Targeting Transcriptional Dysregulation in Huntington’s Disease: Description of Therapeutic Approaches

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1. Introduction

Huntington’s Disease (HD) is a dominantly inherited neurodegenerative disease affecting cognitive, emotional and motor systems. While alterations in the huntingtin gene (HTT) have been identified as causative for nearly two decades, an effective treatment has yet to be developed. Prior studies have shown that mutant huntingtin (mHTT), via its polyglutamine-expanded repeats, can affect cellular function in many ways, such as alteration of gene transcription, one of the best-characterized pathobiological events leading to HD. Microarray studies in mouse models of HD and in postmortem brain samples from HD patients report a decrease in transcriptional levels of hundreds of genes, most of them selectively expressed in the striatum, the affected brain region in HD. mHTT has been shown to inhibit the interactions of several transcription factors and to repress the transcription of genes necessary for neuronal function and survival, such as Brain Derived Neurotrophin (BDNF) or the co-activator Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-alpha).

The main question that arises is how the changes in transcriptional expression are triggered. Several studies from multiple laboratories focus only on one transcription factor as causative of the disease, but a comprehensive view of all the described events is missing and drug treatments able to correct the transcriptional dysregulation in this incurable disease are warranted. Global transcriptional modulators, like Histone deacetylase (HDAC) inhibitors, have been seen as a potential therapy for this disease. On the other hand, transcription can be regulated modulating the activity of histone demethylases, histone acetyl transferases, microRNAs and new approaches have been developed recently. An alternative way to modulate transcription in HD resides in the inhibition of transglutaminase 2 (TGase 2). The multifunctional enzyme TGase 2 is hyperactivated in several neurodegenerative diseases and acute injuries leading to neuronal death and its pharmacological or genetic deletion leads to partial rescue in mouse models of HD. Our study (McConoughey et al., 2010), along with more recent publications (Munsie et al., 2011), unravels the important role of nuclear TGase 2 in HD and defines that in the presence of mHTT, TGase 2 is recruited to chromatin, where it binds to histone H3 and participates in transcriptional silencing of genes that...
control mitochondrial biogenesis, chromatin structure, protein folding and DNA repair. In our results TGase 2 inhibition regulates the gene expression of PGCI1-alpha, a transcriptional coactivator, and cytochrome c, a transcription factor, both important in mitochondrial biogenesis. TGase 2 inhibition can normalize 40% of the dysregulated gene expression in a HD cell model and for this reason TGase 2 may act as a broader transcriptional modulator. TGase 2 might negatively modulate transcription of neuroprotective genes, inhibiting the interaction between transcription factors and their co-activators and thereby repressing gene expression designed to compensate, for instance, for mitochondrial dysfunction in HD. Specific TGase 2 inhibitors, along with other therapies targeting transcriptional dysregulation, may offer a beneficial effect to this incurable disease.

2. Genes dysregulated in HD

Transcriptional profiles of several in vivo and in vitro models of HD revealed a notable dysregulation of coding and non-coding RNAs expression (Tang et al., 2011). The cause of this impairment is linked to an alteration (loss or gain) of mHTT functions. mHTT is susceptible to protein cleavage by caspase-6 and its N-terminal fragments shuttle prevalently into the nuclear compartments where they form inclusions. Several transcription factors and enzymes involved in chromatin regulation were shown to interact with mHTT or to be present in intranuclear aggregates. The loss of these proteins contributes to global transcriptional dysregulation, typical of this neurodegenerative disease (Zhai et al., 2005). A series of very elegant papers published at the beginning of the millennium described the dysregulation of transcription factors and co-activators or co-repressors and their most well characterized downstream genes in HD, such as: the transcription factor CREB (cAMP Responsive Element-Binding), the co-activator CBP (CREB-Binding Protein), the co-repressor NREST (Neuronal Specific Responsive Element 1 (RE1) Silencing Transcription factor) and the DNA binding Specific Protein 1 (Sp1).

2.1 CREB

CREB is a transcription factor known to mediate stimulus-dependent expression of genes critical for plasticity, growth, and survival of neurons (Lonze & Ginty, 2002). The earliest observation that CREB signalling is compromised in HD came from Ross and collaborators in 2001 where the expression of different lengths of mHTT in N2A cells induced aggregation of the co-activator CBP and downregulation of CRE-mediated signalling (Nucifora et al., 2001). In the same year, Wyttenbach et al. confirmed this important observation in PC12 cells, where inducible mHTT expression impairs, primarily, the cAMP-regulated response (Wyttenbach et al., 2001). Subsequent works on the same line demonstrated the early CREB-signalling dysregulation in immortalized striatal cell lines (Gines et al., 2003) and in R6/2 mice (Sugars et al., 2004). Its reduced signalling became a promising target for therapeutic intervention; from a pharmacological point, specific phosphodiesterases inhibitors, like rolipam and TP10, were tested to maintain CREB in its active form (phosphorylated) and preserved neuronal viability (DeMarch et al., 2007; Giampa et al., 2006; Giampa et al., 2009). As a genetic approach, CREB overexpression was sufficient to rescue polyglutamine-dependent lethality in Drosophila (Iijima-Ando et al., 2005).
CREB regulates many genes and controls the transcription of the coactivator PGC1-alpha. Recent data from our group and others indicate that PGC1-alpha is necessary and sufficient to overcome mitochondrial toxicity in rodent models of HD and in other neurodegenerative diseases (Cui et al., 2006; Lin et al., 2004; McConoughey et al., 2010; St-Pierre et al., 2006; Weydt et al., 2006). PGC1-alpha can be regulated by and interact with transcription factors such as CREB, NRF-1, FOXO, MEF-2 and PPARγ to recruit the basal transcriptional machinery to genes involved in mitochondrial biogenesis, mitochondrial function and antioxidant defence (Figure 1). Additional functions of PGC1-alpha have been recently described, such as its role in cholesterol biosynthesis and myelination (Xiang et al., 2011), essential for neuronal functionality.

![Diagram](https://example.com/diagram.png)

**Fig. 1.** The transcription of PGC1-alpha is regulated by metabolic stress. When PGC1-alpha is expressed and phosphorylated by AMPK, translocates to the nucleus and regulates the transcription of several genes involved in mitochondrial biogenesis and oxidative phosphorylation. These events lead to the activation of mitochondrial anti-oxidant adaptation and the increased transcription of several genes such as cytochrome c. mHTT has been shown to block the transcription of PGC1-alpha gene, recruiting CBP in intranuclear aggregates and blocking PolII activation.
2.2 CBP

CBP, best know as CREB co-activator, modulates the activation of many transcription factors (Goldman et al., 1997) by facilitating the recruitment of the transcriptional machinery. CBP has a key role in the nervous system; its mutations or deletions are associated to the Rubinstein-Taybi syndrome. In 2001 Steffan and colleagues showed that CBP and p300/CBP-associated factor (P/CAF) interact directly with mHTT blocking their acetyltransferase function (Figure 1). Additionally, CBP activity is reduced by its presence in polyglutamine aggregates (Nucifora et al., 2001) or by its increased proteasomal degradation (Cong et al., 2005; Jiang et al., 2003; Sadri-Vakili et al., 2007). Of note, CBP regulates the transcription of genes involved in the urea cycle, compromised in the liver of HD patients (Chiang et al., 2007) and this dysfunction contributes to the development of the disease.

2.3 REST/NREST

The Brain-Derived Neurotrophic Factor (BDNF) is an essential neurothrophin for the Central Nervous System. Its decreased levels have been well documented in HD human tissues and in mouse models. Its transcriptional regulation has been thoroughly described by Cattaneo and colleagues and it offers a different example of how mHTT can accomplish its detrimental effects. BDNF transcription can be switch off by a corepressor called REST. Usually REST interacts with wild type huntingtin and resides in the cytosol. mHTT fails to bind REST, which translocates to the nucleus and binds the Repressor-Element 1 (RE1) blocking BDNF gene transcription (Zuccato et al., 2001; Zuccato et al., 2003). Strategies to limit the repressive REST/NREST complex with pharmacological modulators, such as 2-aminothiazole derivatives (Leone et al., 2008) or decoys (Soldati et al., 2011) are now under investigation. Furthermore, REST modulates many microRNAs (miRs) and long non-coding RNAs, important in neuronal functions and dysregulated in HD (Bithell et al., 2009; Buckley et al., 2010; Johnson & Buckley, 2009; Johnson et al., 2008). One of them, miR-9, is downregulated by mHTT and fails to repress REST itself, contributing to the enhancement of its repressive activity (Packer et al., 2008).

2.4 Sp1

Sp1 is a member of an extended family of DNA-binding proteins that has three zinc finger motifs and binds to GC-rich DNA (Bouwman & Philipsen, 2002). Although classically thought to regulate the constitutive expression of numerous housekeeping genes, Sp1 transcriptional activities have been found to change in association with differentiation and proliferation and to regulate gene expression in association with these as well as other functions. In HD, the evidence that Sp1 dependent transcription is inhibited is extensive. mHTT interacts specifically with glutamine rich activation domains in Sp1 (Dunah et al., 2002) and blocks its direct binding to DNA. This aberrant interaction nullifies the ability of Sp1 to induce transcription of important genes including those encoding neurotransmitter receptors, downregulated in HD patients and rodents models (Cha et al., 1998). Sp1 overexpression (Dunah et al., 2002) or Sp1 acetylation (Ryu et al., 2003a) provide protection in HD. Interestingly, two anthracycline antibiotics, mithramycin and chromomycin, were shown to bind DNA inhibiting Sp1 activity and they provided the higher rate of survival reported to date in R6/2 mice (Ferrante et al., 2004; Stack et al., 2007). Unfortunately, the clinical trial on mithramycin was interrupted for low tolerability in humans. A recent paper
from our group described promising analogs and showed the ability of these antibiotics to induce a promoter-specific displacement of Sp1, favouring the pro-survival effects of this transcription factor and inhibiting its pro-death activities (Sleiman et al., 2011).

Fig. 2. mHTT recruits Sp1 and the transcription machinery in intranuclear inclusions, downregulating the expression of Sp1-dependent genes (A). At the same time, mHTT fails to interact and inhibit NREST repressive activity in the nucleus, leading to an aberrant inhibition of BDNF transcription (B).

3. Global histone modifications and transcriptional modulation

Within the eukaryotic nucleus, DNA is packaged into chromatin domain. The basic subunit of chromatin is the nucleosome, which is composed of DNA coiled around an octamer of histone proteins, two molecules each of histone H2A, H2B, H3 and H4. Histone H1 associates with chromatin outside the nucleosome. The amino-terminal tail of each histone is evolutionarily conserved and it is the target of numerous post-translational modifications (PTM). PTM of histones are major players in transcriptional control. These modifications include acetylation, methylation, phosphorylation, ADP-ribosylation, mono-ubiquitylation, citrullination, sumoylation and polyamination. The specific pattern of histone modification,
identified as histone code, is used by proteins involved in chromatin organization to establish a transcriptionally silent or active state.

mHTT impacts transcription not only through the direct binding on DNA (Benn et al., 2008) or transcription factors (e.g. CREB, FOXO) (Zhai et al., 2005) but also inducing a global modification of histone proteins. On one side, mHTT recruits histone acetyl transferases (HATs), such as CBP, in intranuclear aggregates and reduces their ability to acetylate histones; on the other side, mHTT facilitates polycomb repressive complex 2 (PRC2), which methylates histone H3 in lysine 27 and mediates transcriptional repression (Seong et al., 2010).

3.1 Histone acetylation and HDACs

Among the myriad of modifications that are normally occurring at the histone tails, acetylation is the most common. Histone acetylation and deacetylation are regulated by a delicate interplay between Histone Acetyl Transferases (HATs) and Deacetylases (HDACs). In a simplistic view, histone acetylation is usually associated with increase in gene transcription; conversely, histone deacetylation represses transcription. Several works described a global inhibition of acetylation in HD mouse models, human samples and cell lines, due to the propensity of mHTT to recruit HATs such as CBP (Steffan et al., 2000) in intracellular inclusions. HAT activity and global histone acetylation were significantly decreased in several models of HD (Igarashi et al., 2003; Sadri-Vakili et al., 2007). Difficulties in upregulating the acetyl transferase activity moved the attention on the other enzymes involved in the acetylation homeostasis: HDACs. HDAC inhibitors have been tested in various HD models to restore transcription, although their expression and activity are not altered by mHTT (Hockly et al., 2003) (Table 1). The first evidence that HDAC inhibitors would have been promising therapeutic agents in HD came from Leslie Thompson and collaborators in 2001, where butyrate and suberoylanilide hydroxamic acid (SAHA) reduced lethality in two Drosophila models of polyglutamine disease (Steffan et al., 2001). Sodium butyrate ameliorated HD symptoms in R6/2 mice and increased histones and Sp1 acetylation (Ferrante et al., 2003). Phenylbutyrate increased the lifespan of N171-82Q mice (Gardian et al., 2005) and it has been reported as safe and tolerable in humans (Hogarth et al., 2007). Other protective HDAC inhibitors are: SAHA, tested in R6/2 mice (Hockly et al., 2003); trichostatin A (TSA) is effective in immortalized cell lines (Dompierre et al., 2007; Oliveira et al., 2006); the inhibitor 4b effective in R6/2(300Q) transgenic mice (Thomas et al., 2008); valproate alone or in combination with lithium in N171-82Q mice (Zadori et al., 2009; Chiu et al., 2011). Clinical trials for valproate showed some beneficial effects (Saft et al., 2006; Grove et al., 2000). Finally, a role for the NAD+-dependent HDACs is emerging (Pallos et al., 2008; Hathorn et al., 2011) in relation to cholesterol synthesis in the HD brain (Luthi-Carter et al., 2010). Trials to assess the safety, tolerability and pharmacokinetics of sirtuins inhibitors are on going (SEN0014196) (Gray, 2010).

There is an emerging believe that global HDAC inhibition may exert partial toxicity due to the suppression of pro-survival isoforms. Genetic deletion of single isoforms have been performed revealing that HDAC4 may be the only causative in HD. Specific HDAC4 inhibitors are now under investigation (Munoz-Sanjuan & Bates, 2011).
3.1.1 Protein acetylation in HD

Acetylation is important not only on histone tails but on several proteins and transcription factors to recruit specific transcriptional regulatory complexes (Xu et al., 2007) or to mediate signalling. Sp1 acetylation, for instance, is necessary to activate the adaptive response to oxidative stress in vitro and in vivo (Ryu et al., 2003b) and alpha-tubulin acetylation increases BDNF trafficking and release in neurons (Dom pierre et al., 2007). It has been recently reported that ribosomal DNA transcription is also impaired in HD due to decreased acetylation of the upstream binding factor-1 (UBF-1) (Lee et al., 2011); similarly, decreased levels of acetylation in p53 (lysine 382) correlate with the accumulation of DNA damage in HD (Illuzzi et al., 2011). Nevertheless, HTT itself is usually acetylated and degraded by autophagy; mHTT conformation impedes acetylation at lysine 444 and mediates its accumulation in intracellular inclusions (Jeong et al., 2009).

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Table 1. HDAC inhibitors tested in different models of HD.
3.2 Beyond acetylation: Methylation, ubiquitylation, polyamination

Decreased acetylation is associated usually with an increase of histone methylation at specific arginine and lysine residues (e.g. H3K9me, H3K27me). Histone methylation, in fact, has a similar dynamic regulation than histone acetylation and it is controlled by histone demethylases and histone methyltransferases. Levels of trimethylated histone H3 Lysine 9 are upregulated in HD human and mouse tissues by the dysregulated transcription of a Lysine methyl transferase, ESET (Ryu et al., 2006). Accordingly, partial deletion of CBP induces ESET transcription (Lee et al., 2008), suggesting that it is important to preserve the homeostatic equilibrium of the enzymes that regulate chromatin. The decrease of CBP involves reduced acetylation and shifts the equilibrium towards methylation.

Despite the simplistic concept of transcriptional repression mediated by a decrease of acetyl transferases activity and a consequent increase of global histone methylation, other histone modifications can lead to the same repressive result. Due to a disrupted interaction between mHTT and Bmi-1, part of the ubiquitin ligase complex, histone H2A monoubiquitylation is aberrantly increased in genes downregulated in HD. Consequently, monoubiquitylation of histone H2A promotes methylation in histone H3, lysine 9, a repressive mark (Kim et al., 2008). Conversely, the genes that are not altered by mHTT present normal levels of monoubiquitylated H2A and increased levels of monoubiquitylated H2B that induces methylation in histone H3 lysine 4, an active mark. In light of these important results, it is plausible to hypothesizes that new therapeutic avenues will be embraced by the HD scientific community in order to understand better how to modulate histone methylation in relation to dysregulation.

An emerging field in epigenetic modulation involves small cationic metabolites called polyamines. Polyamines are organic compounds with two or more primary amino groups able to regulated gene expression. They interact with DNA, RNA and control cell proliferation and growth. Their avidity for DNA on a charge base makes them ideally suited to regulate its conformation. Attaching them to proteins provides an elegant way to manipulate charge concentrations locally and alter DNA binding affinity (highly negatively charged due to phosphate backbone) to assume a compact (silenced) conformation. Recent papers showed that polyamines or polyamines analogs inhibit Lysine Specific Demethylase 1 (LSD1), a FAD-dependent histone demethylases, able to demethylate mono and dimethyl lysine 4 of histone H3, active marks of transcription (Huang et al., 2007; Shi et al., 2004) and they can block HDACs activity sitting in their catalytic pocket (Varghese et al., 2005). In a number of in vitro studies, polyamines can be crosslinked to glutamine tails of histones by transglutaminase 2 (TGase 2). Indeed, Ballestar identified polyamination of histone H3 in glutamine 5 and 19 and polyamination of histone H2B in glutamine 22 and correlated these modification with a change in the nucleosome structure (Ballestar et al., 1996; Ballestar et al., 2001).

3.2.1 Transglutaminase 2 and HD: Protein crosslinking or protein polyamination?

Transcriptional proteins that are inhibited in HD contain glutamine rich activation domains (Sp1, CBP, TAF4). Glutamines in proteins are substrates for a class of enzymes called transglutaminases (TGase 2) (Jeon et al., 2003). In humans, eight distinct TGases, encoded by different genes and referred to as TGase 1-7 and coagulation factor XIIIa have been previously identified. All members of the class have common catalytic activity and protein
structure. The activity of each of these enzymes leads either to the formation of covalent bonds within or between polypeptide chains (γ-glutamyl-lysine; GGEL; Figure 3A) or the incorporation of polyamines into substrate proteins. This generates one of two possible types of products of TGase 2-polyamination: the N-(γ-glutamyl)polyamine and bis-(γ-glutamyl)polyamine (Figure 3B). In a recent study (Jeitner et al., 2008), increased levels of (γ-glutamyl)polyamines were seen in the CSF of HD patients suggesting a link between TGase 2 activity and polyamination in HD.

Fig. 3. TGase 2 catalyzes cross-links between glutamine and lysines in proteins leading to gamma-glutamyl-lysine covalent bonds (A) or the incorporation of polyamines into substrate proteins (B).

Investigations of TGase 2 in HD date back to 1993. Since then, a number of studies have documented increases in TGase 2 activity in a host of tissues, including in nuclei of human HD brains (Karpuj et al., 1999; Lesort et al., 1999). In the 80s, transglutaminase was first suspected to participate in HD pathogenesis via its ability to promote aggregates of polyglutamine (PolyQ) peptides and polyQ-huntingtin. Subsequently, Finkbeiner and colleagues suggested that aggregates were beneficial rather than pathogenic in HD (Arrasate et al., 2004). These findings suggested that TGase 2 inhibition prevented HD pathology by mechanisms independent of huntingtin aggregation. In the last ten years, several studies described the effect of TGase 2 inhibition in HD. Cystamine, a broad TGase 2 inhibitor, has been shown to be protective in R6/2 mice (Dedeoglu et al., 2002; Karpuj et al., 2002; Wang et al., 2005) and in YAC128 mice (Van Raamsdonk et al., 2005), both established models of the disease. Karpuj et al. in 2002 correlated the beneficial effects of TGase 2 inhibition with the transcriptional upregulation of a DNAJ-type heat shock protein, but did not offer any specific data on how TGase 2 might regulate DNAJ message levels in HD. The general model garnered support through a subsequent study by Borrel-Pages (Borrell-Pages et al., 2006) that showed that the levels of the DNAJ-containing protein HSJ1B are reduced in HD samples and that pharmacological inhibition of TGase 2 could restore message and protein levels in this context. The findings showed that TGase 2-mediated reduction in HSJ1B is critical for HD pathogenesis via its ability to delay brain-derived neurotrophic factor BDNF trafficking and release. Again, the findings were consistent with an effect of TGase 2 on message and protein levels, but did not offer a model of how TGase 2 might exert these effects. The crossbreeding between the TGase 2-/- and R6/1 or R6/2 mice resulted in reduced neuronal
death, improved motor performance and increased survival (Mastroberardino et al., 2002, Bailey & Johnson, 2006). These positive results were not as encouraging as the HD community expected but it is important to consider that TGase 2 is ubiquitously expressed and among its several functions, it also has a role in normal development (Bailey et al., 2004). Deletion of TGase 2 induces compensation by the other seven transglutaminases that probably masked the real beneficial effect of TGase 2 inhibition.

We have proposed a novel TGase 2 function and demonstrated that TGase 2 inhibition normalized transcription in HD (McConoughey et al., 2010). In cells expressing mHTT, TGase 2 is recruited at the promoters or genomic regions of repressed genes. Microarray analysis indicates that TGase 2 inhibition via a selective inhibitor corrects transcriptional dysregulation in HD more efficiently than canonical TGase 2 inhibitors (cystamine) or HDAC inhibitors (TSA). However, TGase 2 inhibition does not affect histone acetylation (H4), suggesting a parallel and additive mechanism for histone regulation by HDAC inhibitors and TGase 2 inhibitors. Our results suggest that TGase 2 inhibition is a significant driver of transcriptional dysregulation in HD and should further stimulate efforts to understand how it exerts this function.

![Proposed mechanism of action for TGase 2 in HD. In the presence of mHTT, TGase 2 is hyperactivated and it can bind to the promoter of genes such as cytochrome c and PGC1-alpha repressing transcription. The use of specific TGase 2 inhibitors displace TGase 2 from these promoters and block synaptic dysfunction and consequent cell death.](image)

**4. Conclusion**

Targeting transcriptional dysregulation is one of the most promising avenues for this untreatable disease. The continuous understanding of how transcriptional regulation occurs in vivo along with the development of more specific modulators of chromatin remodelling enzymes will lead hopefully to a cure for HD in the early future. In the last ten years, since the involvement of transcriptional dysfunction has been reported in the field, huge efforts have been invested by researchers, founding agencies, private foundations and patients, all over the world. Broad HDAC inhibitors, specific HDAC inhibitors, CREB activators, SP1 modulators, TGase 2 inhibitors have been tested so far in mouse models and clinical trials. Unfortunately, the results in humans are not as promising as observed in mouse models, suggesting that a deeper understanding of the molecular mechanisms leading to neurodegeneration and the design of combined therapies are still required.
5. Acknowledgment

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6. References


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Huntington's Disease is one of the well-studied neurodegenerative conditions, a quite devastating and currently incurable one. It is a brain disorder that causes certain types of neurons to become damaged, causing various parts of the brain to deteriorate and lose their function. This results in uncontrolled movements, loss of intellectual capabilities and behavioural disturbances. Since the identification of the causative mutation, there have been many significant developments in understanding the cellular and molecular perturbations. This book, "Huntington's Disease - Core Concepts and Current Advances", was prepared to serve as a source of up-to-date information on a wide range of issues involved in Huntington's Disease. It will help the clinicians, health care providers, researchers, graduate students and life science readers to increase their understanding of the clinical correlates, genetic aspects, neuropathological findings, cellular and molecular events and potential therapeutic interventions involved in HD. The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines, which collectively provide comprehensive description of the key issues in the area.

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