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REVIEW

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.

Keywords Deacetylation · Regulation · Evolution · Transposon · Endogenous retrovirus

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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 (Gregoretti 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; Gregoretti 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; Gregoretti 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; Gregoretti et al. 2004; Ekwall 2005; de Ruijter et al. 2003). No fungal enzymes are classified as class 4 HDACs (Gregoretti et al. 2004; Ledent and Vervoort 2006). Horizonal 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; Gregoretti 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; Gregoretti et al. 2004; de Ruijter et al. 2003). Class 4 enzymes, also zinc dependent, include HDAC11 only (Hildmann et al. 2007; Gregoretti 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	*S. cerevisiae*	Humans
Zinc ion (Zn^{2+})	1	Rpd3	HDAC1
		Hos2	HDAC2
		Hos1	HDAC3
			HDAC8
	2	Hda1	HDAC4
		Hos3	HDAC5
			HDAC6
			HDAC7
			HDAC9
			HDAC10
	4		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 (Gregoretti 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; Gregoretti 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; Heinzel 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; Heinzel 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; Verdel 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-κB) 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 (IκBα), which inhibits NF-κB 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-κB, in p50/p65 heterodimer form, are indispensable to HIV-1 transcription, the p50/p50 homodimer form of NF-κB, 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-κB 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 (H_2O_2) and/or other reactive oxygen species activates IκB kinase, which phosphorylates IκBα at two serine residues, marking IκBα for ubiquitin-mediated proteolysis and releasing the active heterodimeric form of NF-κB from cytoplasmic sequestration (Zhong et al. 2002; Rahman et al. 2004; Pyo et al. 2008; Kamata et al. 2002). Destruction of IκBα also activates protein kinase A, which phosphorylates serine 276 of the p65 component of heterodimeric NF-κB (Zhong et al. 2002; Pyo et al. 2008; Zhong et al. 1998). The active heterodimeric NF-κB, 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-Fluro-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 1 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 (ERα) in ERα-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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References

Alland L, Muhle R, Hou H, Potes J, Chin L, SchreiberAgus N, DePinho RA (1997) Role for N-CoR and histone deacetylase in Sin3-mediated transcriptional repression. Nat 387:49–55

Anderson RM, Bitterman KJ, Wood JG, Medvedik O, Sinclair DA (2003) Nicotinamide and PNC1 govern lifespan extension by calorie restriction in *Saccharomyces cerevisiae*. Nat 423:181–185

Archin NM, Keedy KS, Espeseth A, Dang H, Hazuda DJ, Margolis DM (2009) Expression of latent human immunodeficiency type 1 is induced by novel and selective histone deacetylase inhibitors. AIDS 23:1799–1806

Ashburner BP, Westerheide SD, Baldwin AS (2001) The p65 (RelA) subunit of NF-kappa B interacts with the histone deacetylase (HDAC) corepressors HDAC1 and HDAC2 to negatively regulate gene expression. Mol Cell Biol 21:7065–7077

Ayer DE (1999) Histone deacetylases: transcriptional repression with SINers and NuRDs. Trends Cell Biol 9:193–198

Balada E, Ordi-Ros J, Vilardell-Tarres M (2009) Molecular mechanisms mediated by human endogenous retroviruses (HERVs) in autoimmunity. Rev Med Virol 19:273–286

Balada E, Vilardell-Tarres M, Ordi-Ros J (2010) Implication of human endogenous retroviruses in the development of autoimmune diseases. Internat Rev Immunol 29:351–370

Balmer JE, Blomhoff R (2009) Evolution of transcription factor binding sites in mammalian gene regulatory regions: handling counterintuitive results. J Mol Evol 68:654–664

Bannert N, Kurth R (2004) Retroelements and the human genome: new perspectives on an old relation. Proc Natl Acad Sci USA 101:14572–14579

Bannister AJ, Zegerman P, Partridge JF, Miska EA, Thomas JO, Allshire RC, Kouzarides T (2001) Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain. Nature 410:120–124

Belancio VP, Hedges DJ, Deininger P (2008) Mammalian non-LTR retrotransposons: for better or worse, in sickness and in health. Genome Res 18:343–358

Berger SL (2007) The complex language of chromatin regulation during transcription. Nature 447:407–412

Berletch JB, Liu C, Love WK, Andrews LG, Katiyar SK, Tollefsbol TO (2008) Epigenetic and genetic mechanisms contribute to telomerase inhibition by EGCG. J Cell Biochem 103:509–519

Bernstein BE, Tong JK, Schreiber SL (2001) Genomewide studies of histone deacetylase function in yeast (vol 97, p 13708, 2000). Proc Natl Acad Sci USA 98:5368–5368

Bertos NR, Wang AH, Yang XJ (2001) Class II histone deacetylases: structure, function, and regulation. Biochem Cell Biol 79:243–252

Biancotto A, Grivel JC, Gondois-Rey F, Bettendroffer L, Vigne R, Brown S, Margolis LB, Hirsch I (2004) Dual role of prostratin in inhibition of infection and reactivation of human immunodeficiency virus from latency in primary blood lymphocytes and lymphoid tissue. J Virol 78:10507–10515

Blank M, Shoenfeld Y, Perl A (2009) Cross-talk of the environment with the host genome and the immune system through endogenous retroviruses in systemic lupus erythematosus. Lupus 18:1136–1143

Bolden JE, Peart MJ, Johnstone RW (2006) Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov 5:769–784

Bourque G, Leong B, Vega VB, Chen X, Lee YL, Srinivasan KG, Chew JL, Ruan Y, Wei CL, Ng HH et al (2008) Evolution of the mammalian transcription factor binding repertoire via transposable elements. Genome Res 18:1752–1762

Bowman MC, Archin NM, Margolis DM (2009) Pharmaceutical approaches to eradication of persistent HIV infection. Expert Rev Mol Med 11:e6

Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer PL, Lin YX, Tran H, Ross SE, Mostoslavsky R, Cohen HY et al (2004) Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science 303:2011–2015

Brunmeir R, Lagger S, Simboeck E, Sawicka A, Egger G, Hagelkruys A, Zhang Y, Matthias P, Miller WJ, Seiser C (2010) Epigenetic regulation of a murine retrotransposon by a dual histone modification mark. PLoS Genet 6:e1000927

Burnett JC, Lim KI, Calafi A, Rossi JJ, Schaffer DV, Arkin AP (2010) Combinatorial latency reactivation for HIV-1 subtypes and variants. J Virol 84:5958–5974

Calao M, Burny A, Quivy V, Dekoninck A, Van Lint C (2008) A pervasive role of histone acetyltransferases and deacetylases in an NF-kappa B-signaling code. Trends Biochem Sci 33:339–349

Caron C, Boyault C, Khochbin S (2005) Regulatory cross-talk between lysine acetylation and ubiquitination: role in the control of protein stability. BioEssays 27:408–415

Casillas MA, Brotherton SL, Andrews LG, Ruppert JM, Tollefsbol TO (2003) Induction of endogenous telomerase (hTERT) by c-Myc in WI-38 fibroblasts transformed with specific genetic elements. Gene 316:57–65

Chawla S, Vanhoutte P, Arnold FJL, Huang CLH, Bading H (2003) Neuronal activity-dependent nucleocytoplasmic shuttling of HDAC4 and HDAC5. J Neurochem 85:151–159

Chen JC, Rattner A, Nathans J (2006) Effects of L1 retrotransposon insertion on transcript processing, localization and accumulation: lessons from the retinal degeneration 7 mouse and implications for the genomic ecology of L1 elements. Hum Mol Genet 15:2146–2156

Chen JM, Masson E, Macek M, Raguenes O, Piskackova T, Fercot B, Fila L, Cooper DN, Audrezet MP, Ferec C (2008) Detection of two Alu insertions in the CFTR gene. J Cyst Fibros 7:37–43

Chou CK, Lee DF, Sun HL, Li LY, Lin CY, Huang WC, Hsu JM, Kuo HP, Yamaguchi H, Wang YN et al (2009) The suppression of MAD1 by AKT-mediated phosphorylation activates MAD1 target genes transcription. Mol Carcinog 48:1048–1058

Christensen T (2005) Association of human endogenous retroviruses with multiple sclerosis and possible interactions with herpes viruses. Rev Med Virol 15:179–211

Cohen CJ, Lock WM, Mager DL (2009) Endogenous retroviral LTRs as promoters for human genes: a critical assessment. Gene 448:105–114

Colin L, Van Lint C (2009) Molecular control of HIV-1 post-integration latency: implications for the development of new therapeutic strategies. Retrovirol 6:111

Colmegna I, Garry RF (2006) Role of endogenous retroviruses in autoimmune diseases. Infect Dis Clin N Am 20:913–929

Cong YS, Shay JW (2008) Actions of human telomerase beyond telomeres. Cell Res 18:725–732

Conrad B, Weissmahr RN, Boni J, Arcari R, Schupbach J, Mach B (1997) A human endogenous retroviral superantigen as candidate autoimmune gene in type 1 diabetes. Cell 90:303–313

Coull JJ, Romerio F, Sun JM, Volker JL, Galvin KM, Davie JR, Shi Y, Hansen U, Margolis DM (2000) The human factors YY1 and LSF repress the human immunodeficiency virus type 1 long terminal repeat via recruitment of histone deacetylase 1. J Virol 74:6790–6799

Csoka AB, Szyf M (2009) Epigenetic side-effects of common pharmaceuticals: a potential new field in medicine and pharmacology. Med Hypotheses 73:770–780

Cunningham AP, Love WK, Zhang RW, Andrews LG, Tollefsbol TO (2006) Telomerase inhibition in cancer therapeutics: approaches molecular-based. Curr Med Chem 13:2875–2888

Dahl V, Josefsson L, Palmer S (2010) HIV reservoirs, latency, and reactivation: prospects for eradication. Antivir Res 85:286–294

Dangond F, Hafler DA, Tong JK, Randall J, Kojima R, Utku N, Gullans SR (1998) Differential display cloning of a novel human histone deacetylase (HDAC3) cDNA from PHA-activated immune cells. Biochem Biophys Res Commun 242:648–652

Daujat S, Zeissler U, Waldmann T, Happel N, Schneider R (2005) HP1 binds specifically to Lys(26)-methylated histone H1.4, whereas simultaneous Ser(27) phosphorylation blocks HP1 binding. J Biol Chem 280:38090–38095

De Ruijter AJM, Van Gennip AH, Caron HN, Kemp S, Van Kuilenburg ABP (2003) Histone deacetylases (HDACs): characterization of the classical HDAC family. Biochem J 370:737–749

Deininger PL, Batzer MA (1999) Alu repeats and human disease. Mol Genet Metab 67:183–193

Demonte D, Quivy V, Colette Y, Van Lint C (2004) Administration of HDAC inhibitors to reactivate HIV-1 expression in latent cellular reservoirs: implications for the development of therapeutic strategies. Biochem Pharmacol 68:1231–1238

Dequiedt F, Martin M, Von Blume J, Vertommen D, Lecomte E, Mari N, Heinen MF, Bachmann M, Twizere JC, Huang MC et al (2006) New role for hPar-1 kinases EMK and C-TAK1 in regulating localization and activity of class IIa histone deacetylases. Mol Cell Biol 26:7086–7102

Dokmanovic M, Clarke C, Marks PA (2007) Histone deacetylase inhibitors: overview and perspectives. Mol Cancer Res 5:981–989

Dolei A, Perron H (2009) The multiple sclerosis-associated retrovirus and its HERV-W endogenous family: a biological interface between virology, genetics, and immunology in human physiology and disease. J Neurovirol 15:4–13

Duvic M, Vu J (2007) Vorinostat: a new oral histone deacetylase inhibitor approved for cutaneous T-cell lymphoma. Expert Opin Investig Drugs 16:1111–1120

Ekwall K (2005) Genome-wide analysis of HDAC function. Trends Genet 21:608–615

Feschotte C (2008) Opinion - transposable elements and the evolution of regulatory networks. Nat Rev Genet 9:397–405

Finnin MS, Donigian JR, Cohen A, Richon VM, Rifkind RA, Marks PA, Breslow R, Pavletich NP (1999) Structures of a histone deacetylase homologue bound to the TSA and SAHA inhibitors. Nat 401:188–193

Fischer DD, Cai R, Bhatia U, Asselbergs FAM, Song CZ, Terry R, Trogani N, Widmer R, Atadja P, Cohen D (2002) Isolation and characterization of a novel class II histone deacetylase, HDAC10. J Biol Chem 277:6656–6666

Fischle W, Dequiedt F, Fillion M, Hendzel MJ, Voelter W, Verdin E (2001) Human HDAC7 histone deacetylase activity is associated with HDAC3 in vivo. J Biol Chem 276:35826–35835

Fischle W, Dequiedt F, Hendzel MJ, Guenther MG, Lazar MA, Voelter W, Verdin E (2002) Enzymatic activity associated with class IIHDACs is dependent on a multiprotein complex containing HDAC3 and SMRT/N-CoR. Mol Cell 9:45–57

Foit L, Morgan GJ, Kern MJ, Steimer LR, von Hacht AA, Titchmarsh J, Warriner SL, Radford SE, Bardwell JCA (2009) Optimizing protein stability in vivo. Mol Cell 36:861–871

Friso S, Choi SW, Girelli D, Mason JB, Dolnikowski GG, Bagley PJ, Olivieri O, Jacques PF, Rosenberg IH, Corrocher R et al (2002) A common mutation in the 5, 10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. Proc Natl Acad Sci USA 99:5606–5611

Fromer M, Shifman JM (2009) Tradeoff between stability and multispecificity in the design of promiscuous proteins. PLoS Comput Biol 5:e1000627

Galasinski SC, Resing KA, Goodrich JA, Ahn NG (2002) Phosphatase inhibition leads to histone deacetylases 1 and 2 phosphorylation and disruption of corepressor interactions. J Biol Chem 277:19618–19626

Gao L, Cueto MA, Asselbergs F, Atadja P (2002) Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family. J Biol Chem 277:25748–25755

Gardner JG, Grundy FJ, Henkin TA, Escalante-Semerena JC (2006) Control of acetyl-coenzyme A synthetase (AcsA) activity by acetylation/deacetylation without NAD(+) involvement in Bacillus subtilis. J Bacteriol 188:5460–5468

Geiman TM, Robertson KD (2002) Chromatin remodeling, histone modifications, and DNA methylation—how does it all fit together? J Cell Biochem 87:117–125

Gendrel AV, Lippman Z, Yordan C, Colot V, Martienssen RA (2002) Dependence of heterochromatic histone H3 methylation patterns on the *Arabidopsis* gene DDM1. Sci 297:1871–1873

Gerritsen ME, Williams AJ, Neish AS, Moore S, Shi Y, Collins T (1997) CREB-binding protein p300 are transcriptional coactivators of p65. Proc Nat Acad Sci USA 94:2927–2932

Ghisletti S, Huang W, Ogawa S, Pascual G, Lin ME, Willson TM, Rosenfeld MG, Glass CK (2007) Parallel SUMOylation-dependent pathways mediate gene- and signal-specific transrepression by LXRs and PPAR gamma. Mol Cell 25:57–70

Giannakou ME, Partridge L (2004) The interaction between FOXO and SIRT1: tipping the balance towards survival. Trends Cell Biol 14:408–412

Glozak MA, Sengupta N, Zhang XH, Seto E (2005) Acetylation and deacetylation of non-histone proteins. Gene 363:15–23

Goodier JL, Kazazian HH (2008) Retrotransposons revisited: the restraint and rehabilitation of parasites. Cell 135:23–35

Gorelik G, Richardson B (2009) Aberrant T cell ERK pathway signaling and chromatin structure in lupus. Autoimmun Rev 8:196–198

Gray SG, Iglesias AH, Teh BT, Dangond F (2003) Modulation of splicing events in histone deacetylase 3 by various extracellular and signal transduction pathways. Gene Expr 11:13–21

Greger JG, Katz RA, Ishov AM, Maul GG, Skalka AM (2005) The cellular protein daxx interacts with avian sarcoma virus integrase and viral DNA to repress viral transcription. J Virol 79:4610–4618

Gregoretti IV, Lee YM, Goodson HV (2004) Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. J Mol Biol 338:17–31

Grozinger CM, Schreiber SL (2000) Regulation of histone deacetylase 4 and 5 and transcriptional activity by 14-3-3-dependent cellular localization. Proc Nat Acad Sci USA 97:7835–7840

Grozinger CM, Schreiber SL (2002) Deacetylase enzymes: biological functions and the use of small-molecule inhibitors. Chem Biol 9:3–16

Grunstein M (1997) Histone acetylation in chromatin structure and transcription. Nat 389:349–352

Guardiola AR, Yao TP (2002) Molecular cloning and characterization of a novel histone deacetylase HDAC10. J Biol Chem 277:3350–3356

Guenther MG, Barak O, Lazar MA (2001) The SMRT and N-CoR corepressors are activating cofactors for histone deacetylase 3. Mol Cell Biol 21:6091–6101

Guenther MG, Yu JJ, Kao GD, Yen TJ, Lazar MA (2002) Assembly of the SMRT-histone deacetylase 3 repression complex requires the TCP-1 ring complex. Genes Dev 16:3130–3135

Haigis MC, Guarente LP (2006) Mammalian sirtuins—emerging roles in physiology, aging, and calorie restriction. Genes Dev 20:2913–2921

Haigis MC, Sinclair DA (2010) Mammalian sirtuins: biological insights and disease relevance. Annu Rev Pathol Mech Dis 5:253–295

Hansen JC (2002) Conformational dynamics of the chromatin fiber in solution: determinants, mechanisms, and functions. Annu Rev Biophys Biomol Struct 31:361–392

Hassig CA, Fleischer TC, Billin AN, Schreiber SL, Ayer DE (1997) Histone deacetylase activity is required for full transcriptional repression by mSin3A. Cell 89:341–347

He GC, Margolis DM (2002) Counterregulation of chromatin deacetylation and histone deacetylase occupancy at the integrated promoter of human immunodeficiency virus type 1 (HIV-1) by the HIV-1 repressor YY1 and HIV-1 activator Tat. Mol Cell Biol 22:2965–2973

Heckman DS, Geiser DM, Eidell BR, Stauffer RL, Kardos NL, Hedges SB (2001) Molecular evidence for the early colonization of land by fungi and plants. Sci 293:1129–1133

Heinzel T, Lavinsky RM, Mullen TM, Soderstrom M, Laherty CD, Torchia J, Yang WM, Brard G, Ngo SD, Davie JR et al (1997) A complex containing N-CoR, mSin3 and histone deacetylase mediates transcriptional repression. Nat 387:43–48

Henderson YC, Breau RL, Liu TJ, Clayman GL (2000) Telomerase activity in head and neck tumors after introduction of wild-type p53, p21, p16, and E2F-1 genes by means of recombinant adenovirus. Head Neck 22:347–354

Hildmann C, Ninkovic M, Dietrich R, Wegener D, Riester D, Zimmermann T, Birch OM, Bernegger C, Loidl P, Schwienhorst A (2004) A new amidohydrolase from *Bordetella* or *Alcaligenes* strain FB188 with similarities to histone deacetylases. J Bacteriol 186:2328–2339

Hildmann C, Riester D, Schwienhorst A (2007) Histone deacetylases-an important class of cellular regulators with a variety of functions. Appl Microbiol Biotechnol 75:487–497

Hohenadl C, Germaier H, Walchner M, Hagenhofer M, Herrmann M, Sturzl M, Kind P, Hehlmann R, Erfle V, Leib-Mosch C (1999) Transcriptional activation of endogenous retroviral sequences in human epidermal keratinocytes by UVB irradiation. J Investig Dermatol 113:587–594

Hollenbach AD, McPherson CJ, Mientjes EJ, Iyengar R, Grosveld G (2002) Daxx and histone deacetylase II associate with chromatin through an interaction with core histones and the chromatin-associated protein Dek. J Cell Sci 115:3319–3330

Hu XY, Ray PN, Worton RG (1991) Mechanisms of tandem duplication in the Duchenne muscular-dystrophy gene include both homologous and nonhomologous intrachromasomal recombination. EMBO J 10:2471–2477

Humphrey GW, Wang YH, Russanova VR, Hirai T, Qin J, Nakatani Y, Howard BH (2001) Stable histone deacetylase complexes distinguished by the presence of SANT domain proteins CoREST/kiaa0071 and Mta-L1. J Biol Chem 276:6817–6824

Imai K, Okamoto T (2006) Transcriptional repression of human immunodeficiency virus type 1 by AP-4. J Biol Chem 281:12495–12505

Irvine RA, Lin IG, Hsieh CL (2002) DNA methylation has a local effect on transcription and histone acetylation. Mol Cell Biol 22:6689–6696

Ito A, Kawaguchi Y, Lai CH, Kovacs JJ, Higashimoto Y, Appella E, Yao TP (2002) MDM2-HDAC1-mediated deacetylation of p53 is required for its degradation. EMBO J 21:6236–6245

Johnson CA, White DA, Lavender JS, O'Neill LP, Turner BM (2002) Human class I histone deacetylase complexes show enhanced catalytic activity in the presence of ATP and co-immunoprecipitate with the ATP-dependent chaperone protein Hsp70. J Biol Chem 277:9590–9597

Jordan IK, Rogozin IB, Glazko GV, Koonin EV (2003) Origin of a substantial fraction of human regulatory sequences from transposable elements. Trends Genet 19:68–72

Kamata H, Manabe T, Oka S, Kamata K, Hirata H (2002) Hydrogen peroxide activates I kappa B kinases through phosphorylation of serine residues in the activation loops. FEBS Lett 519:231–237

Kao HY, Downes M, Ordentlich P, Evans RM (2000) Isolation of a novel histone deacetylase reveals that class I and class II deacetylases promote SMRT-mediated repression. Genes Dev 14:55–66

Kao HY, Verdel A, Tsai CC, Simon C, Juguilon H, Khochbin S (2001) Mechanism for nucleocytoplasmic shuttling of histone deacetylase 7. J Biol Chem 276:47496–47507

Kapitonov VV, Jurka J (2005) RAG1 core and V(D)J recombination signal sequences were derived from Transib transposons. PLoS Biol 3:998–1011

Katz RA, Jack-Scott E, Narezkina A, Palagin I, Boimel P, Kulkosky J, Nicolas E, Greger JG, Skalka AM (2007) High-frequency epigenetic repression and silencing of retroviruses can be antagonized by histone deacetylase inhibitors and transcriptional activators, but uniform reactivation in cell clones is restricted by additional mechanisms. J Virol 81:2592–2604

Keedy KS, Archin NM, Gates AT, Espeseth A, Hazuda DJ, Margolis DM (2009) A limited group of class I histone deacetylases acts to repress human immunodeficiency virus type 1 expression. J Virol 83:4749–4756

Keogh MC, Kurdistani SK, Morris SA et al (2005) Cotranscriptional Set2 methylation of histone H3 lysine 36 recruits a repressive Rpd3 complex. Cell 123:593–605

Khan N, Jeffers M, Kumar S, Hackett C, Boldog F, Khramtsov N, Qian XZ, Mills E, Berghs SC, Carey N et al (2008) Determination of the class and isoform selectivity of small-molecule histone deacetylase inhibitors. Biochem J 409:581–589

Kondo Y, Issa JPJ (2003) Enrichment for histone H3 lysine 9 methylation at Alu repeats in human cells. J Biol Chem 278:27658–27662

Kondo Y, Shen L, Cheng AS, Ahmed S, Boumber Y, Charo C, Yamochi T, Urano T, Furukawa K, Kwabi-Addo B et al (2008) Gene silencing in cancer by histone H3 lysine 27 trimethylation independent of promoter DNA methylation. Nat Genet 40:741–750

Korin YD, Brooks DG, Brown S, Korotzer A, Zack JA (2002) Effects of prostratin on T-cell activation and human immunodeficiency virus latency. J Virol 76:8118–8123

Kornreich R, Bishop DF, Desnick RJ (1990) Alpha-galactosidase-A gene rearrangements causing Fabry disease—identification of short direct repeats at breakpoints in an Alu-rich gene. J Biol Chem 265:9319–9326

Kulkosky J, Culnan DM, Roman J, Dornadula G, Schnell M, Boyd MR, Pomerantz RJ (2001) Prostratin: activation of latent HIV-1 expression suggests a potential inductive adjuvant therapy for HAART. Blood 98:3006–3015

Kuriyama M, Udagawa A, Yoshimoto S, Ichinose M, Sato K, Yamazaki K, Matsuno Y, Shiota K, Mori C (2008) DNA methylation changes during cleft palate formation induced by retinoic acid in mice. Cleft Palate Craniofac J 45:545–551

Kuzmichev A, Jenuwein T, Tempst P, Reinberg D (2004) Different Ezh2-containing complexes target methylation of histone H1 or nucleosomal histone H3. Mol Cell 14:183–193

Lagger G, O'Carroll D, Rembold M, Khier H, Tischler J, Weitzer G, Schuettengruber B, Hauser C, Brunmeir R, Jenuwein T et al (2002) Essential function of histone deacetylase 1 in proliferation control and CDK inhibitor repression. EMBO J 21:2672–2681

Lai SR, Cunningham AP, Huynh VQ, Andrews LG, Tollefsbol TO (2007) Evidence of extra-telorneric effects of hTERT and its regulation involving a feedback loop. Exp Cell Res 313:322–330

Latham JA, Dent SYR (2007) Cross-regulation of histone modifications. Nat Struct Mol Biol 14:1017–1024

Le Rouzic A, Boutin TS, Capy P (2007) Long-term evolution of transposable elements. Proc Natl Acad Sci USA 104:19375–19380

Ledent V, Vervoort M (2006) Comparative genomics of the class 4 histone deacetylase family indicates a complex evolutionary history. BMC Biol 4: article 24

Lee IH, Cao L, Mostoslavsky R, Lombard DB, Liu J, Bruns NE, Tsokos M, Alt FW, Finkel T (2008) A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. Proc Natl Acad Sci USA 105:3374–3379

Legrand-Poels S, Vaira D, Pincemail J, Vandevorst A, Piette J (1990) Activation of human-immunodeficiency-virus type-1 by oxidative stress. AIDS Res Hum Retrovir 6:1389–1397

Leipe DD, Landsman D (1997) Histone deacetylases, acetoin utilization proteins and acetylpolyamine amidohydrolases are members of an ancient protein superfamily. Nucleic Acids Res 25:3693–3697

Lewin B (2008) Genes IX. Jones and Bartlett, Sudbury

Li XF, Song S, Liu Y, Ko SH, Kao HY (2004) Phosphorylation of the histone deacetylase 7 modulates its stability and association with 14-3-3 proteins. J Biol Chem 279:34201–34208

Li Y, Yuan Y-Y, Meeran SM, Tollefsbol (2010) Synergistic epigenetic reactivation of estrogen receptor-α (ERα) by combined green tea polyphenol and histone deacetylase inhibitor in ERα-negative breast cancer cells. Mol Cancer 9:274

Lin SJ, Ford E, Haigis M, Liszt G, Guarente L (2004) Calorie restriction extends yeast life span by lowering the level of NADH. Genes Dev 18:12–16

Liu L, Lai S, Andrews LG, Tollefsbol TO (2004) Genetic and epigenetic modulation of telomerase activity in development and disease. Gene 340:1–10

Liu L, Li YY, Tollefsbol TO (2008) Gene-environment interactions and epigenetic basis of human diseases. Curr Issues Mol Biol 10:25–36

Llorens C, Munoz-Pomer A, Bernad L, Botella H, Moya A (2009) Network dynamics of eukaryotic LTR retroelements beyond phylogenetic trees. Biol Direct 4:41

Lu JR, McKinsey TA, Zhang CL, Olson EN (2000) Regulation of skeletal myogenesis by association of the MEF2 transcription factor with class II histone deacetylases. Mol Cell 6:233–244

Lusic M, Marcello A, Cereseto A, Giacca M (2003) Regulation of HIV-1 gene expression by histone acetylation and factor recruitment at the LTR promoter. EMBO J 22:6550–6561

Maksakova IA, Romanish MT, Gagnier L, Dunn CA, de Lagemaat LNV, Mager DL (2006) Retroviral elements and their hosts: Insertional mutagenesis in the mouse germ line. PLoS Genet 2:1–10

Maksakova IA, Mager DL, Reiss D (2008) Keeping active endogenous retroviral-like elements in check: the epigenetic perspective. Cell Mol Life Sci 65:3329–3347

Manco L, Relvas L, Pinto CS, Pereira J, Almeida AB, Ribeiro ML (2006) Molecular characterization of five Portuguese patients with pyrimidine 5′-nucleotidase deficient hemolytic anemia showing three new P5′ N-I mutations. Haematol J 91:266–267

Marban C, Suzanne S, Dequiedt F, de Walque S, Redel L, Van Lint C, Aunis D, Rohr O (2007) Recruitment of chromatin-modifying enzymes by CTIP2 promotes HIV-1 transcriptional silencing. EMBO J 26:412–423

Marguerat S, Wang WYS, Todd JA, Conrad B (2004) Association of human endogenous retrovirus K-18 polymorphisms with type 1 diabetes. Diabetes 53:852–854

Marks PA, Xu WS (2009) Histone deacetylase inhibitors: potential in cancer therapy. J Cell Biochem 107:600–608

Martens JHA, O'Sullivan RJ, Braunschweig U, Opravil S, Radolf M, Steinlein P, Jenuwein T (2005) The profile of repeat-associated histone lysine methylation states in the mouse epigenome. EMBO J 24:800–812

Martin M, Kettmann R, Dequiedt F (2007) Class IIa histone deacetylases: regulating the regulators. Oncogene 26:5450–5467

Martin M, Kettmann R, Dequiedt F (2009) Class IIa histone deacetylases: conducting development and differentiation. Int J Dev Biol 53:291–301

Matzke MA, Mette MF, Matzke AJM (2000) Transgene silencing by the host genome defense: implications for the evolution of epigenetic control mechanisms in plants and vertebrates. Plant Mol Biol 43:401–415

McArthur GA, Foley KP, Fero ML, Walkley CR, Deans AJ, Roberts JM, Eisenman RN (2002) MAD1 and p27(KIP1) cooperate to promote terminal differentiation of granulocytes and to inhibit Myc expression and cyclin E-CDK2 activity. Mol Cell Biol 22:3014–3023

McKinsey TA, Zhang CL, Lu JR, Olson EN (2000a) Signal-dependent nuclear export of a histone deacetylase regulates muscle differentiation. Nat 408:106–111

McKinsey TA, Zhang CL, Olson EN (2000b) Activation of the myocyte enhancer factor-2 transcription factor by calcium/calmodulin-dependent protein kinase-stimulated binding of 14-3-3 to histone deacetylase 5. Proc Natl Acad Sci USA 97:14400–14405

McKinsey TA, Zhang CL, Olson EN (2001) Control of muscle development by dueling HATs and HDACs. Curr Opin Genet Dev 11:497–504

Meylan F, De Smedt M, Leclercq G, Plum J, Leupin O, Marguerat S, Conrad B (2005) Negative thymocyte selection to HERV-K18 superantigens in humans. Blood 105:4377–4382

Miki Y, Nishisho I, Horii A, Miyoshi Y, Utsunomiya J, Kinzler KW, Vogelstein B, Nakamura Y (1992) Disruption of the APC gene by a retrotransposal insertion of L1 sequence in a colon cancer. Cancer Res 52:643–645

Miki Y, Katagiri T, Kasumi F, Yoshimoto T, Nakamura Y (1996) Mutation analysis in the BRCA2 gene in primary breast cancers. Nat Genet 13:245–247

Mills RE, Bennett EA, Iskow RC, Devine SE (2007) Which transposable elements are active in the human genome? Trends Genet 23:183–191

Minucci S, Pelicci PG (2006) Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. Nat Rev Cancer 6:38–51

Mirouze M, Reinders J, Bucher E, Nishimura T, Schneeberger K, Ossowski S, Cao J, Weigel D, Paszkowski J, Mathieu O (2009)

Selective epigenetic control of retrotransposition in Arabidopsis. Nat 461:427–431
Miska EA, Karlsson C, Langley E, Nielsen SJ, Pines J, Kouzarides T (1999) HDAC4 deacetylase associates with and represses the MEF2 transcription factor. EMBO J 18:5099–5107
Motta MC, Divecha N, Lemieux M, Kamel C, Chen D, Gu W, Bultsma Y, McBurney M, Guarente L (2004) Mammalian SIRT1 represses forkhead transcription factors. Cell 116:551–563
Mutskov V, Felsenfeld G (2004) Silencing of transgene transcription precedes methylation of promoter DNA and histone H3 lysine 9. EMBO J 23:138–149
Nakamura TM, Cech TR (1998) Reversing time: origin of telomerase. Cell 92:587–590
Nesse RM, Williams GC (1995) Why we get sick. Random House, New York
Ng HH, Bird A (2000) Histone deacetylases: silencers for hire. Trends Biochem Sci 25:121–126
Nyce J, Leonard S, Canupp D, Schulz S, Wong S (1993) Epigenetic mechanisms of drug-resistance—drug-induced DNA hypermethylation and drug-resistance. Proc Natl Acad Sci USA 90:2960–2964
Oakley F, Mann J, Ruddell RG, Pickford J, Weinmaster G, Mann DA (2003) Basal expression of I kappa B alpha is controlled by the mammalian transcriptional repressor RBP-J (CBF1) and its activator notch1. J Biol Chem 278:24359–24370
O'Hagan HM, Mohammad HP, Baylin SB (2008) Double strand breaks can initiate gene silencing and SIRT1-dependent onset of DNA methylation in an exogenous promoter CpG island. PLoS Genet 4:e1000155
Oliveira-Marques V, Marinho HS, Cyrne L, Antunes F (2009) Modulation of NF-kappa B-dependent gene expression by H2O2: a major role for a simple chemical process in a complex biological response. Antioxid Redox Signaling 11:2043–2053
Ostertag EM, Kazazian HH (2001) Biology of mammalian L1 retrotransposons. Annu Rev Genet 35:501–538
Pace JK, Feschotte C (2007) The evolutionary history of human DNA transposons: evidence for intense activity in the primate lineage. Genome Res 17:422–432
Paroni G, Mizzau M, Henderson C, Del Sal G, Schneider C, Brancolini C (2004) Caspase-dependent regulation of histone deacetylase 4 nuclear-cytoplasmic shuttling promotes apoptosis. Mol Biol Cell 15:2804–2818
Parra M, Mahmoudi T, Verdin E (2007) Myosin phosphatase dephosphorylates HDAC7, controls its nucleocytoplasmic shuttling, and inhibits apoptosis in thymocytes. Genes Dev 21:638–643
Perkins ND, Edwards NL, Duckett CS, Agranoff AB, Schmid RM, Nabel GJ (1993) A cooperative interaction between NF-kappa-B and Sp1 is required for HIV-1 enhancer activation. EMBO J 12:3551–3558
Perrault SD, Hornsby PJ, Betts DH (2005) Global gene expression response to telomerase in bovine adrenocortical cells. Biochem Biophys Res Commun 335:925–936
Petrie K, Guidez F, Howell L, Healy L, Waxman S, Greaves M, Zelent A (2003) The histone deacetylase 9 gene encodes multiple protein isoforms. J Biol Chem 278:16059–16072
Pflum MKH, Tong JK, Lane WS, Schreiber SL (2001) Histone deacetylase I phosphorylation promotes enzymatic activity and complex formation. J Biol Chem 276:47733–47741
Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, Klein PS (2001) Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. J Biol Chem 276:36734–36741
Preston CM, Nicholl MJ (2006) Role of the cellular protein hDaxx in human cytomegalovirus immediate-early gene expression. J Gen Virol 87:1113–1121
Pullmann R, Bonilla E, Phillips PE, Middleton FA, Perl A (2008) Haplotypes of the HRES-1 endogenous retrovirus are associated with development and disease manifestations of systemic lupus erythematosus. Arthritis Rheum 58:532–540
Pyo CW, Yang YL, Yoo NK, Choi SY (2008) Reactive oxygen species activate HIV long terminal repeat via post-translational control of NF-kappa B. Biochem Biophys Res Commun 376:180–185
Rahman I, Marwick J, Kirkham P (2004) Redox modulation of chromatin remodeling: impact on histone acetylation and deacetylation, NF-kappa B and pro-inflammatory gene expression. Biochem Pharmacol 68:1255–1267
Reuse S, Calao M, Kabeya K, Guiguen A, Gatot JS, Quivy V, Vanhulle C, Lamine A, Vaira D, Demonte D et al (2009) Synergistic activation of HIV-1 expression by deacetylase inhibitors and prostratin: implications for treatment of latent infection. PLoS ONE 4:e6093
Robyr D, Suka Y, Xenarios I, Kurdistani SK, Wang A, Suka N, Grunstein M (2002) Microarray deacetylation maps determine genome-wide functions for yeast histone deacetylases. Cell 109:437–446
Robyr D, Kurdistani SK, Grunstein M (2004) Analysis of genome-wide histone acetylation state and enzyme binding using DNA microarrays. Chromatin and chromatin remodel enzym, Pt B. Methods Enzymol 376:289–304
Rundlett SE, Carmen AA, Kobayashi R, Bavykin S, Turner BM, Grunstein M (1996) HDA1 and RPD3 are members of distinct yeast histone deacetylase complexes that regulate silencing and transcription. Proc Natl Acad Sci USA 93:14503–14508
Sasai N, Defossez P-A (2009) Many paths to one goal? the proteins that recognize methylated DNA in eukaryotes. Int J Dev Biol 53:323–334
Sasaki T, Maier B, Bartke A, Scrable H (2006) Progressive loss of SIRT1 with cell cycle withdrawal. Aging Cell 5:413–422
Saunders LR, Verdin E (2007) Sirtuins: critical regulators at the crossroads between cancer and aging. Oncogene 26:5489–5504
Sauve AA, Celic I, Avalos J, Deng HT, Boeke JD, Schramm VL (2001) Chemistry of gene silencing: The mechanism of NAD (+)-dependent deacetylation reactions. Biochem 40:15456–15463
Schubeler D, Lorincz MC, Cimbora DM, Telling A, Feng YQ, Bouhassira EE, Groudine M (2000) Genomic targeting of methylated DNA: influence of methylation on transcription, replication, chromatin structure, and histone acetylation. Mol Cell Biol 20:9103–9112
Sengupta N, Seto E (2004) Regulation of histone deacetylase activities. J Cell Biochem 93:57–67
Sherer Y, Gorstein A, Fritzler MJ, Shoenfeld Y (2004) Autoantibody explosion in systemic lupus erythematosus: more than 100 different antibodies found in SLE patients. Semin Arthritis Rheum 34:501–537
Shimada F, Taira M, Suzuki Y, Hashimoto N, Nozaki O, Tatibana M, Ebina Y, Tawata M, Onaya T, Makino H et al (1990) Insulin-resistant diabetes associated with partial deletion of insulin-receptor gene. Lancet 335:1179–1181
Siggs OM, Makaroff LE, Liston A (2006) The why and how of thymocyte negative selection. Curr Opin Immunol 18:175–183
Slotkin RK, Martienssen R (2007) Transposable elements and the epigenetic regulation of the genome. Nat Rev Genet 8:272–285
So CW, Ma ZG, Price CM, Dong S, Chen SJ, Gu LJ, So CKC, Wiedemann LM, Chan LC (1997) MLL self fusion mediated by Alu repeat homologous recombination and prognosis of AML-M4/M5 subtypes. Cancer Res 57:117–122
Starai VJ, Celic I, Cole RN, Boeke JD, Escalante-Semerena JC (2002) Sir2-dependent activation of acetyl-CoA synthetase by deacetylation of active lysine. Sci 298:2390–2392

Stauffer Y, Marguerat S, Meylan F, Ucla C, Sutkowski N, Huber B, Pelet T, Conrad B (2001) Interferon-α-induced endogenous superantigen: a model linking environment and autoimmunity. Immunity 15:591–601

Strout MP, Marcucci G, Bloomfield CD, Caligiuri MA (1998) The partial tandem duplication of ALL1 (MLL) is consistently generated by Alu-mediated homologous recombination in acute myeloid leukemia. Proc Natl Acad Sci USA 95:2390–2395

Taunton J, Hassig CA, Schreiber SL (1996) A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p. Sci 272:408–411

Taverna SD, Haitao L, Ruthenburg AJ, Allis CD, Patel DJ (2007) How chromatin-binding modules interpret histone modifications: lessons from professional pocket pickers. Nat Struct Mol Biol 14:1025–1040

Terada K, Katamine S, Eguchi K, Moriuchi R, Kita M, Shimada H, Yamashita I, Iwata K, Tsuji Y, Nagataki S et al (1994) Prevalence of serum and salivary antibodies to HTLV-1 in Sjogren's-syndrome. Lancet 344:1116–1119

Thierry S, Marechal V, Rosenzwajg M, Sabbah M, Redeuilh G, Nicolas JC, Gozlan J (2004) Cell cycle arrest in G(2) induces human immunodeficiency virus type 1 transcriptional activation through histone acetylation and recruitment of CBP, NF-kappa B, and c-Jun to the long terminal repeat promoter. J Virol 78:12198–12206

Toffoli G, Russo A, Innocenti F, Corona G, Tumolo S, Sartor F, Mini E, Boiocchi M (2003) Effect of methylenetetrahydrofolate reductase 677C⟶T polymorphism on toxicity and homocysteine plasma level after chronic methotrexate treatment of ovarian cancer patients. Int J Cancer 103:294–299

Tong JK, Hassig CA, Schnitzler GR, Kingston RE, Schreiber SL (1998) Chromatin deacetylation by an ATP-dependent nucleosome remodelling complex. Nat 395:917–921

Tost J (2010) DNA methylation: an introduction to the biology and disease-associated changes of a promising biomarker. Mol Biotechnol 44:71–81

Tsai SC, Seto E (2002) Regulation of histone deacetylase 2 by protein kinase CK2. J Biol Chem 277:31826–31833

Tuch BB, Li H, Johnson AD (2008) Evolution of eukaryotic transcription circuits. Sci 319:1797–1799

Tyagi M, Karn J (2007) CBF-1 promotes transcriptional silencing during the establishment of HIV-1 latency. EMBO J 26:4985–4995

van der Horst A, Tertoolen LGJ, de Vries-Smits LMM, Frye RA, Medema RH, Burgering BMT (2004) FOXO4 is acetylated upon peroxide stress and deacetylated by the longevity protein hSir2 (SIRT1). J Biol Chem 279:28873–28879

VanLint C, Emiliani S, Ott M, Verdin E (1996) Transcriptional activation and chromatin remodeling of the HIV-1 promoter in response to histone acetylation. EMBO J 15:1112–1120

Vaquero A (2009) The conserved role of sirtuins in chromatin regulation. Int J Dev Biol 53:303–322

Vaquero A, Scher M, Lee DH, Erdjument-Bromage H, Tempst P, Reinberg D (2004) Human SirT1 interacts with histone H1 and promotes formation of facultative heterochromatin. Mol Cell 16:93–105

Vaquero A, Scher M, Erdjument-Bromage H, Tempst P, Serrano L, Reinberg D (2007) SIRT1 regulates the histone methyltransferase SUV39H1 during heterochromatin formation. Nature 450:440–444

Vaute O, Nicolas E, Vandel L, Trouche D (2002) Functional and physical interaction between the histone methyl transferase Suv39H1 and histone deacetylases. Nucleic Acids Res 30:475–481

Verdel A, Khochbin S (1999) Identification of a new family of higher eukaryotic histone deacetylases—coordinate expression of differentiation-dependent chromatin modifiers. J Biol Chem 274:2440–2445

Wang AH, Bertos NR, Vezmar M, Pelletier N, Crosato M, Heng HH, Th'ng J, Han JH, Yang XJ (1999) HDAC4, a human histone deacetylase related to yeast HDA1, is a transcriptional corepressor. Mol Cell Biol 19:7816–7827

Wang G, Pierangeli SS, Papalardo E, Ansari KMF (2010) Markers of oxidative and nitrosative stress in systemic lupus erythematosus: correlation with disease activity. Arthritis Rheum 62:2064–2072

Weinhold B (2006) Epigenetics—the science of change. Environ Health Perspect 114:A160–A167

Wen YD, Perissi V, Staszewski LM, Yang WM, Krones A, Glass CK, Rosenfeld MG, Seto E (2000) The histone deacetylase-3 complex contains nuclear receptor corepressors. Proc Natl Acad Sci USA 97:7202–7207

Wick G, Jansen-Durr P, Berger P, Blasko I, Grubeck-Loebenstein B (2000) Diseases of aging. Vaccine 18:1567–1583

Wick G, Berger P, Jansen-Durr P, Grubeck-Loebenstein B (2003) A Darwinian-evolutionary concept of age-related diseases. Exp Gerontol 38:13–25

Williams SA, Chen LF, Kwon H, Ruiz-Jarabo CM, Verdin E, Greene WC (2006) NF-kappa B p50 promotes HIV latency through HDAC recruitment and repression of transcriptional initiation. EMBO J 25:139–149

Wiper-Bergeron N, Wu DM, Pope L, Schild-Poulter C, Hache RJG (2003) Stimulation of preadipocyte differentiation by steroid through targeting of an HDAC1 complex. EMBO J 22:2135–2145

Wray GA, Hahn MW, Abouheif E, Balhoff JP, Pizer M, Rockman MV, Romano LA (2003) The evolution of transcriptional regulation in eukaryotes. Mol Biol Evol 20:1377–1419

Yamamori T, DeRicco J, Naqvi A, Hoffman TA, Mattagajasingh I, Kasuno K, Jung SB, Kim CS, Irani K (2010) SIRT1 deacetylates APE1 and regulates cellular base excision repair. Nucleic Acids Res 38:832–845

Yamamoto H, Schoonjans K, Auwerx J (2007) Sirtuin functions in health and disease. Mol Endocrinol 21:1745–1755

Yamano S, Renard JN, Mizuno F, Narita Y, Uchida Y, Higashiyama H, Sakurai H, Saito I (1997) Retrovirus in salivary glands from patients with Sjogren's syndrome. J Clin Pathol 50:223–230

Yang WM, Tsai SC, Wen YD, Fejer G, Seto E (2002) Functional domains of histone deacetylase-3. J Biol Chem 277:9447–9454

Yeung F, Hoberg JE, Ramsey CS, Keller MD, Jones DR, Frye RA, Mayo MW (2004) Modulation of NF-kappa B-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J 23:2369–2380

Yoder JA, Walsh CP, Bestor TH (1997) Cytosine methylation and the ecology of intragenomic parasites. Trends Genet 13:335–340

You A, Tong JK, Grozinger CM, Schreiber SL (2001) CoREST is an integral component of the CoREST-human histone deacetylase complex. Proc Natl Acad Sci USA 98:1454–1458

Youn HD, Grozinger CM, Liu JO (2000) Calcium regulates transcriptional repression of myocyte enhancer factor 2 by histone deacetylase 4. J Biol Chem 275:22563–22567

Yuan Z, Zhang X, Sengupta N, Lane WS, Seto E (2007) SIRT1 regulates the function of the nijmegen breakage syndrome protein. Mol Cell 27:149–162

Zeh DW, Zeh JA, Ishida Y (2009) Transposable elements and an epigenetic basis for punctuated equilibria. BioEssays 31:715–726

Zhang Y, Iratni R, ErdjumentBromage H, Tempst P, Reinberg D (1997) Histone deacetylases and SAP18, a novel polypeptide, are components of a human Sin3 complex. Cell 89:357–364

Zhang Y, LeRoy G, Seelig HP, Lane WS, Reinberg D (1998) The dermatomyositis-specific autoantigen Mi2 is a component of a complex containing histone deacetylase and nucleosome remodeling activities. Cell 95:279–289

Zhang Y, Ng HH, Erdjument-Bromage H, Tempst P, Bird A, Reinberg D (1999) Analysis of the NuRD subunits reveals a histone

deacetylase core complex and a connection with DNA methylation. Genes Dev 13:1924–1935

Zhang CL, McKinsey TA, Olson EN (2002a) Association of class II histone deacetylases with heterochromatin protein 1: potential role for histone methylation in control of muscle differentiation. Mol Cell Biol 22:7302–7312

Zhang JS, Kalkum M, Chait BT, Roeder RG (2002b) The N-CoR-HDAC3 nuclear receptor corepressor complex inhibits the JNK pathway through the integral subunit GPS2. Mol Cell 9:611–623

Zhang LW, Eugeni EE, Parthun MR, Freitas MA (2003a) Identification of novel histone post-translational modifications by peptide mass fingerprinting. Chromosoma 112:77–86

Zhang Y, Li N, Caron C, Matthias G, Hess D, Khochbin S, Matthias P (2003b) HDAC-6 interacts with and deacetylates tubulin and microtubules in vivo. EMBO J 22:1168–1179

Zhong HH, Voll RE, Ghosh S (1998) Phosphorylation of NF-kappa B p65 by PKA stimulates transcriptional activity by promoting a novel bivalent interaction with the coactivator CBP/p300. Mol Cell 1:661–671

Zhong HH, May MJ, Jimi E, Ghosh S (2002) The phosphorylation status of nuclear NF-kappa B determines its association with CBP/p300 or HDAC-1. Mol Cell 9:625–636

Zhu JD, Blenis J, Yuan JY (2008) Activation of PI3K/Akt and MAPK pathways regulates Myc-mediated transcription by phosphorylating and promoting the degradation of Mad1. Proc Nat Acad Sci USA 105:6584–6589