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Role of HDAC1 in senescence, aging, and cancer

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Abstract

HDAC1 is a member of the class I of histone deacetylases that also includes HDAC2, –3 and –8. Although HDAC1 has been mostly studied in the context of cancer, recent evidence strongly suggests that it plays critical roles in cellular senescence, aging of the liver, myelination, and adult neurogenesis. Here we review such roles and discuss the entangled relationships between HDAC1 with histone acetyltransferases and other HDACs including SIRT1.

Keywords

HDAC1; chromatin structure; aging; melanocytes; neurogenesis; myelination; liver

Introduction

Epigenetics, histone modifications and the histone code

Epigenetics can be applied to the study of virtually every biological process, aging is no exception. The nucleosome is the fundamental unit of chromatin. It consists of an octamer of histones proteins containing 2 units each of histone H3, H4, H2A and H2B around which ~165bp of DNA makes 1.67 turns. In this manner, the histone proteins provide structure and organization to the genome. Histones H3 and H4 are characterized by the presence of a histone fold in the C-terminal half of the protein, which is necessary for histone-histone interactions within the nucleosome, and an unstructured N-terminal tail. For H2A and H2B the histone fold is centrally located. The histone tail is not embedded into the tertiary histone structure, or the final nucleosomal structure, allowing easy access to histone modifying enzymes. Histone post-translational modifications (PTMs) include acetylation, deacetylation, methylation, demethylation, phosphorylation, and ubiquitination (Reviewed in (Rando and Chang, 2009; Richards and Medrano EE, 2009; Yang and Seto, 2008a). It is currently accepted that histone

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PTMs work in concert to form a “histone code” that is read by other proteins to regulate gene expression (Strahl and Allis, 2000).

One of the best-studied histone PTMs is acetylation, the transfer of an acetyl group from acetyl coenzyme A to the ϵ -lysine side chain in the acceptor histone. Histone acetyltransferases (HATs) are responsible for the acetylation of both histone and non-histone proteins. Histone acetylation at specific loci correlate with an open chromatin state which allows transcription factors to access DNA. HATs generally exist as part of a large protein complex that regulates its enzymatic activity and specificity. p300 and CBP, two highly homologous HATs, are found in many complexes endowed with chromatin remodeling activity, and are required for transcriptional regulation. Both also associate with another HAT, PCAF (p300/CBP Associated Factor). Complexes formed by p300/CBP and PCAF have proven to play important roles in processes ranging from muscle differentiation to cancer (Lehrmann et al., 2002). In addition to their HAT activity, HATs are also responsible for the acetylation of non-histone proteins. For example, acetylation of p53 by p300 is critical for its transcriptional activity (Reviewed in (Kruse and Gu, 2009), whereas PCAF is important for acetylation and subsequent stabilization of β -catenin (Iyer et al., 2004; Lill et al., 1997).

Although histone acetylation is important for transcriptional activation, removal of acetyl groups by histone deacetylases (HDACs), is equally important for signal regulation. HDACs are divided into four classes. Class I enzymes (HDAC1, -2, -3, and 8) have high homology to the yeast transcriptional regulator RPD3 and are subunits of multiprotein nuclear complexes. The most phylogenetically related members of the Class 1 HDACs are HDAC1 and HDAC2 (ClustalW score:83), followed by HDAC3 (score:57) and HDAC8 (score:38). Class II enzymes (HDAC4, -5, -6, -7, -9, and -10) are closely related to HDA1, a yeast deacetylases and can traffic between cytoplasm and nucleus. A sequence similarity output between current members of class I and 2 HDACs is shown in Fig 1. In turn, class III HDACs are NAD⁺ dependent and commonly referred to as sirtuins. Class IV (HDAC 11) has some homology to both class I and II enzymes, therefore, it has been grouped into a separate class (Yang and Seto, 2008b). An extensive description of Class 1 and Class 2 functions and localizations can be found in (de Ruijter et al., 2003; Witt et al., 2009).

Notably, a study using wild-type and HDAC1-deficient embryonic stem cells found that HDAC1 has positive and negative effects in transcription (Zupkovitz et al., 2006). Chromatin immunoprecipitations determined that HDAC1 binds to the regulatory region of a large number of genes. Most genes were upregulated under HDAC1 depletion, but a few were repressed. This study also identified a subtle but important cross regulation of HDAC1 and HDAC2 functions (discussed in more details in the next section). HDAC1, like all other HDACs, lacks a DNA binding domain, thus it must associate with a DNA binding protein to target specific chromatin regions (Glozak et al., 2005). For example, HDAC1 interacts with the transcription factor E2F in a complex containing BRM, BRG1, and SUV39H1 to repress transcription (Giacinti and Giordano, 2006). A few of the complexes HDAC1 may associate with are the Sin3 complex, Mi2/NuRD, CoREST and possibly N-CoR/SMRT (Reviewed in (Yang and Seto, 2008b).

Histone modifications can also influence the activity of other histone modifying enzymes (Yang and Seto, 2008a). Deacetylation of lysines in histones primes the histone for methylation by histone methyltransferases (HMT). Lysine residues have the potential to be mono-, di-, or trimethylated, with each level of methylation likely coding for a different functional consequence. HMTs usually contain a Suppressor of variegation, Enhancer of Zeste, Trithorax (SET) domain, which was named for its presence in the position-effects variegation (PEV) modifier, Su(var)3-9 and other chromatin regulators in *Drosophila* (Tschiersch et al., 1994). Although most HMTs have SET domains, the presence of a SET domain is not a requirement

for HMT activity. For instance, Disruptor of Telomeres 1 (DOT1/KMT4) lacks a SET domain and is solely responsible for the mon-, di- and tri- methylation of Histone H3 lysine 79 (Lacoste et al., 2002). Unlike histone acetylation, the transcriptional consequences of histone methylation don't have a consistent function. For example, methylation of histone H3 lysine 27 by EZH1 or EZH2 is associated with gene repression, via the polycomb group proteins (Margueron et al., 2008; Shen et al., 2008), whereas methylation of histone H3 lysine 4 is associated with transcriptional activation (Ruthenburg et al., 2007). Since histone methylation does not yield a consistent pattern, each mark needs to be methodically examined to elucidate its role in the chromatin environment in a cell-type and promoter context dependent. It was initially proposed that the aging in proliferating cells is due to reorganization of the genome in a cell cycle dependent manner (Howard, 1996). This hypothesis has been expanded to include the connection between cellular replication and the state of DNA compaction. In proliferating cells, DNA is mostly found to be in a less condensed euchromatic state, allowing access by the transcription and DNA replication machinery. Conversely, senescent cells, particularly fibroblasts, are characterized by the presence of densely packaged facultative heterochromatin, organized into structures named Senescence-Associated Heterochromatin Foci (SAHF) (Narita et al., 2003). More studies are needed to determine whether SAHFs reflect an increase in heterochromatin or a redistribution of some chromatin into larger heterochromatin structures. If the later is true, it is possible that some areas become more euchromatic.

It has become evident that the structure of chromatin is highly dynamic (Bhaumik et al., 2007), and that the presence or absence of various histone modifications has a significant impact on the activity of other histone modifying enzymes (Suganuma and Workman, 2008). Specifically, HDAC activity is integral to the function of multiple cellular systems. In this brief review, we will discuss some examples showing how histone deacetylases 1 (HDAC1) modifies the chromatin structure of cells in senescence, aging, and cancer.

The Yin and Yang roles of HDAC1 in senescence, aging and cancer

Emerging evidence shows that HDAC1 and HDAC2 play critical, albeit different, roles in proliferating and senescent cells in culture, and in young and old tissues *in vivo*. HDAC1 levels increase in parallel with increasing population doublings (PDs) of human melanocytes but levels of the p300/CBP HAT decrease (Bandyopadhyay et al., 2002). This was a surprising finding in light of the previously identified role of HDAC1 as a positive regulator of the cellular proliferation during embryonic development (Lagger et al., 2002). The causal role of HDAC1 in cellular senescence was demonstrated by using an inducible HDAC1 system in a melanoma cell line. Primary melanocytes are not suitable for this approach since the Tet-On and other inducible gene expression modalities require that the cells proliferate for at least 40–80 PDs. This approach proved to be highly informative for understanding epigenetic pathways leading to growth arrest and senescence induced by HDAC1. Increased HDAC1 levels triggered highly dynamic chromatin remodeling events, which were followed up by growth cessation after 8–10 days, and irreversible growth arrest after three weeks (Bandyopadhyay et al., 2007). Specific events induced by HDAC1 include rapid redistribution of RB, the histone methyltransferase SUV39H1, and HP1 β in nuclear foci. HDAC1 also stimulated a tight association of RB and HP1 β with chromatin. In parallel with these changes, it was found that induction of HDAC1 triggered the formation of transient mega Dalton complexes containing the aforementioned proteins, the ATP-dependent chromatin remodeler Brm, and several yet to be identified proteins. Supporting the biological relevance of these results, it was found that senescent melanocytic nevi display high HDAC1 immunoreactivity (Bandyopadhyay et al., 2007) in >90% of the nevus cells. In contrast, p16^{INK4a} immunoreactivity was highly inconsistent; some nevi contain >50%-positive cells whereas in others p16^{INK4a}-positivity was present in few isolated nests only ((reviewed in (Richards and Medrano, 2009)). HDAC1 immunoreactivity correlated with increased H3K9me3 nuclear staining in >90% of the nevus cells (Curry and

Medrano, unpublished results). High levels of HDAC1 in senescent cells is not melanocyte- or melanocytic nevi-specific, as it was observed in senescent human fibroblasts (Soliman et al., 2008). In these cells, ING1a associates with high levels of HDAC1 to trigger senescence. It is likely that ING1a is also a subunit of the RB/HDAC1 complex observed in senescent melanocytes since this protein is mostly found in HDAC1/2 complexes containing Sin3 and RB (Yang and Seto, 2008b). Together, these results suggest that appropriate levels of HATs and HDACs are needed for a sustained ability to proliferate under favorable environmental cues ((Fig. 2 and (Lehrmann et al., 2002; Bandyopadhyay and Medrano, 2003)).

HDAC1 levels are also critical for regulating apoptosis of melanoma cells. A small increase in HDAC1 levels prevents apoptosis mediated by the HDAC inhibitor (HDACi) sodium butyrate (NaBu) in a p53-dependent manner (Bandyopadhyay et al., 2004). Reinforcing the complexity of HDAC1 functions, it was recently found that its binding to Bach 1, a heme-associated transcription factor, represses p53-induced senescence mediated by oxidative stress (Dohi et al., 2008). Finally, recent evidence shows that the Class III histone deacetylase SIRT1 can negatively regulate HDAC1-dependent transcriptional repression (Binda et al., 2008). Recent data showed that SIRT1 is downregulated in senescent cells (Sasaki et al., 2006); thus, it can be hypothesized that absence of this sirtuin contributes to increase the repressor function of HDAC1 in senescent cells.

In other settings, HDAC1 and HDAC2 redundantly promote the differentiation of neural precursors to mature neurons (Montgomery et al., 2009). HDAC1 and HDAC2 also regulate oligodendrocyte differentiation and activation of myelin genes (Ye et al., 2009; Montgomery et al., 2009). In contrast, HDAC1 and HDAC2 appear to have opposite roles in memory formation, synaptic plasticity and neurotoxicity. Using an inducible p25 overexpression Alzheimer's mouse model, Tsai and colleagues have shown that p25/Cdk5 binds and inactivates HDAC1, inducing DNA damage and cell cycle alterations that precede neuronal death (Kim et al., 2008). The cell death phenotype caused by HDAC1 inactivation via p25 in primary neurons can be rescued by overexpression of HDAC1, indicating that replenishing HDAC1 may prove to be an effective therapy for some degenerative conditions (Kim et al., 2008). Overexpression of HDAC1 or HDAC2 does not impair brain development in transgenic mice. However, overexpression of HDAC2 does impair hippocampus-dependent memory, as well as spatial learning (Guan et al., 2009). In contrast to this data, a recent study using electrophysiological, immunocytochemical and optical methods demonstrated that HDAC2 is necessary for maintaining the excitatory drive of mature neurons without altering synapse numbers (Akhtar et al., 2009).

A better understanding of the differences in roles HDACs play in neuronal function may lie in their association with different co-regulators. HDAC2 can associate with CoREST, a key regulator of neuronal gene expression, but even at elevated levels HDAC1 does not associate with CoREST (Guan et al., 2009). Together the data reinforces the notion that HDAC1 and other member of the HDAC family play critical, but extremely complicated roles in neuronal function. Some HDAC activities are subtle and redundant whereas in other cases, the role is obvious and member-specific.

Epigenetic impairment of liver regeneration in old mice

The regenerative capacity of many tissues is reduced with aging. Aging significantly changes several biological processes in the liver leading to attenuated regenerative capacities, hepatic steatosis and alterations in gluconeogenesis. The liver is a unique tissue which is able to regenerate itself in response to injury and after surgical resections, therefore making it a powerful system to examine, at the molecular level, how aging affects tissue regeneration (Fausto et al., 2006; Michalopoulos, 2007). Liver regeneration after partial hepatectomy (PH) is an experimental system widely used to study the molecular mechanisms involved in liver

proliferation. In this procedure, 2/3 of the liver mass is removed by surgery. The remaining portion of the liver usually proliferates and restores the original mass in 15 days. It is important to note that the “regenerating liver” does not restore the architecture of the liver. Therefore, the more accurate term for this process is a compensatory growth of the liver. Nevertheless, we will use the term of liver regeneration since it was widely adopted in studies of liver proliferation after PH.

Use of genetically altered mouse models revealed that deletion or modifications of a single gene are not sufficient to stop liver regeneration, strongly suggesting that a large number of genes and signaling pathways are involved in this process (Michalopoulos, 2007; Timchenko, 2009). Many studies have shown that liver regeneration is significantly reduced with age ((reviewed in (Timchenko, 2009)). The livers of old mice fail to activate c-Myc, DNA polymerase α and FoxM1B to the levels observed in young mice (Timchenko, 2009). However, further studies revealed that alterations of cell cycle proteins in aging liver are very complex, and are associated with changes of several signal transduction pathways. Aged livers display altered transcription and translation, and histone PTMs involved in the epigenetic control of gene expression. Examination of protein-protein complexes in livers of old mice and rats showed that levels of the chromatin remodeling protein Brm increases with age and that such increase leads to the association of Brm in a complex containing E2F4, C/EBP α and RB (Conboy et al., 2005; Iakova et al., 2003). More recently it has been shown that the age-associated elevation of C/EBP α -Brm complex is mediated by hyperphosphorylation of C/EBP α at S193, and that this phosphorylation is required for the interactions of C/EBP α with Brm (Wang et al., 2006). In livers of old mice, the levels of cyclin D3 are increased due to protein stabilization. This increase leads to activation of cdk4 which is followed by phosphorylation of C/EBP α at S193 (Timchenko et al., 2006; Wang et al., 2006). Decline of GSK3 β levels with age stabilizes cyclin D3 in livers of old mice (Jin et al., 2009). In agreement with these findings, reduction of glycogen synthase kinase 3beta (GSK3 β) by specific inhibitors effectively induces a senescence phenotype in human liver-derived Chang cells (Seo et al., 2008).

The age-associated increase of the C/EBP α /Brm complex can be corrected by the use of growth hormone (Timchenko et al., 2006; Wang et al., 2007), or by a shared circulatory system (parabiosis) between old and young mice (Conboy et al., 2005). Recent studies have revealed critical roles of HDAC1 in the epigenetic attenuation of liver regeneration in old rodents. Examination of additional components of the C/EBP α -Brm complex revealed that it also contains HDAC1 and HP1 α . HDAC1 is responsible for deacetylating histone H3 on E2F-dependent promoters (Fig. 3a and (Wang et al., 2008a)). Interestingly, HDAC1 levels are increased by a translational mechanism in old mice; but no changes were detected in mRNA levels. Old livers contain abundant levels of the RNA binding protein CUGBP1 in a complex with the elongation factor 2 (eIF2). This translational complex binds to the 5' regions of several mRNAs, including HDAC1 mRNA, and an mRNA coding for another member of C/EBP family, C/EBP β , which results in increased translational activity (Fig. 3a). Consistent with the elevation of HDAC1 in old livers, recent studies by Kawakami et al show that acetylation of histone H3K9, an HDAC1 target, is decreased in livers of old mice (Kawakami et al., 2009). Together, these studies suggest that high levels of HDAC1 in the livers of old mice suppress gene expression via epigenetic silencing. It is important to note that the liver-specific overexpression of HDAC1 results in steatosis, a hallmark of liver aging (Wang et al., 2005). Since C/EBP β regulates expression of a number of adipose genes, we suggest that HDAC1-C/EBP β complexes are likely to be involved in the development of steatosis in livers of old mice (Fig. 3a). Taken together, these observations indicate that HDAC1 is one of the key proteins likely involved in inducing aging phenotypes in the liver via changes in the structure of chromatin.

Based on the above observations, it was surprising to find that HDAC1 is also elevated in proliferating livers from young mice after PH and in liver cancer (Wang et al., 2008b). In these setting, HDAC1 forms a repressive complex with C/EBP β leading to epigenetic silencing of C/EBP β targets including C/EBP α (Fig. 3b). Since C/EBP α is a strong inhibitor of liver proliferation (Timchenko, 2009), its repression by HDAC1-C/EBP β complexes promotes liver proliferation (Fig. 3b). Thus, the growth-promoting activity of HDAC1 in young livers is consistent with its elevation in several human cancers. However, its role as prognostic marker has been recently challenged (Weichert, 2009).

In summary, the above studies indicate that generalizing HDAC1 functions based only on its levels is risky because its targets are also defined by the proteins to which it associates in a cellular-environment and promoter-dependent context. In livers of old mice, HDAC1 forms two independent complexes, C/EBP α -Brm-Rb/HDAC1 and C/EBP β -HDAC1. The C/EBP α -Brm-HDAC1 complexes repress E2F-dependent promoters leading to epigenetic silencing of cell cycle genes in the liver. The HDAC1-C/EBP β complex occupies the promoter of the GSK3 β gene, inhibiting its expression and leading to alterations in GSK β -cyclin D3 pathways (Jin et al., 2009). In young proliferating livers, HDAC1 also forms complexes with C/EBP β ; however, in this context the C/EBP β -HDAC1 complex represses promoters of tumor suppressor genes (such as C/EBP α) and promotes liver proliferation. Although it remains to be established whether HDAC1 interacts with other transcription factors in livers of old mice, it is likely that its elevation diversifies its function allowing its association with different complexes. Future studies can elucidate a whole new range of alterations mediated by the elevation of HDAC1 in livers of old mice. It would also be important to determine which roles if any HDAC1 plays in liver cancer.

Conclusions

The entangled relationship between HATs and HDACs

Only a handful of studies have focused on the role of HDAC1 and other members of its class of histone deacetylases in senescence and aging. In contrast, there are hundreds of studies on HDAC1 function in cancer including the use of various HDACi in cancer cell lines and *in vivo*. A recent example is the use of a FDA-approved HDACi, Vorinostat, for the treatment of cutaneous T cell lymphomas. Ongoing clinical trials are testing other deacetylases inhibitors for the treatment of a variety of human cancers. Although many efforts are currently involved in the design of specific inhibitors that target a particular member of the HDAC family, it was recently shown that tumor cell death is only achievable when both HDAC1 and HDAC2 are deleted. In this scenario, the cells display nuclear bridging, nuclear fragmentation and mitotic catastrophe (Haberland et al., 2009). Together, these studies highlight the significance of chromatin remodeling in cancer biology (Reviewed in (Jones and Baylin, 2007)). It is important to mention, though, that emerging evidence suggests that HDACi could have some serious effects after prolonged use since HDACs are required for maintaining homeostasis of various tissues and organs. For example HDAC1 and HDAC2 control myocardial growth and contractility (Montgomery et al., 2007), angiogenesis, and possibly maintain a low p53 activity (via its deacetylation) to prevent growth arrest of proliferating tissues such as the skin and the gut.

Co-transcriptional regulators are normally tightly controlled in normal cells. In the last few years it was discovered that HDAC1 is differentially regulated by p300 and SIRT1; reciprocally, p300 is catalytically regulated by HDAC1. For example, acetylation of HDAC1 by p300 changes its corepressor function allowing HDAC1 to become the coactivator of the glucocorticoid receptor (Qiu et al., 2006). Although not yet demonstrated, acetylation of HDAC1 may also be required by other transcriptional regulatory pathways and/or alter its interaction with subunits of protein complexes (Qiu et al., 2006). SIRT1, a member of the class

III of HDACs that has been associated with dietary restriction, aging and cancer (For a recent review see (Finkel et al., 2009)), inhibits HDAC1 function by preventing the association of the mSIN3A/HDAC1 complex to the HDAC-dependent repression domain of RB (Binda et al., 2008). It would be interesting to determine whether such regulation also implies deacetylation of HDAC1 by Sirt1. In turn HDAC1 binds to the C/H3 domain of p300 and competes with binding of MyoD and p53 (Simone et al., 2004). Adding to the complexity of this interplay, HDAC1 can also homo-oligomerize under artificial overexpression (Taplick et al., 2001) but perhaps also when it is naturally overexpressed in senescent cells and tissues such as old livers. In these tissues HDAC1 is up-regulated via increased translation. More recent data suggested that HDAC1 may be also be transcriptionally regulated since CpG islands at the *HDAC1* locus show decreased methylation with aging (Christensen et al., 2009). The “dance of HAT and HDACs” offers multiple opportunities to the cells to regulate their functions in specific manners. We previously suggested that imbalance in the levels and/or activity of such players could result in unscheduled changes in the structure of chromatin leading to feed forward mechanisms of aberrant gene expression and aging ((Bandyopadhyay and Medrano, 2003; Richards and Medrano EE, 2009) and Fig. 2). We hope that new discoveries will help determine whether dysregulated acetylation and deacetylation activities may predispose to feed forward mechanisms leading to aging and perhaps predict some age-associated diseases.

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Figure 1. Human histone deacetylase align cladogram

Class I HDACs are underlined in red, Class II in green. HDAC11, which is underlined in yellow, is a class by itself since it has very little sequence homology with either Class I or class II.

“Homeostatic Chromatin” → young cells

Altered distribution/activity of chromatin remodelers → Aging

Figure 2. Imbalance of HATs/HDACs ratios lead to disruption of “chromatin homeostasis”
The model suggests that stability of HATs and HDACs activities is required for maintaining appropriate cell and tissue function.

Figure 3. The dual function of HDAC1 in young and old livers is regulated by its association with different protein complexes

The *in vitro* and *in vivo* results suggest a model whereby high levels of HDAC1, in association with chromatin remodelers and tissue-specific factors, promotes an ever changing chromatin structure leading to failure of growth-promoting gene activation and aging.