

The transposon-driven evolutionary origin and basis of histone deacetylase functions and limitations in disease prevention

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Abstract Histone deacetylases (HDACs) are homologous to prokaryotic enzymes that removed acetyl groups from non-histone proteins before the evolution of eukaryotic histones. Enzymes inherited from prokaryotes or from a common ancestor were adapted for histone deacetylation, while useful deacetylation of non-histone proteins was selectively retained. Histone deacetylation served to prevent transcriptions with pathological consequences, including the expression of viral DNA and the deletion or dysregulation of vital genes by random transposon insertions. Viruses are believed to have evolved from transposons, with transposons providing the earliest impetus of HDAC evolution. Because of the wide range of genes potentially

affected by transposon insertions, the range of diseases that can be prevented by HDACs is vast and inclusive. Repressive chromatin modifications that may prevent transcription also include methylation of selective lysine residues of histones H3 and H4 and the methylation of selective DNA cytosines following specific histone lysine methylation. Methylation and acetylation of individual histone residues are mutually exclusive. While transposons were sources of disease to be prevented by HDAC evolution, they were also the source of numerous and valuable coding and regulatory sequences recruited by “molecular domestication.” Those sequences contribute to evolved complex transcription regulation in which components with contradictory effects, such as HDACs and HATs, may be coordinated and complementary. Within complex transcription regulation, however, HDACs remain ineffective as defense against some critical infectious and non-infectious diseases because evolutionary compromises have rendered their activity transient.

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Introduction

Histone deacetylases (HDACs) form repressive chromatin by removing acetyl groups from histones and are an essential part of defense against a wide range of infectious and non-infectious disease conditions (Gregoretto et al. 2004). Beneficial biological functions have evolutionary origins. Most functions are imperfect, if not seriously flawed, because they reflect evolutionary compromises between competing requirements of the organism (Nesse and Williams 1995; Fromer and Shifman 2009; Foit et al.

2009). An understanding of the functions and limitations of HDACs in disease prevention may be enhanced by an examination of their evolutionary origins.

Histone acetylation and deacetylation began after the evolution of histones, the protein components of eukaryotic nucleosomes that organize chromatin and regulate the DNA binding of other proteins that determine whether transcription takes place (Berger 2007; Taverna et al. 2007; Zhang et al. 2003a). Although enzymes with considerable homology to eukaryotic HDACs of all four classes are widespread in prokaryotes, their functions are different (Hildmann et al. 2007; Gregoretta et al. 2004; Ledent and Vervoort 2006). Most, if not all, such enzymes, in fact, existed before the evolution of histones (Hildmann et al. 2007; Gregoretta et al. 2004; Ledent and Vervoort 2006). Their functions include deacetylation of polyamines, acetyl coenzyme A synthetase and other non-histone proteins (Leipe and Landsman 1997; Gardner et al. 2006). The deacetylase capacity that eukaryotic HDACs inherited from prokaryotes or from a common ancestor could be easily adapted to deacetylation of eukaryotic histones, as demonstrated experimentally (Finnin et al. 1999; Hildmann et al. 2004). Eukaryotic HDACs selectively maintain the inherited ability to deacetylate non-histone proteins (Zhang et al. 2003b; Ito et al. 2002). HDACs have been well conserved in eukaryotes for at least 100 Ma (Ekwall 2005; Heckman et al. 2001).

Histone modifications and transcription

In addition to histone deacetylation, repressive chromatin modification includes the methylation of a number of lysine residues in the amino (N)-terminal tails of histone 3 (H3) and histone 4 (H4), including lysine 9 (H3K9) of histone 3 (Martens et al. 2005; Maksakova et al. 2008; Kondo and Issa 2003; Lewin 2008; Gendrel et al. 2002; Liu et al. 2008; Latham and Dent 2007). H3K9 methylation following H3K9 deacetylation initiates recruitment of DNA methyltransferase which adds a methyl group to DNA cytosines in CpG context (Geiman and Robertson 2002; Martens et al. 2005; Maksakova et al. 2008; Yoder et al. 1997; Lewin 2008; Gendrel et al. 2002).

Histone acetylation involves the covalent bonding of an acetyl group transferred from acetyl coenzyme A to a lysine residue in the histone N-terminal tail (Grunstein 1997; Martin et al. 2007; Sengupta and Seto 2004). The acetyl group is widely believed to partially neutralize the positive electrostatic charge of the histone and reduce the ionic bonding between the histone and the negatively charged DNA, thereby making local DNA more accessible to transcription factor binding (Grunstein 1997; Zhang et al. 2003a; Liu et al. 2008; Sengupta and Seto 2004). Acetylated lysines are also reported to recruit chromatin remodeling proteins and protein

complexes such as SWI/SNF (Liu et al. 2008; Latham and Dent 2007; Taverna et al. 2007; Sengupta and Seto 2004; Lewin 2008). Histone methylation is believed to stabilize the positive charge of histones (Latham and Dent 2007; Grunstein 1997; Maksakova et al. 2008). Methylated lysines are also reported to serve as binding sites for the recruitment of proteins and protein complexes that impact transcription (Liu et al. 2008; Latham and Dent 2007; Maksakova et al. 2008; Zhang et al. 2003a; Bannister et al. 2001; Taverna et al. 2007).

Dimethylated or trimethylated H3K9 provides for the binding of heterochromatin protein 1 (HP1) through its chromodomain (Liu et al. 2008; Latham and Dent 2007; Zhang et al. 2002a; Bannister et al. 2001; Taverna et al. 2007). Since HP1 complexes with both histone deacetylases and the histone methyltransferase SUV39H1, it recruits to the methylated residue the capacity to replace acetylation with methylation on nearby histone residues and thereby spread repressive chromatin by a positive feedback loop to create heterochromatin (Zhang et al. 2002a; Latham and Dent 2007; Bannister et al. 2001; Vaute et al. 2002; Taverna et al. 2007). H3K36 methylated by histone methyltransferase Set2 has been shown to recruit a complex containing yeast HDAC Rpd3 through the chromodomain of the component Eaf3 (Keogh et al. 2005; Latham and Dent 2007). Additional effector proteins that bind at methylated H4K20 and H3K4 have been characterized (Taverna et al. 2007). Most of the known binding at methylated H3K4 has been shown to actually promote acetylation of other histone residues and often transcription activation (Latham and Dent 2007; Liu et al. 2008; Taverna et al. 2007; Berger 2007).

Specific lysine residues on histones H3 and H4 are subject to methylation and/or acetylation to alter the DNA binding of regulatory proteins (Martens et al. 2005; Lewin 2008; Liu et al. 2008; Kondo et al. 2008). On histone H3, lysines 9, 14, 18, 23, 27, 36, and 56 and on histone H4, lysines 5, 8, 12, 16, and 20 may be acetylated (Liu et al. 2008; Latham and Dent 2007; Berger 2007). A negative charge can also be added to histone H3 by phosphorylation of serine 10 or 28 (Liu et al. 2008). Histone modification is not limited to acetylation and methylation and occurs in numerous patterns, with extensive cross-regulation (Latham and Dent 2007; Maksakova et al. 2008; Taverna et al. 2007; Berger 2007; Zhang et al. 2003a). Methylation and acetylation of lysine residues are mutually exclusive and competitive (Maksakova et al. 2008; Liu et al. 2008; Latham and Dent 2007; Taverna et al. 2007; Mutskov and Felsenfeld 2004; Schubeler et al. 2000; Irvine et al. 2002). Lysine methylation requires deacetylation and lysine acetylation requires demethylation (Maksakova et al. 2008; Latham and Dent 2007; Mutskov and Felsenfeld 2004; Schubeler et al. 2000; Irvine et al. 2002).

DNA is methylated by DNA methyltransferases (DNMTs), which convert target cytosines to 5-methylcytosine (Tost 2010; Geiman and Robertson 2002; Liu et al. 2008). Target cytosines are predominantly found in CpG dinucleotides and are especially prevalent in promoter regions (Tost 2010; Liu et al. 2008; Geiman and Robertson 2002). DNA methyltransferases DNMT3A and DNMT3B transfer a methyl group from *S*-adenosyl-L-methionine to cytosines de novo, while DNMT1 establishes methylation on the new strand produced during the S phase of interphase (Tost 2010; Geiman and Robertson). Methylated DNA becomes bound by DNA-methyl-binding domain (MBD) proteins (MBD1, MBD2, and MBD4), SRA domain proteins (UHRF1 and UHRF2) and certain zinc finger proteins (kaiso, ZBTB4, and ZBTB38), all of which recruit components with transcription repression activity, including histone deacetylation and methylation (Tost 2010; Sasai and Defossez 2009). Repressive chromatin is thereby spread. Repressive chromatin at the transcription start site or at the binding sites of activation transcription factors prevents transcription (Tost 2010).

HDACs as protection from transposons and viruses

The functions and limitations of human HDACs are illustrated by their response to newly integrated viral DNA. As reported (Greger et al. 2005; Katz et al. 2007), human HeLa cells have been experimentally infected with avian sarcoma virus (ASV), a retrovirus that normally infects birds. It has been shown (Greger et al. 2005; Katz et al. 2007) that histone deacetylases HDAC1 and HDAC2 are recruited by the host nuclear protein Daxx and quickly accumulate at ASV DNA recently integrated into human chromosomal DNA. Modifying local chromatin by removing acetyl groups from histone tails, the HDACs create repressive chromatin to prevent transcription of viral DNA by the long terminal repeat (LTR) promoter and prevent reproduction of the virus (Greger et al. 2005; Katz et al. 2007). Reproduction of integrated human cytomegalovirus by LTR promoter transcription is also prevented by HDACs recruited by Daxx (Preston and Nicholl 2006; Hollenbach et al. 2002). In addition, human transcription factors YY1 and LSF recruit HDAC1 to the LTR of integrated human immunodeficiency virus type 1 (HIV-1), where it represses transcription of the HIV-1 provirus (Coull et al. 2000).

The evolutionary relationships between viruses and transposons and between retroviruses and retrotransposons have been a long-standing controversy. Sequencing and comprehensive phylogenetic analysis and network analysis have now provided evidence that retroviruses and other reverse transcribing viruses evolved from LTR retrotransposons (Llorens et al. 2009). They are reportedly contained,

along with the LTR retrotransposons, within five families present within plants, fungi and animals (Llorens et al. 2009). It should come as no surprise, therefore, that the epigenetic mechanisms currently applied to suppress transcription of integrated provirus are believed to have evolved to prevent expression and transposition of transposon DNA, which can interrupt vital host genes through random insertion and pathologically alter gene function or activity (Slotkin and Martienssen 2007; Martens et al. 2005; Mirouze et al. 2009; Brunmeir et al. 2010; Maksakova et al. 2008; Maksakova et al. 2006; Goodier and Kazazian 2008; Zeh et al. 2009; Matzke et al. 2000; Yoder et al. 1997). Human diseases known to result from random transposon insertions number at least 65 (Goodier and Kazazian 2008; Belancio et al. 2008; Deininger and Batzer 1999) and their diversity is virtually unlimited, as illustrated by Table 1.

Repressive chromatin, resulting from HDACs and histone methyltransferases, prevents transposons from transcribing proteins necessary for transposition (Slotkin and Martienssen 2007). The histone and DNA methylation required to silence a newly integrated transposon or provirus occurs only after substantial silencing by deacetylation has already begun (Maksakova et al. 2008; Latham and Dent 2007; Mutskov and Felsenfeld 2004).

Domestication and its legacy

Transposon-inspired defense mechanisms are not limited to methylation and deacetylation-mediated transcription repression but include post-transcriptional processes involving non-coding RNA and additional back-up defense mechanisms (Goodier and Kazazian 2008; Zeh et al. 2009; Mirouze et al. 2009). Even the acquired immunity mediated by B cell-produced antibodies and T cell receptors appears to owe its existence to transposons (Kapitonov and Jurka 2005; Slotkin and Martienssen 2007). In the case of antibodies and T cell receptors, the RAG1 protein responsible for the V(D)J recombination, upon which antibodies and T cell receptors depend for their variable specificity, has been shown to be likely derived from a transposase encoded by a DNA transposon of the *Transib* superfamily circulating in fruit fly, mosquito, sea urchin and other genomes (Kapitonov and Jurka 2005). In the case of the RAG1 protein, a transposon was not a threat inspiring protective adaptation but rather an apparent source of a valuable mechanism (Kapitonov and Jurka 2005; Slotkin and Martienssen 2007).

Host genomes have, at low frequency, recruited and adapted both protein coding and regulatory sequences from transposons, in a process known as “molecular domestication,” even as they have experienced success in the restraint

Table 1 Examples of human diseases associated with transposon insertions

Disease	Reference
Chronic hemolytic anemia	Manco et al. (2006)
Cystic fibrosis	Chen et al. (2008)
Duchenne's muscular dystrophy	Ostertag and Kazazian (2001) and Hu et al. (1991)
Hemophilia A	Ostertag and Kazazian (2001)
X-linked retinitis pigmentosa	Chen et al. (2006)
Colon cancer	Ostertag and Kazazian (2001) and Miki et al. (1992)
Beta-thalassemia	Ostertag and Kazazian (2001)
Huntington disease	Ostertag and Kazazian (2001)
Breast cancer	Ostertag and Kazazian (2001) and Miki et al. (1996)
Insulin-resistant diabetes	Shimada et al. (1990)
Fabry disease	Kornreich et al. (1990)
Acute myelogenous leukemia	Strout et al. (1998) and So et al. (1997)

of transposon transposition (Zeh et al. 2009; Feschotte 2008; Goodier and Kazazian 2008). Even the essential gene *human telomerase reverse transcriptase (hTERT)* is reported to have originated from a non-LTR retrotransposon (Nakamura and Cech 1998). Transposons contain, in the LTR, their own promoters and enhancers (Katz et al. 2007; Zeh et al. 2009; Lewin 2008; Cohen et al. 2009). According to Jordan et al. (2003), hundreds of human genes are regulated in part by sequences derived from either regulatory or coding segments of transposons. Bourque et al. (2008) revealed that mammalian transcription factor binding sites are substantially derived from transposons.

Success in the inhibition of transposon movement is exhibited by the finding, according to Pace and Feschotte (2007), that the mobility of primate DNA transposons ended 37 Ma ago, even though DNA transposons in 125 families continue to make up about 3% of the human genome. With the possible exception of an endogenous retrovirus, the only transposons known to be now actively transposing in the human genome are non-LTR retrotransposons (Goodier and Kazazian 2008; Mills et al. 2007). As demonstrated in the studies by Arnaud Le Rouzic et al. (Le Rouzic et al. 2007), loss of transposition occurs over thousands of generations only if and when the rate of actual transposition is held below the rate by which mutations eliminate the enabling molecular mechanisms. Due to mutations of transposition machinery, the number of autonomous transposons, with transposition capacity, declines slowly while the number of non-autonomous copies increases as a result (Le Rouzic et al. 2007). Mutations of transposition machinery are generally adaptive and not selected against (Le Rouzic et al. 2007).

Gain of adaptive functions through “domestication” in combination with loss of the dangers of transposition seems to represent the best in natural selection. Because of “domestication” of useful transposon sequences, regulation of gene expression is fundamentally and profoundly

changed and more complex (Jordan et al. 2003; Bourque et al. 2008; Zeh et al. 2009; Feschotte 2008).

HDACs in yeast and humans

As shown in Table 2, four classes of human HDACs are recognized, with homologous counterparts in both yeast and prokaryotes (Hildmann et al. 2007; Gregoretta et al. 2004; Ekwall 2005; de Ruijter et al. 2003). No fungal enzymes are classified as class 4 HDACs (Gregoretta et al. 2004; Ledent and Vervoort 2006). Horizontal transfer as a part of class 4 evolution has been suggested (Ledent and Vervoort 2006). Human class 1 enzymes are zinc ion dependent and include HDAC1, HDAC2, HDAC3, and HDAC8 (Hildmann et al. 2007; Gregoretta et al. 2004; de Ruijter et al. 2003). Class 2 enzymes, also zinc ion dependent, include HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10 (Hildmann et al. 2007; Gregoretta et al. 2004; de Ruijter et al. 2003). Class 4 enzymes, also zinc dependent, include HDAC11 only (Hildmann et al. 2007; Gregoretta et al. 2004; Gao et al. 2002). Class 3 HDACs, also called sirtuins, are structurally dissimilar to other human HDACs and are dependent on nicotinamide adenine dinucleotide (NAD⁺) (Hildmann et al. 2007; Grozinger and Schreiber 2002; Finnin et al. 1999; Vaquero 2009; Sauve et al. 2001). Class 3 HDACs do not release acetyl groups as acetate as do other HDACs (Vaquero 2009; Sauve et al. 2001). Historically, sirtuins conducted ADP-ribosylation before they performed deacetylation (Vaquero 2009; Saunders and Verdin 2007; Starai et al. 2002).

The budding yeast *Saccharomyces cerevisiae* has only three class 1 HDACs (Rpd3, Hos2, and Hos1) and two class 2 HDACs (Hda1 and Hos3) but multiple class 3 HDACs (Sir2, Hst1, Hst2, Hst3, and Hst4) (Ekwall 2005). Genome-wide expression profiles have shown that the *S. cerevisiae* HDACs most consistently required for gene

Table 2 HDACs in humans and in *Saccharomyces cerevisiae*

Mechanism Requirement	Class	<i>S. cerevisiae</i>	Humans
Zinc ion (Zn^{2+})	1	Rpd3	HDAC1
		Hos2	HDAC2
		Hos1	HDAC3
			HDAC8
	2	Hda1	HDAC4
		Hos3	HDAC5
			HDAC6
			HDAC7
			HDAC9
			HDAC10
			HDAC11
Nicotinamide adenine dinucleotide (NAD^+)	3 (Sirtuins)	Sir2	SIRT1–SIRT7
		Hst1	
		Hst2	
		Hst3	
		Hst4	

regulation involving metabolism, biosynthesis and cell-cycle regulation are Rpd3, Hda1, and Sir2 (Ekwall 2005; Bernstein et al. 2001; Robyr et al. 2002; Robyr et al. 2004). The formation of heterochromatin in *S. cerevisiae* depends on Sir2 (Vaquero 2009). Human class 1 HDACs are closely related to the yeast Rpd3 (Martin et al. 2009; Rundlett et al. 1996; Taunton et al. 1996), while human class 2 HDACs are homologous to yeast Hda1 (Martin et al. 2009; Fischer et al. 2002; Fischle et al. 2001; Fischle et al. 2002; Kao et al. 2000; Miska et al. 1999; Guardiola and Yao 2002). Human class 3 HDACs, SIRT1–SIRT7, are homologous to yeast Sir2 (Vaquero 2009; Martin et al. 2007; Haigis and Sinclair 2010; Haigis and Guarente 2006).

Human HDAC regulation and transcription regulation

HDACs are not independent. They do not choose their deacetylation targets independently (Sengupta and Seto 2004; Martin et al. 2007; de Ruijter et al. 2003). They do not arrive at their targets or bind DNA independently (Sengupta and Seto 2004; Martin et al. 2007). Most are in an inactive form when translated from mRNA and require cofactors for activation (Sengupta and Seto 2004; de Ruijter et al. 2003).

Human HDAC1 and its paralog HDAC2 are only slightly divergent from each other in both sequence and function (Gregoretto et al. 2004; de Ruijter et al. 2003). To bind DNA and perform deacetylation activity, they must be part of a large protein complex, either Sin3, NuRD/NRD/Mi2, or CoREST (Sengupta and Seto 2004; Gregoretto et al. 2004; de Ruijter et al. 2003; You et al. 2001; Humphrey et al. 2001; Zhang et al. 1998; Zhang et al. 1997; Tong et al.

1998; Ayer 1999; Ng and Bird 2000). Cofactors and co-repressors are also required (Galasinski et al. 2002; Zhang et al. 1999; Heinzl et al. 1997; Ashburner et al. 2001). Both complex association and deacetylation activity are impacted by phosphorylation of HDAC1 and/or HDAC2 (de Ruijter et al. 2003; Galasinski et al. 2002; Pflum et al. 2001; Tsai and Seto 2002).

Human HDAC3 must be activated by complexing with silencing mediator for retinoic acid and thyroid hormone receptors (SMRT) and nuclear receptor co-repressor (N-CoR) (Sengupta and Seto 2004; Heinzl et al. 1997; Alland et al. 1997; Wen et al. 2000; Guenther et al. 2001; Zhang et al. 2002a, b; Bertos et al. 2001; Kao et al. 2000). SMRT activation of HDAC3 also requires interaction with TCP-1 ring complex (Guenther et al. 2002) and can be affected by interaction with HSP70 (Johnson et al. 2002). HDAC4, HDAC5, and HDAC7 are activated due to complexing with HDAC3/SMRT/N-CoR (Fischle et al. 2001; Fischle et al. 2002; Martin et al. 2007; Yang et al. 2002).

The N-terminal domains of class 2 HDACs 4, 5, 7, and 9 contain sites for binding or complexing with a vast number of regulatory proteins, including DNA binding factors, hormone receptors, protein kinases, protein phosphatases, a methyltransferase, and regulatory complexes such as Sin3A, SMRT, and N-CoR (Fischle et al. 2001; Fischle et al. 2002; Kao et al. 2000; Miska et al. 1999; Martin et al. 2007; Verdell and Khochbin 1999; Wang et al. 1999; Kao et al. 2001; Lu et al. 2000; Ghisletti et al. 2007; Zhang et al. 2002a, b; Grozinger and Schreiber 2000; Dequiedt et al. 2006; Parra et al. 2007). They are systematically transported in and out of the nucleus, where they have access to histone substrates (Fischle et al. 2001; Miska et al. 1999; Grozinger and Schreiber 2000; Dequiedt et al. 2006; Parra

et al. 2007), and are subjected to cleavage, ubiquitination, sumolation, and phosphorylation (Grozinger and Schreiber 2000; Dequiedt et al. 2006; Parra et al. 2007; Paroni et al. 2004; Li et al. 2004; Petrie et al. 2003). Access to DNA is controlled in a signal-dependent manner by multiple protein kinases, protein kinase inhibitors, and phosphatases (Martin et al. 2007; Kao et al. 2001; Dequiedt et al. 2006; Parra et al. 2007; McKinsey et al. 2000a; Chawla et al. 2003). HDAC binding to the transcription factor myocyte enhancer factor-2 (MEF2) is critical to the ability of the HDACs to remain securely bound at the promoter (Miska et al. 1999; Verdel and Khochbin 1999; Lu et al. 2000; Grozinger and Schreiber 2000; McKinsey et al. 2000a; McKinsey et al. 2000b). Deacetylase-mediated gene regulation can be disrupted by the calcium/calmodulin-dependent protein kinase reversal of HDAC-MEF2 binding (McKinsey et al. 2000a; Chawla et al. 2003; McKinsey et al. 2000b). The MEF2 transcription factor can regulate gene expression as either a repressor or activator depending on which epigenetic modulators, histone acetyltransferases (HATs) or HDACs, are recruited and bound (Lu et al. 2000; McKinsey et al. 2001; Youn et al. 2000).

Of the human class 3 HDACs (sirtuins), only SIRT1-SIRT3 and SIRT6 preferentially deacetylate histones as opposed to deacetylation of non-histone proteins or ADP-ribosylation (Vaquero 2009; Saunders and Verdin 2007, 72; Vaquero et al. 2004).

SIRT1 has essential roles in chromatin regulation, metabolism, differentiation and cellular response to stress conditions (Vaquero 2009; Yamamoto et al. 2007). In its central role of heterochromatin formation, SIRT1 interacts with a variety of proteins and protein complexes, including those required for DNA binding and including the histone H1, which it both recruits to the nucleosome and deacetylates (Vaquero 2009; Vaquero et al. 2004; Hansen 2002; Kuzmichev et al. 2004), thereby leading to H1K26 methylation by methyltransferase EZH2 (Kuzmichev et al. 2004) and to HP1 binding (Daujat et al. 2005). SIRT1 implements methylation of H3K9 by H3K9 deacetylation and the recruitment, binding, and deacetylation of the methyltransferase SUV39H1 (Vaquero 2009; Vaquero et al. 2007).

Among the most important functions of SIRT1 is stress-induced DNA repair, in which its protein–protein interactions coordinate multiple responses (Haigis and Guarente 2006; Giannakou and Partridge 2004), including cell-cycle arrest and detoxification as well as DNA repair and cellular repair (Vaquero 2009; Brunet et al. 2004; Motta et al. 2004; van der Horst et al. 2004; Yamamori et al. 2010; Yeung et al. 2004; Yuan et al. 2007; O'Hagan et al. 2008; Sasaki et al. 2006; Lee et al. 2008). SIRT1 activates DNA base excision repair by reversing stress-induced hyperacetylation of apurinic/apyrimidinic endonuclease-1 (Yamamori et al.

2010). SIRT1 also joins the MRE11-RAD50-NBS1 complex and facilitates DNA double-strand break repair by accommodating NSB1 phosphorylation by first reversing acetylation of the same serine 343 residue (Yuan et al. 2007).

As described by Sengupta and Seto (2004), the regulation of HDACs amounts to the regulation of the proteins that regulate the HDACs, and a small portion of that regulation has been described here. Extra levels of regulation include sequestration, HDAC expression levels, alternative splicing, cofactor levels and proteolytic activation or inactivation (Miska et al. 1999; Kao et al. 2001; Lagger et al. 2002; Dangond et al. 1998; Gray et al. 2003; Lin et al. 2004; Anderson et al. 2003; Wiper-Bergeron et al. 2003).

Regulation of the expression of a gene (or provirus, transposon, or endogenous retrovirus) depends on DNA regulatory sequences within its promoter or extended regulatory region, on environmental input and on the availability of all transcription factors and other regulatory proteins and all components of all associated multi-unit complexes, including epigenetic modulators and their cofactors (Sengupta and Seto 2004; Wray et al. 2003; Tuch et al. 2008; Balmer and Blomhoff 2009).

Wray et al. (2003) summarized the patterns of gene functions that forecast the evolution of either simple or complex transcription regulation. Accordingly, simple patterns of regulation may be expected for genes that are either constitutively expressed or expressed only in one differentiated cell type, while complex regulation may be expected for genes which are expressed in early stages of development, which produce more than one unique product or which are directly responsive to environmental and/or multiple input (Wray et al. 2003). Complex regulation may be characterized by combinations of both positive and negative regulatory mechanisms, combinations of both positive and negative feedback loops, redundancy and competition in binding between factors with contrasting effects (Wray et al. 2003; Liu et al. 2004; Casillas et al. 2003).

The described relationships between gene functions and regulation complexity can work in both directions. Complexity can presumably identify genes whose regulation evolved to accommodate contrasting functions and therefore has likely undergone evolutionary compromises (Nesse and Williams 1995; Wray et al. 2003).

A classic example of a gene with complex regulation is *hTERT*. Liu et al. (2004) described as many as ten repressors and five activators of *hTERT*, with the binding of each transcription factor dependent on local chromatin modifications. Competing requirements that *hTERT* regulation was required to accommodate include embryonic development, differentiation, proliferation of germ-line

cells, rapid proliferation of lymphocytes and other cells of immune function following infection, rapid replacement of hematopoietic cells following blood loss, tissue repair and prevention of the unrestrained cell proliferation that sustains cancer (McArthur et al. 2002; Cunningham et al. 2006; Henderson et al. 2000). The transcription factor MAD1 must recruit the entire Sin3A-HDAC complex in order to repress transcription (Chou et al. 2009; Hassig et al. 1997). MAD1 transcriptional repression is essential for the prevention of unrestrained expression of *hTERT* (Chou et al. 2009; Casillas et al. 2003; Liu et al. 2004; McArthur et al. 2002; Zhu et al. 2008; Lai et al. 2007), upon which at least 95% of human cancer cells depend for immortalization (Berletch et al. 2008; Perrault et al. 2005; Cong and Shay 2008). The activator c-MYC competes with MAD1 for the same binding sites of the *hTERT* regulatory region (Liu et al. 2004; Casillas et al. 2003).

HDAC limitations

While HDACs participate in defense against virtually the full range of human disease, their response for many diseases is inadequate because of evolutionary compromises (Nesse and Williams 1995; Wray et al. 2003). A specific level of expression of a gene such as *hTERT* may be protective against one disease and generate another (Lai et al. 2007; McArthur et al. 2002; Henderson et al. 2000). Natural selection does not design defense against diseases that materialize only subsequent to the age of reproduction (Nesse and Williams 1995; Wick et al. 2003; Wick et al. 2000). While cancer and heart disease can occur before or during child-bearing years, they most often present at a more advanced age. Their defense mechanisms, therefore, are insufficiently subjected to evolutionary pressure and are disproportionately available for evolutionary compromise (Nesse and Williams 1995; Wick et al. 2003; Wick et al. 2000). If disease defenses are flawed by evolutionary compromises with other requirements of the organism, they are more flawed when a promoter, enhancer, and coding sequences are donated by an integrated provirus or transposon. The donated sequences have been shaped by evolution for the benefit of the virus or transposon more than the benefit of the host (Katz et al. 2007; Lewin 2008; Cohen et al. 2009). The donated DNA brings not just a compromise but a conflict of interest.

HDAC-mediated repression of HIV provirus is unsuccessful. C-promoter binding factor-1 (CBF-1) is an effective transcription repressor which binds to the enhancer region of the HIV-1 provirus LTR shortly after integration and recruits HDAC1 to silence transcription (Tyagi and Karn 2007; Colin and Van Lint 2009). Its binding site overlaps that of the activator nuclear factor kappa-light-

chain-enhancer of activated B cells) (NF- κ B) which, if present, is able to replace CBF-1 at the HIV-1 LTR (Tyagi and Karn 2007). CBF-1 is also an effective transcription repressor at the promoter of nuclear factor of kappa-light polypeptide gene enhancer in B cells inhibitor, alpha (I κ B α), which inhibits NF- κ B by sequestration outside the nucleus (Oakley et al. 2003). CBF-1, thereby, provides negative feedback to its own suppression of HIV-1 transcription. As with other HDAC repression of provirus transcription, CBF-1 mediated repression is neither total nor permanent but only ensures continuation of infection which is both contagious and presumably fatal (Colin and Van Lint 2009).

Although the transcription factors Sp1 and NF- κ B, in p50/p65 heterodimer form, are indispensable to HIV-1 transcription, the p50/p50 homodimer form of NF- κ B, present in T cells before activation, recruits HDAC1 (Colin and Van Lint 2009; Perkins et al. 1993; Williams et al. 2006; Zhong et al. 2002). HDAC1 is also recruited to the HIV-1 LTR by YY1 and activating protein-4 (AP-4) (He and Margolis 2002; Imai and Okamoto 2006). Sp1, with or without COUP-TF interacting protein 2 as cofactor, recruits both HDAC1 and HDAC2 (Colin and Van Lint 2009; Marban et al. 2007).

Studies have shown that oxidative stress inhibits HDAC activity, activates NF- κ B and activates HIV LTR transcription (Rahman et al. 2004; Pyo et al. 2008; Oliveira-Marques et al. 2009; Legrand-Poels et al. 1990). Oxidative stress related to hydrogen peroxide (H₂O₂) and/or other reactive oxygen species activates I κ B kinase, which phosphorylates I κ B α at two serine residues, marking I κ B α for ubiquitin-mediated proteolysis and releasing the active heterodimeric form of NF- κ B from cytoplasmic sequestration (Zhong et al. 2002; Rahman et al. 2004; Pyo et al. 2008; Kamata et al. 2002). Destruction of I κ B α also activates protein kinase A, which phosphorylates serine 276 of the p65 component of heterodimeric NF- κ B (Zhong et al. 2002; Pyo et al. 2008; Zhong et al. 1998). The active heterodimeric NF- κ B, with phosphorylated p65, relocates to the nucleus and recruits HATs such as p300 and CREB-binding protein (Colin and Van Lint 2009; Zhong et al. 2002; Rahman et al. 2004; Zhong et al. 1998; Gerritsen et al. 1997). The repressive homodimer with HDAC1 activity is displaced and HIV transcription is accommodated (Lusic et al. 2003; Thierry et al. 2004; Calao et al. 2008).

Not only can HDAC-initiated repression of an integrated retrovirus be reversed by environmental influences, epigenetic repression of mere remnants of retrovirus integration into ancestral germ-line DNA thousands of generations ago can also be reversed by similar environmental influences to apparently cause disease conditions (Colmegna and Garry 2006).

Autoimmune reactions often appear to be in response to stress-exposed endogenous retrovirus DNA or to the

products coded by such DNA (Colmegna and Garry 2006; Blank et al. 2009; Balada et al. 2009). While endogenous retroviruses contain numerous mutations accumulated during their long history, some contain unaltered or unaffected genes that may be expressed when epigenetic silencing is interrupted (Colmegna and Garry 2006; Balada et al. 2009). Interruption can result from oxidative and nitrosative stress, ultraviolet radiation, extreme temperature, psychological stress, infections, and hormones and other chemicals (Blank et al. 2009; Balada et al. 2009; Hohenadl et al. 1999; Csoka and Szyf 2009; Wang et al. 2010; Zeh et al. 2009).

Antibodies against retrovirus proteins have been found in the serum of autoimmune patients with no history of viral infection (Colmegna and Garry 2006; Blank et al. 2009; Balada et al. 2009). Phospholipid cross-reacting antiviral antibodies and antigens homologous to viral antigens have been found in patients with systemic lupus erythematosus (SLE) (Colmegna and Garry 2006; Blank et al. 2009; Balada et al. 2009). SLE is a unique systemic autoimmune disease with autoantibodies directed against so many organs and tissues that they might as well be directed against a patient's DNA. Sherer et al. (2004) reported SLE autoantibodies with 116 different specificities. Identified specificities such as nucleosomes, double-stranded DNA, single-stranded DNA, telomeres, histones, nucleosides, and multiple proteins involved in genome maintenance support the characterization of an immune system in rebellion against its DNA (Sherer et al. 2004).

An endogenous retrovirus associated with SLE is located at 1q42 on human chromosome 1 (Pullmann et al. 2008). A study using SLE patients and control groups established haplotypes at 1q42 based on single-nucleotide polymorphisms (Pullmann et al. 2008). The lupus patients were significantly associated with the same haplotype (Pullmann et al. 2008).

Antibodies against endogenous retrovirus antigens are recovered from cerebral spinal fluid of multiple sclerosis patients (Christensen 2005), while Gag (retroviral structural protein) antigens exclusively of retrotransposon and retrovirus origin are found abnormally in brain neurons of multiple sclerosis patients (Dolei and Perron 2009; Balada et al. 2009). Proteins present in salivary gland tissues of persons with Sjögren's syndrome have reacted with antibodies directed against HIV-1 proteins (Yamano et al. 1997) or HTLV-1 proteins (Terada et al. 1994). T lymphocytes with T cell receptors reactive to endogenous retroviral HERV-K18 superantigen have been found in the pancreas of persons with type 1 diabetes, with haplotype association (Marguerat et al. 2004; Balada et al. 2009).

With the endogenous retrovirus HERV-K18 superantigen, Meylan et al. (2005) demonstrated that immune tolerance to antigens of endogenous retroviral origin can be established provided that antigens are sufficiently

available for the required presentation for central tolerance and/or peripheral tolerance. It would appear that HDAC-mediated repression of an endogenous retrovirus may interfere with the development of immune tolerance, while environmental disruption of epigenetic repression unleashes an intolerant immune reaction that is self-reactive (Meylan et al. 2005; Siggs et al. 2006; Balada et al. 2009). The problem would seem to lie, at least in part, in the evolutionary derived transient nature of HDAC-mediated repression. The superantigen coded by HERV-K18 induces a response by T cells known to be reactive or cross-reactive against human beta cells in type 1 diabetes (Meylan et al. 2005; Marguerat et al. 2004; Conrad et al. 1997; Stauffer et al. 2001; Balada et al. 2009). Other endogenous retrovirus antigens with expression associated with autoimmune reactions are subject to similar transient HDAC-mediated transcription repression (Balada et al. 2009, 2010). Increased populations of CD4 T cells reactive to the HERV-K18 superantigen and to other endogenous retroviral antigens have been associated with environmental interventions known to disrupt HDAC suppression of transcription (Balada et al. 2009; Stauffer et al. 2001).

Exogenous chemicals that disrupt epigenetic regulation include heavy metals, cyclic hydrocarbons, pesticides and pharmaceutical products introduced for health benefits (Weinhold 2006; Csoka and Szyf 2009). Table 3 lists some pharmaceutical products and their reported epigenetic effects.

Is it realistic to contemplate strategies to overcome HDAC limitations? One approach to elimination of latent HIV infection suggests possibilities.

If HDAC-mediated transcription silencing is too vulnerable to disruption to provide defense against a transcription-dependent disease as deadly and resilient as that from HIV infection, perhaps the opposite approach might provide protection (Dahl et al. 2010; Demonte et al. 2004; Bowman et al. 2009). Activation of transcription of HIV-1 provirus by treatment of latently infected cells with HDAC inhibitors has been demonstrated (Demonte et al. 2004; VanLint et al. 1996). Latently infected cells escape detection by surveillance of the immune system and are little affected by drugs that purge extra-cellular virus (Dahl et al. 2010; Demonte et al. 2004; Bowman et al. 2009; Keedy et al. 2009). By inducing expression of latent provirus, HDAC inhibitors could bring about the expression of viral antigens that expose infected cells to elimination by T lymphocytes, while escaping virions could be eliminated by antibodies and anti-viral drugs (Demonte et al. 2004; Bowman et al. 2009). As with defense mediated by HDACs, defense mediated by HDAC inhibitors must eliminate all potential re-emergence of latent but deadly virus (Bowman et al. 2009). HDAC inhibitors, some with anti-cancer properties

Table 3 Pharmaceutical epigenetic effects

Chemical	Reported epigenetic effect
Valproic acid	Histone deacetylase inhibition (Phiel et al. 2001)
5-Fluoro-2'-deoxyuridine	DNA hypermethylation (Nyce et al. 1993)
Hydralazine	Inhibition of DNA methylation (Gorelik and Richardson 2009)
Procainamide	Inhibition of DNA methylation (Gorelik and Richardson 2009)
Retinoic acid	Reduction of DNA methylation (Kuriyama et al. 2008)
Methotrexate	Reduction of DNA methylation (Toffoli et al. 2003; Friso et al. 2002)
Suberoylanilide hydroxamic acid	Histone deacetylase inhibition (Duvic and Vu 2007)
Sodium butyrate	Histone deacetylase inhibition (Reuse et al. 2009)

(Marks and Xu 2009; Minucci and Pelicci 2006), belong to multiple families (Marks and Xu 2009; Minucci and Pelicci 2006) and target all four classes of HDACs with different specificities (Khan et al. 2008; Bolden et al. 2006). Only inhibition of class I HDACs is required for activation of HIV-1 transcription, and a more global inhibition of HDACs appears to present unintended consequences (Colin and Van Lint 2009; Keedy et al. 2009; Archin et al. 2009; Bolden et al. 2006; Caron et al. 2005; Dokmanovic et al. 2007; Glozak et al. 2005).

In human HeLa cells experimentally infected with the ASV retrovirus, Katz et al. (2007) tested a variety of histone deacetylase inhibitors, as well as other activators including the promising phorbol ester prostratin (Kulkosky et al. 2001; Biancotto et al. 2004; Korin et al. 2002), for their ability to reverse silencing by HDACs. A significant level of reactivation was indicated by the reporter gene for several activators and especially for the HDAC inhibitor trichostatin A (Katz et al. 2007). At no point in any experiment with any activator was the percent of cells in activated status a substantial majority (Katz et al. 2007). The study concluded that a mechanism was present that rendered regulatory access to HDAC inhibitors and other activators transient (Katz et al. 2007).

Reuse et al. (2009) demonstrated far more significant benefits in provirus activation from synergy attained through the combined treatment of HIV-infected cells with both prostratin and HDAC inhibitors. Effective combinations involved valproic acid, sodium butyrate or suberoylanilide hydroxamic acid (SAHA) as the HDAC inhibitors (Reuse et al. 2009). Burnett et al. (2010) exhibited the benefits of treatment with SAHA in combination with prostratin. The merits of a synergistic approach to altered transcription regulation, even involving HIV, have been demonstrated (Katz et al. 2007; Reuse et al. 2009; Burnett et al. 2010) and provide evidence that a synergistic approach to compensate for the limitations of epigenetic modulation is realistic. The same has been demonstrated by synergistic reactivation of estrogen receptor- α (ER α) in ER α -negative breast cancer cells (Li et al. 2010).

Conclusions

After 100 Ma of evolution in eukaryotes, early adaptation for defense and the development of highly sophisticated regulation, HDACs remain ineffective as defense against some of the most lethal human diseases, due to evolutionary compromises (Ekwall 2005; Heckman et al. 2001; Feschotte 2008; Sengupta and Seto 2004; Colin and Van Lint 2009; Miki et al. 1996). The complex gene regulation, developed with the molecular domestication of new regulatory sequences, provides that the contributions of components with contrasting outcomes, such as HDACs and HATs, may be complementary rather than mutually exclusive and is adequate and appropriate for most disease conditions (Jordan et al. 2003; Bourque et al. 2008; Kapitonov and Jurka 2005; Feschotte 2008; Zeh et al. 2009; Goodier and Kazazian 2008; Nakamura and Cech 1998; Wray et al. 2003; Sengupta and Seto 2004; Gregoretti et al. 2004; Tuch et al. 2008; Balmer and Blomhoff 2009). Most disease conditions we are, in fact, unaware of because our evolved regulatory network prevents their occurrence (Liu et al. 2008; Latham and Dent 2007; Sengupta and Seto 2004; Goodier and Kazazian 2008; Hildmann et al. 2007; Feschotte 2008; Slotkin and Martienssen 2007).

For exceptional diseases, including those generated by some oncogenes or by a virus as virulent as HIV, only total and permanent transcription elimination is protective (Colin and Van Lint 2009). For such diseases, a single therapeutic agent appears unlikely to overcome the consequences of compromise, and evolution does not appear likely to escape compromise (Nesse and Williams 1995; Fromer and Shifman 2009; Foit et al. 2009; Li et al. 2010). It appears that we may need to more effectively address the challenges of evolved gene regulation complexity (Wray et al. 2003). In molecular terms, we may need to better address multiple components of protein–protein interactions and pathway interactions, including perhaps interactions that constitute negative feedback (Katz et al. 2007; Oakley et al. 2003; Chou et al. 2009; Feschotte 2008; McArthur et al. 2002; Sengupta and Seto 2004; Wray et al. 2003; Colin and Van Lint 2009).

Evidence has been presented (Goodier and Kazazian 2008; Zeh et al. 2009; Feschotte 2008; Bannert and Kurth 2004; Slotkin and Martienssen 2007) that even a pathological exposure of a transposition-competent exogenous or endogenous retrovirus may provide a net benefit to the species because of potential benefits from domestication and recombination. When reactivation is uniformly lethal, a net benefit seems unlikely.

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