring CBP function and transcriptional balance [25]. Transcriptional arrest in HD is multifactorial, convening both genetic and epigenetic factors; it follows those multi-modal epigenetic therapies, addressing and considering multiple aspects of the disease, will yield more sustainable and auspicious results.

More broadly, therapeutic methods have appeared in genres which bypass the CREB pathway, targeting genes upstream of CREB and CBP. For example, phosphodiesterase 4 inhibitor (PDE4i) rolipram can prevent the hydrolysis of cAMP and increase PKA-dependent signaling upstream of CREB and CBP [23]. Studies have demonstrated that rolipram treatment of cell cultures can reverse CREB hypo-phosphorylation (usually induced by glutamate), indicating a potential trajectory for future studies [26].

Despite preclinical successes, similar challenges as the DNMTI implementation persist, namely off-target effects and ineffective delivery to the central nervous system (CNS). Adeno-associated viruses (AAV) and lipid nanoparticles are being explored to overcome these barriers and enhance therapeutic efficacy. Provisionally, gene targeted therapeutics - regarding the CBP gene or other upstream products - offer a promising approach to addressing transcriptional dysregulation; more concretely, harnessing the transcription factors which participate in said pathways is essential. Refined delivery technologies, will, thereby, facilitate the implementation of engineered molecular mechanisms in a clinical setting.

3.3 cRNA in Therapeutics

MicroRNA (miRNA)-targeted therapies are emerging as promising approaches for modulating gene expression in HD. Currently, miRNA targeted therapeutic research are rare, and even fewer have embarked on clinical trials; the most prominent of this species of studies uses a viral vector to carry miRNAs into the host organism, enhancing the function of a miRNA [27]. The viral vector and artificial miRNA strategy enhances natural miRNA mechanisms, such as casting in RNA-induced silencing complexes (RISC); such methods facilitate the continuous expression of the miRNA package in the host, discarding the need for redundant re-administrations and ensuring the long-term efficacy of the treatment. A preclinical study in a humanized mouse model of HD Hu128/21 has demonstrated the ability of miRNA-based interventions to mitigate disease progression. Using an adeno-associated viral vector AAV serotype 5 (AAV5) to deliver a miRNA targeting exon 1 of HTT (miHTT), the team showed suppression of certain HD behavioral and neuropathological symptomes by AAV5-miHTT, sustaining over 7 months post-injection [28]. Similarly, another study proved the use of miRNA, targeting the CAG repeats of the mHTT gene, in lowing mHTT level by 50%, without damaging endogenous mouse huntingtin levels [29].

Yet, because the targeting of HTT is non-selective, this therapeutic method risks dose-dependent side effects, including astrogliosis, motor impairment, and striatal atrophy. As miRNAs play a central role in HD progression, many studies have also shown its prospects as biomarkers for the disease, potentially able to serve as diagnostic or prognostic tools by detection in blood plasma [30].

Research into miRNA’s role as a biomarker is substantially more mature and prolific than regarding its central role as a therapeutic agent: this could be explained by the presence of major challenges, including the lack of safe and effective delivery methods, lack of specificity, or lack of an ideal target for miRNA-based therapies [31]. Such trends emphasize the integration of miRNA therapies with other RNA-based strategies, such as antisense oligonucleotides (ASOs) or small interfering RNAs (siRNAs), to enhance therapeutic efficacy, with miRNAs playing a supportive role, rather than central.

Similarly, siRNAs are effective tools for silencing toxic ncRNAs, such as those involved in chromatin remodeling errors or splicing defects, which are common in HD. These small RNAs leverage the RNA interference (RNAi) pathway to degrade specific targets and modulate downstream cellular pathways. A study has shown siRNA capabilities of gene silencing in HD: by targeting Msh3 mRNA -a genetic modifier which promotes CAG expansions in the HTT gene-, siRNAs effectively

reduced MSH3 protein levels in a dose-dependent manner, demonstrating their role in modulating somatic instability, a key pathological contributor in HD [32].

Aside from miRNAs and siRNAs, lncRNAs and ncRNAs are emerging as promising marking or diagnostic factors which may expedite therapeutics.

LncRNAs play crucial roles in regulating gene expression and chromatin remodeling, making them attractive therapeutic targets; lncRNAs are regulated by siRNAs, antisense oligonucleotides, CRISPR-Cas9, or other molecular inhibitors, thus illustrates lncRNA's versatile and responsive role [33].NEAT1, a lncRNA implicated in stress granule formation and neuroinflammation, is overexpressed in HD and contributes to synaptic dysfunction and neuronal degeneration and constitutes a possible therapeutic target [34].

CircRNAs, which act as miRNA sponges and modulate transcriptional processes, are another promising alley for exploration. Dysregulated circRNAs in HD affect neuronal gene expression, and therapies may aim to restore their normal activity either by modulating endogenous circRNAs or designing synthetic circRNAs that sequester toxic miRNAs or proteins [35].

Additionally, snoRNAs, which are integral to RNA modification and stability, are being investigated as a potential biomarker for HD. Plasma SNORD13 levels were notably higher in individuals with HD (n=9) compared to controls(n=8), correlating with both mutant huntingtin carrier status and the duration of the disease. The study shows SNORD13 can reliably differentiate HD patients from other groups (AUC = 0.963) [36].

The success of these therapies depends heavily on advanced delivery mechanisms, as crossing the blood-brain barrier and achieving neuron-specific targeting remain significant challenges. Evidently, delivery is a major impediment to the success of various modes of treatment, positing itself in the spotlight for targeted research with clinical implications. By integrating lncRNA, circRNA, siRNA, and snoRNA strategies, a myriad of combinative tactics are unveiled, and ncRNAs prove to be an ever promising yet woefully underexplored strategy for HD therapeutics.

4. Conclusion

Epigenetic mechanisms are central to understanding the onset and progression of HD. Such processes are both highly coordinated and collaborative; they operate to manipulate gene expression in ways that lead to neuronal atrophy. Understanding these intricate pathways have yielded valuable insights into the pathology of HD and illuminated prospective candidates for treatment and auspicious curative strategies.

Treatments that target epigenetic factors are a promising yet elusive frontier in HD research. Pharmacological agents that reabilitate gene expression on the epigenetic level, such as by restoring proper histone acetylation, reversing abnormal DNA methylation or modulating non-coding RNA activity, may help mitigate neuronal damage and restrain disease progression. Nevertheless, more comprehensive and expansive clinical testing, producing analyzable clinical data, is paramount to the development of therapeutics in HD.

Yet, numerous challenges remain, in viable delivery of these treatments to the disease locale, in precisely and consistently targeting pathological facets, and in designing feasible and ethical clinical regimens. As the understanding of epigenetic alterations grows, so does the possibility of developing more precise, patient-tailored interventions that address the underlying causes of individuals rather than merely managing the symptoms. Moreover, refining combinatory methods, engineering precise molecular mechanisms like ncRNAs to offset the diversity of HD haplotypes, surmounting current issue of off-target risks, may be yet another motif in the direction of HD research. Thus, the trajectory of epigenetic solutions to HD lies in developing personalized therapeutics, bioinformatic analysis, and delivery strategies.

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