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Review

Epigenetic-based therapies in the preclinical and clinical treatment of Huntington's disease☆

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ABSTRACT

The study of epigenetics is providing novel insights about the functional and developmental complexity of the nervous system. In neuropathology, therapies aimed at correcting epigenetic dysregulation have been extensively documented in a large variety of models for neurodegenerative, neurodevelopmental and psychiatric disorders. Taking the treatment of Huntington's disease as a paradigm for the study of these ameliorative strategies, this review updates the main conclusions derived from the use of epigenetic drugs at the preclinical and clinical stages, including actions beyond epigenetics.

This article is part of a Directed Issue entitled: Epigenetics dynamics in development and disease.

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1. Introduction

Huntington's disease (HD) is the most prevalent polyglutamine (polyQ) disorder caused by an aberrant expansion of CAG repeats (>36) in exon 1 of the Huntingtin (*HTT*) gene (The HD Collaborative Research Group, 1993), resulting in the loss of a functional allele and in the production of a misfolded and toxic mutant huntingtin (mHtt). In consequence, several brain areas can degenerate, being the striatum the most severely affected (Bates et al., 2004). Among the multiple cellular processes disrupted by this dominant mutation, transcription may have a special relevance in understanding the etiology and progression of the disease, as well as in the identification of traceable biomarkers, since its dysregulation occur before the onset of overt symptomatology in both brain and peripheral tissues. The catalog of altered transcripts is in the range of dozens to hundreds (Valor, 2015).

Epigenetics mechanisms have been examined to explain such extensive transcriptional dysregulation. Compaction degree and higher-order structure of the chromatin define the transcriptional environment of active, silent and ready-for-transcription ("poised")

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genes. Post-translational modifications (PTMs) in histones and methylation in DNA affect their interactions with transcription factors, contributing to an accessible chromatin for transcriptional activators or to a highly compacted and transcriptionally inactive configuration (Kouzarides, 2007). The first indications of perturbed epigenetics in HD and polyQ disorders came more than 15 years ago with the detection of chromatin-associated cofactors in the intracellular aggregates of mHtt (Kazantsev et al., 1999; Boutell et al., 1999; Steffan et al., 2000). Since then, accumulative evidences indicate the disruption of multiple PTMs with several examples of ameliorative strategies aimed at correcting these imbalances (Valor and Guiretti, 2014). Since gene downregulation in HD is typically associated with synaptic transmission and neuronal homeostasis, special effort has been made to find correlative reductions in marks associated with active genes (histone acetylation, H3K4 trimethylation, H2B ubiquitylation, H3 phosphorylation, etc.) and increases in marks associated with repression (H3K9 di/trimethylation, H2A ubiquitylation, 5-cytosine methylation, etc.) However, our poor knowledge of the role of epigenetics in postmitotic neurons and the relatively low specificity of the available epigenetic-related drugs make difficult to define the molecular mechanisms underlying amelioration in HD and other disorders. In this review I will describe the diverse substrates and actions of current epigenetic drugs in preclinical and clinical studies, and discuss some considerations for the design of further translational approaches in neurodegenerative disorders.

2. Epigenetic drugs and their diverse actions

2.1. HDAC inhibitors and anthracyclines

Two pharmacological approaches have been tested in HD models: inhibition of HDAC activity and reversal of methyltransferase gene expression increase. In the first case, histone hypoacetylation in HD models is paralleled with a reduction in the activity of the lysine acetyltransferase CREB-binding protein (CBP) and a potential increase in histone deacetylase (HDAC) activity (Valor and Guiretti, 2014). HDAC inhibitors (HDACis) pretend to balance both counteracting enzymatic activities, a strategy that has been also beneficial in other neuropathologies (Fischer et al., 2010). HDACis comprise a heterogeneous group of compounds: hydroxamates (TSA, SAHA), aliphatic acids (butyrate, valproate), benzamides (MS-275, 4b) and cyclic peptides. They are mostly non-specific as inhibit classes I and II of HDACs (HDAC1–10), as in the case of the pan-inhibitors TSA and SAHA, although some selectivity has been documented for members of class I (e.g., valproate, MS-275) or class II (e.g., tubacin) (Bieliauskas and Pflum, 2008). Class III, sirtuins, are not affected by HDACis but blocked by interference with NAD^+ binding (Yuan and Marmorstein, 2012).

The anthracyclines mithramycin and chromomycin also ameliorate HD models. Their interaction with the minor groove of DNA GC-rich regions inhibit the binding of the transcription activators Sp1 and Sp3 to the promoter of the methyltransferase SET domain bifurcated 1 (SETDB1) gene, resulting in the correction of SETDB1-dependent hypermethylation at K9 of histone H3 (Ryu et al., 2006). Interestingly, mithramycin has a protective role against brain ischemia and chemically-induced toxicity in neurons (Osada et al., 2013), which opens the possibility of a general treatment for neurodegenerative conditions.

2.2. Restoring the overall epigenetic status of the pathological chromatin

Epigenetic-based strategies can restore the overall altered epigenetic status of nucleosomes through both direct and indirect effects, via the cross-talk between different epigenetic marks. For instance, a model for the intellectual disability disorder known as Kabuki syndrome, associated with defective trimethylation of histone H3K4, can be treated with the HDACi AR-42 (Bjornsson et al., 2014) thus circumventing the lack of suitable drugs for this modification. In HD, GC-binding anthracyclines at the same time reverse the hypermethylation of histone H3K9 and rescue the deficits of histones H3 and H4 acetylation (Stack et al., 2007). CpG methylation of DNA can be also influenced by HDACi 4b treatment, apparently by modulating the expression of genes related with DNA modification. Changes in DNA methylation in turn affects H3K4 methylation through changes in the expression of the upstream demethylase Kdm5d (Jia et al., 2015). Strikingly, HDACi 4b also affects DNA sperm methylation, opening the possibility of transgenerational inheritance of pharmacological benefits to the progeny, as suggested by the amelioration of cognitive and motor impairments in the offspring of HD mice treated with the inhibitor (Jia et al., 2015).

2.3. Restoring transcriptional dysregulation

Single-gene experiments have demonstrated that epigenetic-based treatments can restore the altered expression of selected genes. However, genome-wide studies have recently showed a low overlap between epigenetic and transcriptional dysregulation in HD (Valor and Guiretti, 2014), which challenge our poor understanding concerning the role of neuroepigenetics in regulating gene expression. In fact, it is has been proposed a permissive rather than an instructive role for histone acetylation in brain transcription (Lopez-Atalaya and Barco, 2014). Therefore it is not surprising the limited influence of epigenetic ameliorative strategies in the transcriptome (Valor, 2015). However, HDAC 4b treatment may be exceptional because it normalizes one third of the HD transcriptional profile of the R6/2 strain (Thomas et al., 2008). How this specific HDAC1/3 inhibitor can promote such profound reversion compared to more unselective HDACis remains unexplained.

Nonetheless, epigenetic dysregulation in HD occurs at early stages, suggesting a potential relevance in the pathology that remains to be fully undisclosed. In any case, both altered expression and epigenetic modification still converge in highly relevant genes for neuronal function, and amelioration after epigenetic treatment may be consequence of affecting the expression of a small number of candidates (Valor, 2015). Also, the acetylation status of transcription factors can be altered by mHtt expression (Jiang et al., 2012) and modulated by HDACi treatment in HD (Ferrante et al., 2003). In addition, a broader action of anthracyclines is expected beyond SETDB1 expression, due to the genomic abundance of the DNA binding motifs for Sp1 members (Suske, 1999). Examining the potential coordination between epigenetic marks and transcription factors may provide further molecular insights about the causality of altered transcriptome in HD.

2.4. Beyond epigenetics and transcription

Proteomics analyses demonstrate that hundreds of proteins are susceptible to be acetylated by these compounds (Choudhary et al., 2009), including nuclear, cytoplasmic and mitochondrial proteins, and suggest that lysine acetylation may be a protein PTM as frequent as serine phosphorylation. HDACis actions can be even more complex because of their potential capability of achieving neuroprotection through HDAC-independent mechanisms (Sleiman et al., 2014). This is also illustrated by the anticonvulsant valproate, in which it is difficult to attribute its beneficial effects in HD models to actions on HDAC activity, GABA transmission or NMDA-mediated excitotoxicity (Zadori et al., 2009). Therefore it is not surprising to report epigenetic- and transcriptional-independent effects in HD as a result of HDACi treatment: clearance of misfolded mHtt by promoting its degradation, and rescue of the impairment in