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REVIEW

Targeting Huntington's disease through histone deacetylases

Steven G. Gray

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Abstract Huntington's disease (HD) is a debilitating neurodegenerative condition with significant burdens on both patient and healthcare costs. Despite extensive research, treatment options for patients with this condition remain limited. Aberrant post-translational modification (PTM) of proteins is emerging as an important element in the pathogenesis of HD. These PTMs include acetylation, phosphorylation, methylation, sumoylation and ubiquitination. Several families of proteins are involved with the regulation of these PTMs. In this review, I discuss the current evidence linking aberrant PTMs and/or aberrant regulation of the cellular machinery regulating these PTMs to HD pathogenesis. Finally, I discuss the evidence suggesting that pharmacologically targeting one of these protein families the histone deacetylases may be of potential therapeutic benefit in the treatment of HD.

Keywords Histone deacetylase · Huntington's disease · Histone post-translational modifications

Introduction

Huntington's disease (HD) is an autosomal dominant, late-onset neurodegenerative disease characterized by cognitive dysfunction, psychiatric symptoms and movement disorders (Walker 2007). The disease is caused by an expansion of a polyglutamine repeat within the amino terminus of the predominantly cytosolic protein huntingtin (Htt; DiFiglia et al. 1995; Group 1993). The expanded repeat region results in nuclear translocation and aggregation of huntingtin and has been implicated as the causative event in the pathogenesis of this disease (Klement et al. 1998; Sieradzan et al. 1999; Saudou et al. 1998).

Epigenetic regulation of gene expression involves stable and heritable changes in gene expression which are not due to changes in the primary DNA sequence. Current known epigenetic mechanisms involve the following: DNA CpG methylation, histone post-translational modifications (PTMs), gene imprinting and non-coding RNA.

The 'histone code' is a well-established hypothesis describing the idea that specific patterns of post-translational modifications to histones act like a molecular 'code' recognised and used by non-histone proteins to regulate specific chromatin functions. These modifications include acetylation, methylation, phosphorylation, sumoylation and ubiquitination, and various families of proteins have been identified which function to place or remove these PTMs. The best studied of these families are the K-acetyltransferases (KATs), histone deacetylases (HDACs), K-methyltransferases (KMTs) and K-demethylases (KDMs; Allis et al. 2007).

KATs (formerly known as either histone acetyltransferases or lysine acetyltransferases; Allis et al. 2007) function to covalently add acetyl groups to lysine residues on proteins. Likewise, KMTs add methyl groups to lysine residues either as mono-, di- or tri-methylation (Albert and Helin 2010), whilst HDACs and KDMs remove these respective modifications (Allis et al. 2007). Whilst many of these PTMs were originally identified on histones, it is becoming increasingly evident that these PTMs play important roles on many proteins leading to the notion of a 'protein code' exemplified by the proteins p53 (Sims and Reinberg 2008) and nuclear factor kappa-B (NFkB; Calao et al. 2008).

S. G. Gray (✉)
Translational Cancer Research Group, Department of Clinical Medicine, Institute of Molecular Medicine,
Trinity Centre for Health Sciences, St James's Hospital,
James's Street,
Dublin 8, Ireland
e-mail: sgray@stjames.ie

Indeed, the Htt protein has been found to be extensively modified by several PTMs including acetylation, sumoylation, ubiquitination and phosphorylation (Table 1). Focusing on Huntington's disease (HD), I discuss the current knowledge supporting the notion that the proteins involved with histone/protein PTMs play important regulatory roles in the pathogenesis of this disease and discuss whether inhibitors which target HDACs may have potential for use in targeting this disease.

Linking histone PTM machinery with HD

Lysine acetylation/deacetylation in HD

Much evidence has emerged directly linking KATs and HDACs with HD (Table 2). For instance, mutant Htt protein was quickly shown to form a complex with the lysine acetyltransferases KAT3A (CBP) and KAT2B (P/CAF; Nucifora et al. 2001; Steffan et al. 2001, 2000; Kazantsev et al. 1999). Once this complex is established, it in turn can then interact with p53 and repress transcription of p21WAF1/CIP1 and MDR-1 (Steffan et al. 2000). Evidence has also accumulated linking functional associations between huntingtin and HDACs. Huntingtin associates with the co-repressors mSin3a and N-CoR which recruit HDACs to repress transcription (Boutell et al. 1999; Steffan et al. 2000). Indeed in the absence or presence of ligand, mutant huntingtin has been shown to both increase nuclear co-repressor function and enhance ligand-dependent nuclear hormone receptor activation (Yohrling et al. 2003).

The potential importance of histone deacetylases in HD was highlighted in a *Caenorhabditis elegans* model of HD, where specifically targeting HDACs reduced neurodegeneration (Bates et al. 2006). Defects in microtubule-based transport have been shown to contribute to neuronal toxicity in Huntington's disease (Muchowski et al. 2002; Hoffner et al. 2002; Trushina et al. 2003). HDAC6 has been shown to be a microtubule-associated deacetylase (Hubbert et al. 2002). Levels of acetylated tubulin have been found to be reduced in the brains of Huntington's patients, and in vitro cell studies targeting HDAC6 resulted in the alleviation of transport- and release-defect phenotypes in the cell models via increased acetylation at lysine 40 of alpha-tubulin (Dompierre et al. 2007).

Table 1 Sites in the Htt protein which undergo PTMs

Acetylation
K6 (Aiken et al. 2009)
Palmitoylation
C214 (Yanai et al. 2006)
Phosphorylation
T3 (Aiken et al. 2009)
S13 (Aiken et al. 2009; Thompson et al. 2009; Gu et al. 2009)
S16 (Aiken et al. 2009; Gu et al. 2009)
T407 (Dephoure et al. 2008)
S413 (Dephoure et al. 2008)
S421 (Colin et al. 2008; Humbert et al. 2002; Pardo et al. 2006; Rangone et al. 2004; Warby et al. 2009; Zala et al. 2008)
S434 (Luo et al. 2005)
S533 (Schilling et al. 2006)
S535 (Schilling et al. 2006)
S536 (Schilling et al. 2006)
S1181 (Anne et al. 2007; Daub et al. 2008; Schilling et al. 2006)
S1872 (Daub et al. 2008; Dephoure et al. 2008)
S1876 (Dephoure et al. 2008; Xia et al. 2008)
S1201 (Anne et al. 2007; Brill et al. 2009; Daub et al. 2008; Schilling et al. 2006)
S2076 (Schilling et al. 2006)
S2653 (Schilling et al. 2006)
S2657 (Schilling et al. 2006)
T2940 (Dephoure et al. 2008)
Sumoylation
K6, K9, K15 (Steffan et al. 2004)
Ubiquitination
K6, K9, K15 (Steffan et al. 2004)

The table was generated through the use of SysPTM (http://lifecenter.sgst.cn/SysPTM; Li et al. 2009), PhosphoSitePlus® (http://www.phosphosite.org/) and literature searches

Table 2 Histone modifying proteins linked to HD discussed within the text

Enzyme	Activity
HDAC1	Histone deacetylase
HDAC2	Histone deacetylase
HDAC3	Histone deacetylase
HDAC4	Histone deacetylase
HDAC5	Histone deacetylase
HDAC6	Histone deacetylase
HDAC7	Histone deacetylase
SIRT1	Histone deacetylase
KAT2B	K-acetyltransferase
KAT3A	K-acetyltransferase
KMT1E	K-methyltransferase
KMT3A	K-methyltransferase
KMT6	K-methyltransferase
KDM1	K-demethylase
MSK-1	Histone phosphorylation
CDK5	Htt phosphorylation
IKK (IKKα, β, γ)	Htt phosphorylation
Bmi-1, hPRC1L E3	Histone ubiquitin
Rhes	Htt sumoylation

Critically, acetylation of Htt has been shown to target the mutant protein to autophagosomes for degradation. Increased acetylation at a single lysine (K444) was recently shown to facilitate the trafficking of mutant Htt into autophagosomes and significantly improved the clearance of the mutant protein by macroautophagy. In experimental models, this reversed the toxic effects of mutant huntingtin in primary striatal and cortical neurons and in a transgenic *C. elegans* model of HD. If the protein was altered to be resistant to acetylation, this resulted in dramatic aggregation leading to neurodegeneration in cultured neurons and in mouse brain (Jeong et al. 2009). Overexpression of I-kappa-B kinase (IKK)β, an important regulator of the NFkB transcription factor (Mankan et al. 2009), results in acetylation of Htt at K9 and phosphorylation at S13, leading to elevated nuclear translocation of Htt protein (Thompson et al. 2009).

Lysine ubiquitination/sumoylation in HD

The mutant huntingtin protein has been shown to alter levels of histone monoubiquitination, through an altered ability to interact with Bmi-1, a component of the hPRC1L E3 ubiquitin ligase complex, resulting in increased levels of monoubiquitinated histone H2A (uH2A) and aberrant gene expression (Kim et al. 2008). When gene expression patterns were examined in the brains of transgenic R6/2 mice, promoters of genes which were repressed were found to have increased levels of ubiquitinated H2A (uH2A) and decreased levels of ubiquitinated H2B (uH2B), whilst active promoters had the opposite (increased u2H2B and decreased uH2A). Furthermore, targeting histone ubiquitin in cell line models demonstrated that reducing uH2A led to the reactivation of repressed genes associated with a reduction in levels of histone lysine 9 methylation (H3K9me)2 and trimethylated histone H3 lysine 9 (H3K9me3) at the reactivated promoters. Conversely reductions of uH2B induced transcriptional repression through inhibition of monomethylation at histone H3 lysine 4 (Fig. 1; Kim et al. 2008).

Modification of proteins with polyubiquitin chains regulates many essential cellular processes including protein degradation, cell cycle, transcription, DNA repair and membrane trafficking. As discussed in previous sections, in Huntington's disease, monoubiquitination of histones results in aberrant gene expression patterns. Evidence now links Htt ubiquitination to HD pathogenesis. Aggregation-prone proteins such as Htt have been suggested to overwhelm and impair the ubiquitin/proteasome system (UPS) in polyglutamine (polyQ) disorders. One study found that accumulation of ubiquitin conjugates in a HD disease model occurred without impairment of the ubiquitin/proteasome system (Maynard et al. 2009). However, two other studies have shown that UPS dysfunction is a consistent feature of HD pathology with impaired UPS in the synapses of HD mice (Wang et al. 2008) and with polyubiquitination chains occurring on Htt lysines 11, 48 and 63 (Bennett et al. 2007).

Htt has also been shown to be either ubiquitinated or sumoylated at the same lysine residues (K6, K9 and K15). Sumoylation stabilizes Htt and reduces its ability to form aggregates, whilst enhancing transcriptional repression, and exacerbated neurodegeneration in a drosophila model of HD, whereas ubiquitination of these residues abrogated neurodegeneration in the same model (Steffan et al. 2004). More recently, a novel striatal protein, Rhes, has been shown to associate with Htt. This protein has now been shown to induce Htt sumoylation leading to neuronal cytotoxicity (Subramaniam et al. 2009).

Lysine methylation in HD

H3K9me3 levels are elevated in both HD patients and in R6/2 transgenic mice and are associated with increased amounts of KMT1E (also known as known as ESET/SETDB1; Table 2; Ryu et al. 2006). This enzyme methylates H3K9me3, and whilst this is generally considered to be a mark of transcriptional repression and heterochromatinization (Hublitz et al. 2009), it has also been associated with active transcription genes particularly in disease states such as cancer (Wiencke et al. 2008). Within the neuronal setting, monoallelic deletion of the lysine acetyltransferase KAT3A (CBP) results in the induction of KMT1E (ESET) with concomitant increased H3K9me3 in neurons (Lee et al. 2008), suggesting that KAT3A (CBP) may be a regulator of KMT1E (ESET) gene expression and raising the notion that increased KAT activity may be a way of targeting the aberrant KMT1E (ESET)-mediated H3K9me3 levels in patients with HD (Table 2).

Deubiquitination of H2B in yeast initiates the recruitment of a complex containing the kinase Ctk1. This kinase subsequently phosphorylates the RNA polymerase II (Pol II) C-terminal domain, an event essential for the subsequent recruitment of KMT3A (Set2/HYBP) lysine methyltransferase (Wyce et al. 2007). One of the functions of this KMT is to regulate RNA Pol II elongation (Krogan et al. 2003; Wyce et al. 2007; Li et al. 2003; Xiao et al. 2003; Schaft et al. 2003; Morris et al. 2005). However, KMT3A (Set2/HYPB)-mediated H3K36 methylation also functions to recruit histone deacetylase complexes to restore normal chromatin structure in the wake of elongating Pol II (Keogh et al. 2005; Lee and Shilatifard 2007). Indeed KMT3A would appear to be essential for all H3K36me3 during gene induction both in vitro (Edmunds et al. 2008) and in vivo (Yuan et al. 2009). The human homologue of this KMT was originally described as huntingtin interacting protein B (HYPB; Sun et al. 2005a), suggesting that KMT3A (Set2/

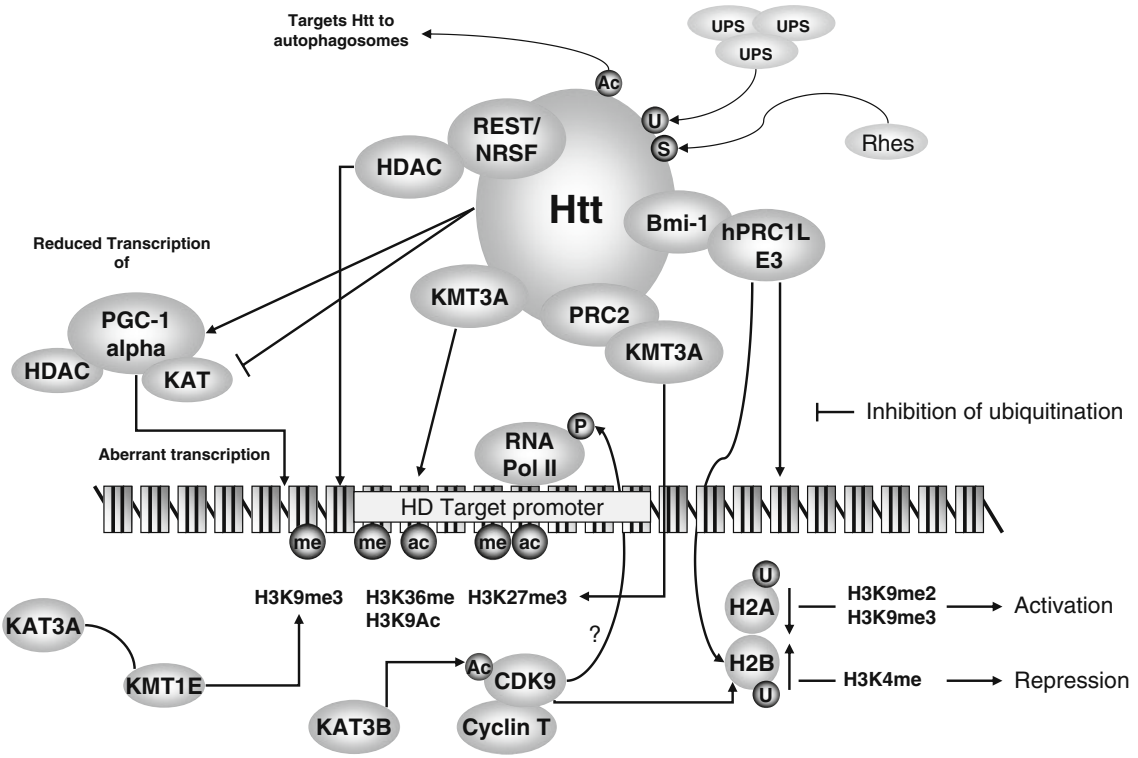

Fig. 1 Overview of epigenetic regulators affecting gene expression in Huntington's disease. *p* phosphorylation, *u* ubiquitination, *s* sumoylation, *ac* acetylation, *me* methylation, *ups* ubiquitin/proteasome system, *KAT* K-acetyltransferase, *KMT* K-methyltransferase

HYPB) may coordinate histone methylation and transcriptional regulation and play critical roles in the pathogenesis of HD (Sun et al. 2005a).

The Htt protein has now been shown to associate with the Polycomb repressive complex 2 (Seong et al. 2010). EZH2 (also known as KMT6) is the catalytic subunit of Polycomb repressive complex 2 (PRC2) and is a highly conserved histone methyltransferase that targets lysine-27 of histone H3 (Cao et al. 2002; Kuzmichev et al. 2002). Mutant Htt was found to be associated with reduced histone H3K27 tri-methylation, whilst recombinant wild-type Htt was found to significantly enhance the histone H3K27 tri-methylase activity of reconstituted PRC2 in vitro (Seong et al. 2010). Whilst there is currently little evidence demonstrating aberrant KDM activity in the pathogenesis of neurodegeneration, it has recently been shown that a neurospecific splice variant of KDM1 (LSD1) exists which is dynamically regulated throughout cortical development and functions to modulate neurite morphogenesis (Zibetti et al. 2010).

Lysine phosphorylation

In the R6/2 transgenic mouse model of HD, nuclear activation of the mitogen-activated protein kinase/extracellular regulated kinase (ERK) failed to induce histone H3 phosphorylation, an expected response of nuclear ERK activation. It was subsequently found that this was due to a decrease in expression of mitogen- and stress-activated kinase-1 (MSK-1), a kinase downstream ERK, critically involved in H3 phosphorylation, a finding subsequently confirmed in the striatal neurons and postmortem brains of HD patients and suggesting that aberrant MSK-1 expression is involved with the transcriptional dysregulation and striatal degeneration in patients with HD (Roze et al. 2008).

Recently, it has been shown that phosphorylation of mutant Htt by the inflammatory kinase complex (IKK) regulates additional post-translational modifications, including Htt ubiquitination, sumoylation and acetylation, resulting in increased Htt nuclear localization, cleavage and clearance mediated by lysosomal-associated membrane protein 2A and Hsc70 (Thompson et al. 2009). In particular, phosphorylation of serines (S6/S13) promotes the degradation of Htt by both the proteasome and lysosomes. These modifications, however, also result in enhanced translocation of Htt to the nucleus, which may result in both aberrant gene expression and enhanced neurodegeneration over time (Thompson et al. 2009). However, phosphorylation of Htt on serine 421 (S421) can reduce nuclear accumulation of huntingtin fragments by (a) reducing huntingtin cleavage by caspase-6, (b) affecting the levels of full-length huntingtin and (c) altering its nuclear localization (Warby et al. 2009). Phosphorylation of serine 434 (S434) by CDK5 has also been found to reduce caspase-mediated Htt cleavage at alanine residue 513 (Luo

et al. 2005). Additionally, phosphorylation of Htt may also directly regulate Htt function, as phosphorylation at S431 restores its axonal transport (Zala et al. 2008), whilst phosphorylation of Htt at S431 by Akt is critical to controlling the direction of vesicle movement in neurons (Colin et al. 2008). Furthermore, phosphorylation at Htt serines S1181 and S1201 are critical to HD pathogenesis. If phosphorylation is absent, this confers toxic properties to wild-type huntingtin in a p53-dependent manner in striatal neurons and accelerates neuronal death induced by DNA damage, whilst if present they prevent this toxicity (Anne et al. 2007).

Consequences of mutant Htt and aberrant PTMs in HD

Clear links between aberrant histone post-translational modifications and disease pathogenesis have been demonstrated, and one of the most extensively studied of these modifications is histone acetylation. Indeed, acetylation of histones in brain neuronal fractions was observed as early as 1975 (Sarkander et al. 1975), and it has now been demonstrated that HDACs play important roles in both neuron differentiation (Liu et al. 2008), expression of neuron-specific genes (Lakowski et al. 2006) and the regulation of diverse cues such as maternal grooming (Weaver et al. 2004) and addiction (Renthal et al. 2007). Class II and class III histone deacetylases play pivotal roles in both neuronal proliferation and differentiation (Horio et al. 2003; Kyrylenko et al. 2003; Ajamian et al. 2003; Hoshino et al. 2003). SIRT1 has also been shown to protect primary cultures of cerebral granule neurons from FOXO-induced cell death (Brunet et al. 2004).

Because Htt has been shown to associate with the cellular machinery responsible for regulating the histone code, it has been postulated that this may lead to aberrant gene expression in patients suffering from HD. Three potential mechanisms as to how this might occur have been identified: (1) mislocalization of KATs. The association of mutant Htt and KATs affects the nuclear localization of KATs in neuronal cells into intranuclear inclusions (Steffan et al. 2000; Nucifora et al. 2001). As such depletion of this KAT from its normal localization by this aggregation may result in aberrant transcriptional control; (2) direct inhibition of KATs. Cell-free assays have shown that mutant huntingtin protein can directly inhibit KAT activity (Steffan et al. 2001), indicating a direct interference mechanism; and (3) enhanced degradation of KATs. A cell line of mutant Htt protein found that this was associated with enhanced degradation of KAT3A (CBP) indicating that the mutant Htt may actively eliminate this KAT from the affected neurons (Jiang et al. 2003, 2006; Cong et al. 2005).

As a consequence, gene expression is altered in patients with HD. Microarray gene profiling studies on HD patients have identified a subset of upregulated mRNAs that can distinguish between controls, presymptomatic HD mutation carriers and symptomatic HD patients (Borovecki et al. 2005). Furthermore, in a microarray analysis of a yeast model of expanded polyglutamine tracts, the changes in gene expression profiles closely matched those of yeast strains deleted for components of the Spt/Ada/Gcn5 acetyltransferase lysine acetyltransferase complex (Hughes et al. 2001). Additional evidence for aberrant gene expression comes from transgenic mice models of HD. For example, histone H3 is hypo-acetylated at the promoters of downregulated genes in R6/2 transgenic mice (Sadri-Vakili et al. 2007; Stack et al. 2007), whilst in transgenic N171-82Q (82Q) and R6/2 HD mice, the reduced histone 3 lysine 9 acetylation is concomitant with increased H3K9me and associated gene expression changes (Stack et al. 2007). In the sections below, I shall describe in more detail some of the mechanisms involving histone modifying complexes by which aberrant gene expression occurs in HD.

PGC-1 alpha

It is well established that PPAR gamma co-activator 1 alpha (PGC-1alpha) functions as a transcriptional co-activator/co-repressor through associations with both KATs and HDACs to regulate expression of genes involved with mitochondrial energy and metabolism (Lawless et al. 2009c). PGC-1alpha has also been linked to the development and pathogenesis of HD. Small nucleotide polymorphisms (SNPs) studies have identified particular SNPs within intron-2 of the PGC-1alpha gene that are associated with a delay in age at onset of motor symptoms in patients with Huntington's disease (Taherzadeh-Fard et al. 2009; Weydt et al. 2009). Another SNP study has identified a SNP (rs2970870) within the promoter associated with earlier onset of HD in the homozygous state and a SNP within the transcribed region (rs7665116) associated with a delayed onset (Che et al. 2011). Significantly reduced levels of PGC-1alpha occur in the muscle of HD patients and HD transgenic mice, whilst 'knockdown' of mutant Htt in myoblasts leads to increased PGC-1alpha (Chaturvedi et al. 2009). Reduced expression of PGC-1alpha target genes also is found in the striatum of HD patients and mouse models (Weydt et al. 2006). When PGC-1alpha knockout mice were crossbred with HD knockin mice, increased neurodegeneration of striatal neurons and motor abnormalities was found to occur. Ectopic expression of PGC-1alpha was able to partially ablate the toxic effects of mutant huntingtin in cultured striatal neurons, whilst lentiviral-mediated PGC-1alpha provided neuroprotection in the striatum of transgenic HD

mice (Cui et al. 2006). When adipose stem cells were transplanted into the striatum of R6/2 HD mice, increased survival, attenuation of striatal neuron loss and reductions in levels of huntingtin aggregates were observed which correlated with elevated levels of PGC-1alpha (Lee et al. 2009).

HDAC/REST complexes

One of the best established mechanisms in the regulation of neuronal development relates to genes which are regulated by the repressor element-1 (RE1)/neuronal restrictive silencer element. A specific protein called repressor element silencing transcription factor (REST), also known as neuron-restrictive silencing factor (NRSF), binds to this element and prevents the expression of these genes in non-neuronal cells (Seth and Majzoub 2001; Belyaev et al. 2004). REST is a critical protein in development (Chen et al. 1998) and is essential for proper neuronal differentiation and maturation (Paquette et al. 2000; Abrajano et al. 2009a, b). A functional link to aberrant REST activity and selective loss of neurons has been shown in a study of Down's syndrome (Bahn et al. 2002). In addition, a Nurr1/CoREST pathway in microglia and astrocytes has been shown to protect neurons from inflammation-induced death in Parkinson's disease (Saijo et al. 2009).

REST contains two distinct repressor domains, one located at the N terminus and the other at the C terminus of the protein (Thiel et al. 1998; Tapia-Ramirez et al. 1997). Two distinct neuronal repressor complexes have now been isolated containing both REST and HDACs. The first of these complexes involves direct interactions with mSin3A/B at the N terminus which then recruits HDACs to repress gene expression (Grimes et al. 2000; Huang et al. 1999; Naruse et al. 1999; Roopra et al. 2000). The C-terminal repression domain associates with a novel protein called CoREST (Andres et al. 1999). This protein also interacts with HDACs through its SANT domain and has been shown to be essential for repression (You et al. 2001) and in particular actively represses genes essential for neuronal phenotype (Ballas et al. 2005). The ATP-dependent remodelling complex SWI/SNF also plays a role in REST-mediated neuronal gene regulation as CoREST recruits several SWI/SNF members, indicating that active chromatin remodelling is an element in REST-mediated repression (Battaglioli et al. 2002; Watanabe et al. 2006). CoREST complexes have also been shown to contain lysine demethylases, and recently, a KDM1–CoREST–CtBP co-repressor complex was shown to be required for late cell-lineage determination and differentiation during pituitary organogenesis (Wang et al. 2007a).

In HD, levels of a microRNA miR-9/miR-9A are downregulated. This microRNA has been identified as a critical regulator of REST/NRSF (Packer et al. 2008), and loss of this miRNA results in increased levels of nuclear REST/NRSF activity (Bithell et al. 2009). As REST/NRSF has been shown to associate with Htt (Zuccato et al. 2003), KMTs and HDACs (Gray 2009), this may result in aberrant regulation of gene expression. Indeed, in this context, REST/NRSF has been shown to regulate several miRNAs (Conaco et al. 2006; Wu and Xie 2006). Because nuclear REST/NRSF activity is increased in HD patients as a consequence of loss of miR-9/miR-9A, this results in the further loss of expression of a series of miRNAs regulated by REST/NRSF in HD patients (Bithell et al. 2009).

For instance, a novel non-coding RNA human accelerated region 1, specifically transcribed in the nervous system, is regulated by REST/NRSF and has been shown to be downregulated in HD patients (Johnson et al. 2010). Expression of another miRNA, mIR-22, has been shown to be downregulated in two transgenic mouse models of HD (YAC128 and R6/2; Lee et al. 2011). This miRNA has recently been shown to be involved with the regulation of HDAC4 in hepatocellular carcinoma, in that cancers with low levels of this miRNA had elevated levels of HDAC4 (Zhang et al. 2010). It must be noted that in the R6/2 HD mouse model, decreased levels of HDAC4 protein were observed in the cortex (Quinti et al. 2010).

Motor neuron genes modulated by HDACs

In addition to RE1/NSRE-directed repression of specific genes, motor neurons also express unique combinations of LIM-type homeodomain factors. These function to define motor column identity by regulating particular gene expression profiles (Sharma et al. 1998). LIM homeodomain transcription factors have been shown to be regulated through a complex containing HDACs (Bach et al. 1999), and as such motor neuron pathfinding may be guided through an HDAC-directed process.

HDACs within the neuronal setting of HD

E2F, HDACs and neuronal survival mechanisms

An essential feature for neuronal survival has also been linked to constitutive repression of E2F1 transcriptional activity through HDAC proteins (Boutillier et al. 2002). Elevated levels of E2F1 lead to neuronal apoptosis (Konishi and Bonni 2003; Hou et al. 2000) and enhanced immune cell proliferation (Wu et al. 2001), factors that could be deleterious in HD. Indeed, elevated levels of E2F have been found in the brains of patients suffering from HD (Pelegri et al. 2008). Subsequently, we demonstrated that HDAC inhibitors reduce levels of E2F class I proteins in vivo (Camelo et al. 2005), data which have been recapitulated by others in vitro (Suzuki et al. 2000; Said et

al. 2001). These observations may therefore help to explain why HDAC inhibitors block immune cell proliferation (Dangond et al. 1998) and enhance neuronal survival (Ryu et al. 2003).

HDACs play important roles in stem cell neuronal differentiation

Increased neurogenesis has been observed in primary HD patient material (Curtis et al. 2005), and mutant Htt has been demonstrated to stimulate neuronal differentiation of embryonic and neural stem cells (Lorincz and Zawistowski 2009). HDACs play important roles in neuronal stem cell (NSC) differentiation. When Flag-tagged HDACs with reduced enzymatic activity were used within a 'dominant negative' setting in stem cell lines, Howard and colleagues found that mutant HDAC1 reduced neuron differentiation by 50% (Humphrey et al. 2007). During murine development, HDAC1 is expressed in neural stem cells/progenitors and glia, whereas HDAC2 is found in neural progenitors and is upregulated in post-mitotic neuroblasts and neurons, but not in fully differentiated glia (MacDonald and Roskams 2008). Using mice lacking HDAC1 or HDAC2, Olson and colleagues demonstrate that these deacetylases do not have an overt phenotype in neuronal progenitors. However, once neuron development is initiated, these mice develop severe hippocampal abnormalities, absence of cerebellar foliation, disorganization of cortical neurons and lethality by postnatal day 7, attributed to a failure of neuronal precursors to differentiate into mature neurons and excessive cell death (Montgomery et al. 2009). Prozorovski et al. (2008) have also linked the SIRT1 HDAC to differentiate neural progenitor cells. A direct role for histone deacetylases in the regulation of neural stem cell proliferation has been shown where the orphan nuclear receptor TLX, a critical regulator of stem cell proliferation, was found to associate with HDAC3 and HDAC5. Inhibition of HDAC activity or knockdown of HDAC expression led to marked induction of TLX target gene expression and dramatically reduced neural stem cell proliferation (Sun et al. 2007).

In vitro studies have also been shown to differentiate neuronal precursor cells. Trichostatin A (TSA) treatment of embryonic mouse NSCs increased neuronal differentiation of the NSCs and decreased astrocyte differentiation (Balasubramaniyan et al. 2006), whilst embryonic stem cells can also be induced to differentiate into neurons following inhibition of histone deacetylases (Yao et al. 2010). Furthermore, valproic acid has also been shown to promote neuronal differentiation by inducing proneural factors such as Ngn1, Math1 and p15 in association with H4 acetylation at their promoters indicating that the mechanism involved concerns inhibition of HDACs (Yu et al. 2009).

Inhibition of histone deacetylases in lineage-committed oligodendrocyte precursor cells activity acted as a priming event in the induction of developmental plasticity (Lyssiotis et al. 2007). A similar study examining the ability of oligodendrocyte progenitors to acquire the identity of myelin-expressing cells or choose alternative fates found that the activity of histone deacetylases was critical to these processes (Liu et al. 2007), and the transcription factor Yin Yang 1 was shown to be a critical regulator of oligodendrocyte progenitor differentiation, acting as a lineage-specific repressor of transcriptional inhibitors of myelin gene expression (Tcf4 and Id4), through the recruitment of histone deacetylase-1 to their promoters during oligodendrocyte differentiation (He et al. 2007).

REST is also critically involved with neural stem cell differentiation. Activation of REST is sufficient to cause neuronal differentiation (Su et al. 2004). REST complexes are able to both silence and repress neuronal genes in embryonic neural stem cells through the creation of chromatin environments that contain both repressive and active local epigenetic signatures (Greenway et al. 2007; Sun et al. 2005b; Ballas et al. 2005). Neurons treated with a combination of HDAC and transcription inhibitors display an acetylation and transcription-dependent increase in neural outgrowth, associated with KAT3A/KAt3B and KAT2B-dependent p53 acetylation (Gaub et al. 2010).

HDACs, ER stress and pro-inflammatory pathways in HD

Inflammation is a critical element associated with cancer (Grivennikov et al. 2010), diabetes (Lawless et al. 2009b), but also is increasingly linked to neurodegenerative disease (Esiri 2007). Endoplasmic reticulum (ER) stress is another cellular event which has also been implicated as a critical component in all these conditions (Lawless et al. 2009a). HDACs have been shown to be critical regulators of many important cellular processes, and evidence is emerging linking these enzymes in the regulation of inflammation and ER stress responses. Whilst HD is not primarily considered to be a pro-inflammatory disease as mouse models of HD show little evidence for the involvement of inflammation (Schwab et al. 2010), nevertheless it is well established that one central mediator of inflammation, NFkB, plays some role in HD pathogenesis. Over the sections below, I shall link HDACs to both of these important pathways within the context of HD.

HATs/HDACs, NFkB and HD

NFkB is a key mediator of inflammatory cascades, playing important roles in regulating NFkB activation (Lawless et

al. 2009a; Mankan et al. 2009). NFkB typically consists of a heterodimeric protein comprised of a p50 and a p65 (RelA) subunit. Initial studies identified lysine acetyltransferases KAT3A and KAT3B as key coactivators in regulating NFkB-driven gene expression (Gerritsen et al. 1997; Perkins et al. 1997; Wadgaonkar et al. 1999). A further lysine acetyltransferase KAT13A was also found to potentiate NFkB transactivation through interactions with p50 (Sirianni et al. 1998). It was then shown that the RelA/p65 subunit can associate with HDACs 1–3 to repress expression of NFkB-regulated genes as well as to control the induced level of expression of these genes (Ashburner et al. 2001; Hoberg et al. 2004, 2006). The histone deacetylase SIRT1 also regulates NFkB transactivation by deacetylating a critical lysine at position 310 of the RelA/p65 subunit thereby inhibiting transcription (Yeung et al. 2004). A critical regulator of NFkB activation is IKKα. NFkB transcription requires IKKα to phosphorylate silencing mediator for retinoic acid and thyroid hormone receptor which in turn stimulates the exchange of co-repressor for co-activator complexes. In the initial stages of NFkB activation, the phosphorylation event causes HDAC3 to be displaced from RelA/p65, allowing KAT3B to acetylate RelA/p65 (Hoberg et al. 2004, 2006). IL-6 and IL-8 are pro-inflammatory cytokines associated with responses to NFkB activation (Esposito et al. 2003; Dandona et al. 2004a, b), and NFkB utilises the lysine acetyltransferase activity of KAT3A/KAT3B to stimulate the transcription of these genes (Vanden Berghe et al. 1999).

The protein Daxx regulates NFkB activation by binding to a region which includes the major sites of acetylation mediated by KAT3A/KAT3B (Park et al. 2007). However, Daxx also directly associates with HDAC2 (Hollenbach et al. 2002) and so may represent a mechanism by which KATs and HDACs compete for critical lysines on NFkB subunits. In this regard, small ubiquitin-like modifier modification of KAT3A negatively modulates its transcriptional activity by recruiting a Daxx complex which contains HDAC2 (Kuo et al. 2005)

It is well established that inflammation is also a central element in HD. Elevated NFkB activity has been found in cultured cells expressing mutant Htt and striatal cells from HD transgenic mice (Khoshnan et al. 2004). Furthermore, several family members of the IKK proteins have been shown to be functionally involved in HD. The IKK proteins are critical regulators of NFkB. Indeed in the study demonstrating activation of NFkB, it was found that mutant Htt associated with and activated IKKγ (Khoshnan et al. 2004). Additional studies have shown that both IKKα and IKKβ are involved in the proteolysis of Htt in response to external cues such as DNA damage (Khoshnan et al. 2009). IKK has also been shown to phosphorylate huntingtin which targets it for degradation by the proteasome and lysosome (Thompson et al. 2009). Critically once phosphorylated, IKK regulates additional post-translational modifications, of Htt including ubiquitination, sumoylation and acetylation. Furthermore, this subsequently enhances Htt nuclear localization, cleavage and clearance mediated by lysosomal-associated membrane protein 2A and Hsc70. The authors propose that IKK activates mutant Htt clearance until an age-related loss of proteasome/lysosome function promotes accumulation of toxic post-translationally modified mutant Htt (Thompson et al. 2009).

HATs/HDACs, ER stress and HD

The ability of a cell to sense, response to and circumvent stress is essential for maintaining homeostasis. There are many ways in which stress, either endogenous or exogenous, can be manifested in a cell; these include pathogenic infection, chemical insult, genetic mutation, nutrient deprivation and even normal differentiation. The process of mutant protein folding is particularly sensitive to such insults. As such for the cellular compartments in which mutant proteins are processed and folded, there are adaptive programmes that enable both their detection and correction for more efficient processing (Rutkowski and Kaufman 2004).

The ER is a large cellular organelle comprising a network of interconnected, closed membrane-bound vesicles. It is the site of synthesis, folding and modification of secretory and cell-surface proteins and serves many essential functions, including the production of the components of cellular membranes, proteins, lipids and sterols (Hebert and Molinari 2007). Only correctly folded proteins are transported out of the ER whilst incompletely folded proteins are retained in the organelle to complete the folding process or to be targeted for destruction (Rapoport 2007). Due to the important roles of the ER, its proper functioning is therefore essential to cellular homeostasis. Various conditions can, however, interfere with the ER function leading to situation known as ER stress. Stress is the response of any system to perturbations of its normal state. Thus, ER stress can arise from a disturbance in protein folding which results in an accumulation of unfolded or misfolded proteins within the organelle (Lai et al. 2007). During such disturbances, in order to carry out the correct folding of proteins, the ER has evolved as a specialized protein folding machine with cellular mechanisms that promote proper folding of aberrant protein, thus preventing its aggregation. When ER homeostasis is altered by misfolded proteins, the ER responds by inducing specific genes and attempting to restore normal ER function and maintain stability (Caruso and Chevet 2007). The four elements of ER stress are (1) protein degradation, (2) endoplasmic overload response (EOR), (3) unfolded protein response (UPR) and (4) cellular death pathway. This four-

stage model of ER stress toxicity helps to explain this organelles role in the onset of clinical manifestations. Two ER stress-induced signal transduction pathways have been described: the UPR (Ron and Walter 2007) and the EOR (Pahl and Baeuerle 1997). These pathways once activated attempt to adapt to the disturbance and re-establish normal ER function (Xu et al. 2005). In the case of misfolded proteins, this is known as ER-associated degradation (ERAD), the process by which these misfolded proteins are exported to the cytosol for degradation by proteasomes (Vembar and Brodsky 2008). Excessive or prolonged ER stress can overwhelm the cells ability to cope and elicits the cell death programme or apoptosis (Rao et al. 2004). Evidence linking KATs/HDACs to ER stress is not as well established as that for inflammation, with most studies utilising histone deacetylase inhibitors. However, in a recent study in hepatocytes on Mallory body (cytokeratin aggresomes) formation, decreased histone acetyltransferase and increased histone deacetylase activity were observed (Bardag-Gorce et al. 2007). In a similar model of oxidative stress-induced inclusion formation, treatment of cells with 4-phenylbutyrate (PB) was found to alleviate formation of these inclusions (Hanada et al. 2007).

In terms of neurodegeneration, evidence is clearly emerging linking ER stress to the pathogenesis of HD (Vidal et al. 2011). The first indication that ER stress may be involved with Huntington's disease came from a study of aggresome-like perinuclear inclusions generated using a huntingtin exon 1 truncated protein model in human 293 Tet-Off cells. In depth analysis of these inclusion bodies demonstrated the presence of markers of ER stress including the molecular chaperones BiP/GRP78, Hsp70 and Hsp40 (Waelter et al. 2001).

Mutant huntingtin fragment proteins have now been shown to elevate Bip (an ER chaperone), increase levels of C/EBP homologous protein (CHOP; an ER stress-induced regulator of cell death), increase the phosphorylation of c-Jun-N-terminal kinase (a regulator of cell death) and cleavage of caspase-3 and caspase-12 (mediators of cell death; Reijonen et al. 2008). Inhibition of ER stress using salubrinal counteracted both neuronal cell death and protein aggregation by mutant Htt (Reijonen et al. 2008). Functional analysis of Htt identified an amphipathic alpha helical membrane-binding domain that can reversibly target it to vesicles and the ER (Atwal and Truant 2008; Atwal et al. 2007). Normal Htt is released from these membranes in response to ER stress and rapidly translocates into the nucleus. Once ER stress has been alleviated, the Htt is capable of nuclear export and re-association with the ER. However, this release is inhibited when huntingtin contains the polyglutamine expansion seen in Huntington's disease. As a result, mutant huntingtin expressing cells have a perturbed ER and an increase in autophagic vesicles, indicating that one of Htt's functions is to act as ER sentinel, potentially regulating autophagy in response to ER stress (Atwal and Truant 2008; Atwal et al. 2007). Mutant Htt has also been shown to interact with and abrogate the function of grp78, a critical ER membrane-anchored ubiquitin ligase (E3) involved in ERAD resulting in the induction of ER stress (Yang et al. 2010). Furthermore, an additional protein, SCAMP5, which functions to regulate the formation of expanded polyglutamine repeat protein aggregates has been shown to be induced in cultured striatal neurons by either ER stress or mutant HTT (Noh et al. 2009). The heat shock protein HspB8, when overexpressed, has been shown to prevent mutant Htt aggregation through an autophagic activity (Carra et al. 2005, 2008a, b, 2009).

In a presymptomatic knockin mouse model of HD, early markers of disease regulator of ribosome synthesis Rrs1 and its interacting protein 3D3/lyric (also known as metadherin and astrocyte elevated gene-1) were found to be localised in the ER, are induced by ER stress and are involved in the ER stress response in neuronal cells (Carnemolla et al. 2009). Indeed, levels of Rrs1 mRNA have been shown to be elevated in the brains of HD patients (Fossale et al. 2002). Furthermore, in the HD knockin mice, ER stress was found to occur prior to the formation of amyloid intranuclear or cytoplasmic inclusions indicating that it plays a critical role in the pathogenesis of HD (Carnemolla et al. 2009). Postmortem analysis of patient brains has found increased mRNA expression of the ER stress-related genes BiP, CHOP and Herpud1 in HD postmortem brain (Carnemolla et al. 2009).

Direct physical evidence for the association of KATs and HDACs with critical regulatory elements within the ER stress pathway is emerging. CHOP is an ER stress-inducible protein which plays a critical role in regulating programmed cell death. CHOP has recently been shown to directly associate with the histone acetyltransferase p300, and inhibition of HDACs prevents its degradation (Ohoka et al. 2007). Chromatin immunoprecipitation analyses have shown that ER stress regulators are regulated at the transcriptional level via histone post-translational modifications (Donati et al. 2006). KAT3B has been shown to bind to the promoter for the GRP78/BiP (Baumeister et al. 2005), whilst regulation of the CHOP promoter involves a complex containing JDP2 and HDAC3 (Cherasse et al. 2008).

B lymphocyte-induced maturation protein-1 (BLIMP-1) has been shown to be associated with cellular stress and is rapidly upregulated during the UPR in some models (Doody et al. 2006). This protein directly associates with HDACs to repress transcription (Yu et al. 2000) and may therefore indicate that BLIMP-1 may utilise HDACs to downregulate important genes during ER stress.

Aggregation-prone proteins have been suggested to overwhelm and impair the UPS in polyQ disorders, such

as HD. Two separate studies have found that UPS dysfunction is a consistent feature of HD pathology with impaired UPS in the synapses of HD mice (Bennett et al. 2007; Wang et al. 2008). ER stress has been shown to have a general inhibitory effect on the UPS (Menendez-Benito et al. 2005), which may explain the long-term gradual accumulation of misfolded proteins in patients with HD. Intriguingly in a neurodegenerative model for spinobulbar muscular atrophy, autophagy was induced to compensate for impaired UPS function in an HDAC6-dependent manner (Pandey et al. 2007), whilst HDAC6 overexpression was sufficient to rescue the degeneration associated with UPS dysfunction in vivo in an autophagy-dependent manner (Pandey et al. 2007). Therefore, antagonists of HDAC6 could potentially be used as an intervention to induce compensatory autophagy in HD. Indeed inhibitors targeting HDAC6 have been shown to alleviate the microtubule transport- and release-defect phenotypes associated with HD (Dompierre et al. 2007). HDAC6 would therefore appear to be the critical regulator controlling cellular response pathways to cytotoxic accumulation of ubiquitinated protein aggregates and interacts with both dynenin motors and misfolded proteins to form an active transport system to transport misfolded proteins to the aggresome (Kawaguchi et al. 2003). HDAC6 also plays a role in regulating chaperone-mediated responses to cellular stress. Ubiquitinated cellular aggregates impairing proteasome activity triggers a HDAC6-dependent cell response involving the induction of major cellular chaperones via dissociation of a repressive HDAC6/heat shock factor 1/heat shock protein 90 complex (Boyault et al. 2007). These and other data showing that HDAC6 is a critical component of environmentally induced stress granules (Kwon et al. 2007) point to an essential role for HDAC6 as a cellular stress surveillance factor, where it can be both a sensor of stressful stimuli and an effector mediating and coordinating appropriate cellular responses (Matthias et al. 2008).

Targeting HD using HDACi

From the previous sections, it could be argued that targeting HDACs may be a way to target the neurodegenerative effects of HD. In the sections below, I shall summarize the current literature on the effects of HDACi in HD.

Neuroprotective effects of HDACi in models of HD

Sodium butyrate

In a cell culture model of HD, treatment of cells with sodium butyrate caused the redistribution of huntingtin-positive nuclear bodies (Kegel et al. 2002). The first indications that HDAC inhibitors may prove useful in the treatment of Huntington's came from yeast and fly models where treatments of Huntington's disease models were found arrest neurodegeneration or mitigated the effects on affected gene promoters (Hughes et al. 2001; Steffan et al. 2001). Sodium butyrate has also been shown to ameliorate motor deficits in mouse HD model (Ferrante et al. 2003)

Phenylbutyrate

Following on from these studies, it has since been shown that the HDAC inhibitors PB can also ameliorate Huntington motor deficits in mouse models (Gardian et al. 2005). In vitro and in vivo models of Huntington's using ST14a/STHdh cells and R2/6 mice demonstrated a marked histone H3 hypoacetylation in downregulated genes, and treatment with HDAC inhibitors was found to both reverse the mRNA abnormalities and led to histone acetylation at the promoters of these genes (Sadri-Vakili et al. 2007).

Currently, clinical trials are undergoing in relation to the use of PB to treat HD. A phase II safety and tolerability trial (NCT00212316) has been completed, and a serum analysis has identified individual-specific patterns of ca. 20 metabolites which could provide a means for the selection of subjects for extended trials using this drug (Ebbel et al. 2010).

Valproic acid (Depakene® Depakote®)

High-dose valproate treatment of the transgenic mouse N171-82Q model of HD significantly prolonged survival and ameliorated diminished spontaneous locomotor activity, without exerting any noteworthy side effect on their behaviour or the striatal dopamine content at the dose administered (daily i.p., 100 mg/kg; Zadori et al. 2009). It must be noted that there has also been one report linking valproic acid treatment with the development of Pisa syndrome in a patient with HD (Salazar et al. 2008).

Suberoylanilide hydroxamic acid (Vorinostat, Zolinza®)

Several studies have now shown that the first FDA approved histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA; Zolinza®) has efficacy in modulating the severity of HD models. The earliest such study demonstrated that SAHA was able to ameliorate motor deficits in a mouse model of Huntington's disease (Hockly et al. 2003).

SAHA is a pan-specific HDACi broadly inhibiting the classes I, II and IV HDACs (Khan et al. 2008), but it has

also been shown to specifically downregulate HDAC7 (Dokmanovic et al. 2007). SAHA can functionally decrease the levels of HDAC7 in wild-type and the R6/2 transgenic mouse model of HD (Benn et al. 2009). Despite this, complete genetic loss of HDAC7 did not alleviate the symptoms in HD models (Benn et al. 2009). As such, HDAC7 would not appear to be the main target for the therapeutic benefits of HDACi in HD models. SAHA has also been shown to inhibit HDAC6. This deacetylase has a special function in that it deacetylates microtubules in vitro and in vivo (Hubbert et al. 2002). HDAC6 may therefore be an important target in HD as levels of tubulin acetylation were also found to be reduced in HD brains, whilst treatment with the HDACi TSA ameliorated the phenotypic effects of HD (Dompierre et al. 2007). Indeed, microtubule dynamics associated with HDAC6 have also been shown to be of broad potential interest in conditions of neurodegeneration. In Alzheimer's disease, the protein tau has been shown to inhibit HDAC6 resulting in increased microtubule acetylation and prevents the induction of autophagy by inhibiting proteasome function (Perez et al. 2009). Similarly, HDAC6 has also been shown to regulate the cellular location of Parkin, a protein-ubiquitin E3 ligase linked to Parkinson's disease (Jiang et al. 2008).

Other HDACi

In the R6/2 transgenic mouse model of HD, a novel pimelic diphenylamide HDAC inhibitor, HDACi 4b, significantly improved motor performance, overall appearance and body weight of symptomatic mice, with associated significant attenuation of gross brain-size decline and striatal atrophy (Thomas et al. 2008).

Potential use of HDACi to alleviate ER stress in HD

Data from in vitro studies are emerging demonstrating the efficacy of the histone deacetylase inhibitor 4-phenylbutyrate in relieving ER stress in cell line models of cystic fibrosis (Rubenstein and Zeitlin 2000) and mutant alpha1-ATZ liver disease (Burrows et al. 2000). Since these initial observations, several studies have shown that 4-phenylbutyrate may act as a chemical chaperone to relieve ER stress induced in models of ischemia (Qi et al. 2004; Vilatoba et al. 2005). Similar data have emerged for models of cataract formation (Mulhern et al. 2007), Parkinson's disease (Kubota et al. 2006), retinitis pigmentosa (Bonapace et al. 2004), glaucoma (Yam et al. 2007a) and reconfirmation of its ability to alleviate stress in cystic fibrosis (Vij et al. 2006).

In diabetes, 4-phenylbutyrate has also been shown to both relieve ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. This occurs by the restoration of systemic insulin sensitivity, resolution of fatty liver disease and enhancement of insulin action in liver, muscle and adipose tissues (Ozcan et al. 2006).

ER stress in liver-induced ischemia has been shown to be ameliorated by treatments with 4-phenylbutyrate (Vilatoba et al. 2005). This compound has also been shown to alleviate oxidative stress-induced ER tress in cultured hepatocytes and hepatoma cells (Hanada et al. 2007) and prevents ER stress-mediated aggregate formation in a model of hereditary haemochromatosis (de Almeida et al. 2007).

Valproate/valproic acid, another histone deacetylase inhibitor, has also been shown to have potential in the treatment of ER stress. Initial studies demonstrated that treatment of cells with valproate caused the upregulation of GRP78/BiP, a key ER-mediated chaperone (Wang et al. 1999). Subsequent studies confirmed that valproate could increase the expression of additional important endoplasmic reticulum stress proteins, GRP94 and calreticulin (Bown et al. 2000; Chen et al. 2000; Shao et al. 2006). Valproate has also been shown to protect against oxidative stress induced protein damage and had provided neuroprotection in the same model system (Wang et al. 2003; Shao et al. 2005; Cui et al. 2007).

Using HDACi to potentially modulate chaperone activity in HD

A plethora of studies have clearly shown that histone deacetylase inhibitors can reactivate or alter gene expression. However, histone deacetylases and histone deacetylase inhibitors may also play important roles in regulating chaperone expression and function. Obviously, this has important implications in conditions such as HD where aberrant misfolding of proteins can result in ER stress (Vidal et al. 2011) and can be highlighted by the fact that HDAC6 is recognised as a major regulator of cellular responses aimed at counteracting the effects of misfolded protein accumulation (Kovacs et al. 2005; Boyault et al. 2006, 2007; Gao et al. 2007). Inhibition or depletion of HDAC6 leads to induction of Hsp90 acetylation resulting in inhibition of its chaperone activity (Fiskus et al. 2007; Wang et al. 2007b; Scroggins et al. 2007; Edwards et al. 2007; Bali et al. 2005; Kong et al. 2006). The class I HDACs (HDACs 1–3) have also been shown to associate with the ATP-dependent chaperone Hsp70, and this association enhances deacetylase catalytic activity (Johnson et al. 2002).

Histone deacetylase inhibitors have emerged as potential therapeutic agents in the relief of ER stress induced in cell line models. Many of these studies have utilised the chemical PB. For example, in a hepatocyte cell line model of oxidative stress induced ER stress, treatment of cells with PB was found to alleviate the ER

stress in these cells (Hanada et al. 2007). Other examples of the benefits of PB as a chemical chaperone relieving apoptosis and/or ER stress have been reported in models of eye disease (Bonapace et al. 2004; Yam et al. 2007a), defective trafficking of nephrin in kidney (Liu et al. 2004), rescue of protein trafficking in the lysosomal storage disorder Fabry disease (Yam et al. 2007b), correction of autodominant hypoparathyroidism-induced apoptosis (Datta et al. 2007) and relief of ER stress-mediated programmed cell death in *Arabidopsis* (Watanabe and Lam 2007).

Other evidence for the potential of HDACi influencing chaperone-like activities to relieve ER stress are emerging. In cystic fibrosis models, phenylbutyrate can restore CFTR trafficking and function (Zeitlin et al. 2002; Singh et al. 2006; Rubenstein and Zeitlin 1998, 2000; Rubenstein and Lyons 2001; Rubenstein et al. 1997; Lim et al. 2004; Kontopoulos et al. 2006; Choo-Kang and Zeitlin 2001), through the induction of Hsp90 (Choo-Kang and Zeitlin 2001), and additional lung conditions for which beneficial responses have been observed using HDACi as chemical chaperones include respiratory distress syndrome (Cheong et al. 2006) and emphysema (Burrows et al. 2000). HDACi can also act as chemical chaperones in the liver. For example, PB was used to protect liver cells from ER stress-mediated apoptosis induced by liver ischemia (Vilatoba et al. 2005), can enhance the cell-surface expression and transport capacity of mutated bile salt export pumps (Hayashi and Sugiyama 2007) and also reduce ER stress-induced formation of Mallory bodies in hepatocytes (Hanada et al. 2007).

However, it must be noted that within the neuronal setting, initial studies on mood stabilizing drugs such as valproic acid demonstrated increased expression of ER stress proteins in cerebral cortex, hippocampus, neuronal and glial cells (Wang et al. 1999; Bown et al. 2000; Chen et al. 2000; Corson et al. 2004; Wang et al. 2001; Shao et al. 2006).

Use of HDACi in patients with HD

Initial clinical trials testing the use of valproate in the treatment of HD proved disappointing and did not show any clinical benefit (Bachman et al. 1977; Pearce et al. 1977; Symington et al. 1978). More recent studies have, however, demonstrated some benefit in HD patients either as specific monotherapy (Saft et al. 2006) or as a combination therapy with olanzipine (Grove et al. 2000).

Intensive pharmaceutical efforts have generated many agents targeting histone deacetylases, and of these, currently two have received FDA approval, SAHA/Vorinostat (Zolinza) and FK228/Romidepsin (Istodax), and both are currently licensed for the treatment of cutaneous T cell lymphoma (Mann et al. 2007a; b; Hymes 2010). Several histone deacetylase inhibitors which are undergoing clinical trials have, or currently include, patients with neurodegenerative diseases including HD, and as these trials proceed, a better understanding of the potential side effects and dose-limiting toxicities of these drugs will emerge for patients with these conditions. For the most part, the first generation inhibitors have shown well-tolerated safety profiles (Lawless et al. 2009a).

A randomized, double-blind and placebo-controlled phase I clinical trial by Elixir Pharmaceuticals of an orally active, selective Sirt1 inhibitor SEN0014196 (6-chloro-2,3,4,9-tetrahydro-1H-carbazole-1-carboxamide), has been initiated as a disease-modifying therapy in Huntington's disease, but results from this are not yet known.

Likewise, a phase I study examining the safety and tolerability of phenylbutyrate in HD (PHEND-HD) has recently been completed (Clinical Trials identifier—NCT00212316). In this study, phenylbutyrate was found to be both safe and well tolerated in early symptomatic HD subjects taking 15 g daily, and levels leukocyte histone acetylation were measurable, indicating that HDAC inhibition was occurring in response to treatment (Moser et al. 2008) A similar dose escalation/de-escalation study using sodium phenylbutyrate in HD patients agreed with the MTD of 15 g daily (Hogarth et al. 2007), and at 12 g/daily was found to correct gene expression of a 12 gene biomarker set previously identified by this group (Borovecki et al. 2005).

Future directions

Clearly, the potential utility of HDACi for the treatment of HD exists. Several HDAC inhibitors have good safety/tolerability profiles and are undergoing clinical trials in neurodegenerative disease. It therefore seems imperative that these drugs should continue to be tested for their potential therapeutic role in patients afflicted with HD. Further clinical trials are, however, required to demonstrate their efficacy in alleviating the symptoms of this disease, and indeed, it may be that HDACi may be more effective in a combinatorial setting with other agents, particularly for diseases such as HD. These and other questions remain to be addressed, but it is clear that these inhibitors may play important roles in both targeting neurodegenerative conditions through their activity on gene transcription and potentially through additionally alleviating ER stress or modulating chaperone activity. Further experiments will, however, be required to functionally address these possibilities.

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