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The Effects of Rpd3 on Fly Metabolism, Health, and Longevity

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Abstract

The epigenetic regulation of DNA structure and function is essential for changes in gene expression involved in development, growth, and maintenance of cellular function. Epigenetic changes include histone modifications such as methylation, acetylation, ubiquitination, and phosphorylation. Histone deacetylase (HDAC) proteins have a major role in epigenetic regulation of chromatin structure. HDACs are enzymes that catalyze the removal of acetyl groups from lysine residues within histones, as well as a range of other proteins including transcriptional factors. HDACs are highly conserved proteins divided into two families and based on sequence similarity in four classes. Here we will discuss the roles of Rpd3 in physiology and longevity with emphasis on its role in flies. Rpd3, the *Drosophila* HDAC1 homologue, is a class I lysine deacetylase and a member of a large family of HDAC proteins. Rpd3 has multiple functions including control of proliferation, development, metabolism, and aging. Pharmacological and dietary HDAC inhibitors have been used as therapeutics in psychiatry, cancer, and neurology.

Keywords

HDAC; *rpd3*; *dSir2*; *Drosophila melanogaster*; dietary restriction; aging; longevity

1. Introduction

Epigenetic regulations of the chromatin include phosphorylation, acetylation, methylation, and ubiquitination. Histone acetylation occurs mostly at the amino-terminal tail of histones and is mediated by the histone/lysine acetyltransferase enzymes (HATs). Histone deacetylases (HDACs) are enzymes that remove acetyl groups. Deacetylation of histone tails leads to an increase in positive charge and increased affinity of a histone for DNA. This results in tight chromatin structure, which reduces transcriptional activity by preventing the

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binding of RNA polymerase and transcription factors to the chromatin. Furthermore, recent reports showed that acetylation affects stability and activity of metabolic enzymes (Zhao et al., 2010; Gut and Verdin, 2013). Such changes in enzymatic activity allow shifting from one metabolic pathway to another, which mediates adaptation to changes in metabolic requirements as well as nutrient availability (Zhao et al., 2010). Accordingly, changes in HDAC activity represent another way of regulating cellular metabolism. These data highlight the important and evolutionarily conserved roles of HDAC proteins as transcriptional regulators and regulators of metabolic enzyme function.

Members of Class I, Class II, and Class III HDACs have been implicated as key players affecting health and longevity in a variety of species. Genetic manipulations that decrease yeast and fly *rpd3* levels extend longevity (Kim et al., 1999; Rogina et al., 2002; Rogina and Helfand, 2004; Pallos et al., 2008; Cao et al., 2014; Kopp et al., 2015; Frankel et al., 2015). On the other hand, overexpression of *Sir2* genetically or pharmacologically in yeast, worm, fly, and mice extends healthspan and/or longevity (Kaeberlain et al., 1999; Imai et al., 2000; Tissenbaum and Guarente, 2001; Rogina and Helfand, 2004; Wood et al., 2004; Frankel et al., 2011; Whitaker et al., 2013, Banerjee et al., 2012; Kanfi et al., 2012). However, overexpression of Sir2 in yeast and flies did not affect longevity extension in some studies (Burnett et al., 2011). A recent study addressed the difference between these findings and demonstrated that the longevity effect in flies depends on the levels of *dSir2* overexpression (Whitaker et al., 2013). The maximal effect on fly longevity was observed when *dSir2* was overexpressed 2 to 5-fold. In contrast, high levels of *dSir2* overexpression decrease fly life span and can induce cellular toxicity, which most likely explains differences in findings (Griswold et al, 2008; Burnett et al., 2011; Whitaker et al., 2013). Additional evidence for the role of dSir2 in fly longevity has been provided by other labs (Banerjee et al., 2012; Hoffmann et al., 2013).

2. HDAC Families and Classes

There are 18 members of HDAC enzymes in vertebrates divided into the zinc-dependent HDAC family and the NAD^+-dependent Sir2 regulator family (Table 1). Based on sequence similarity HDACs are divided into four classes: the Class I Rpd3-like protein (HDAC1, 2, 3, and 8); the Class IIa Hda1-like proteins (HDAC4, 5, 7, and 9); the Class IIb (HDAC6 and 10); the Class III Sir2-like proteins (SIRT1, 2, 3, 4, 5, 6, and 7); and the Class IV protein (HDAC11). Classes I and II are referred to as “classical” HDACs. Class II HDACs were identified based on their sequence similarities to the Class I HDACs (Grozinger et al., 1999). Class I and Class II HDAC proteins share 86% amino acid sequence identity in mice and humans (Seto and Yoshida, 2014). The conserved N-terminus catalytic domain is present in both Class I and Class II. Due to high structural similarity, members of HDAC Classes I and II have partially overlapping roles. However, they have specific roles associated with their distinct isoforms. Their enzymatic activity can be inhibited by trichostatin A (TSA). The Silent information regulator 2 (Sir2) proteins, or Sirtuins, are members of a highly conserved family of the Class III histone deacetylases. Sirtuins are nicotinamide adenine dinucleotide (NAD^+)-dependent protein deacetylases or mono-ADP-ribosyltransferases (Haigis and Sinclair, 2010). Sirtuin protein structure is unrelated to Class I and II HDACs. Their activity can be inhibited by nicotinamide (NAM) but not by TSA. Class IV HDACs share sequence

similarity to both Class I and II HDACs (Seto and Yoshida, 2014). HDAC11 is currently the only known member of Class IV. It was identified based on sequence similarity to the Class I and II HDACs (Seto and Yoshida, 2014). HDAC11 has a role in protein stability of DNA replication factor CDT1 (Glozak and Seto, 2009). We will focus our review on the role of Class I HDACs.

3. The Class I HDACs

Rpd3 (Reduced Potassium Dependency-3) is a zinc-dependent histone deacetylase (HDAC) in yeast and *Drosophila* whose mammalian homologue is HDAC1. HDACs were initially named histone deacetylases (HDACs) because the first discovered target of deacetylation was the ε-amino group of lysine residues in histones (Inoue and Fujimoto, 1969). *Rpd3* was first cloned in *Saccharomyces cerevisiae*, and its gene product was determined to encode a 433-amino acid protein with a molecular weight of 48 kDa (Vidal and Gaber, 1991). In the same report, Vidal and Gaber showed that while Rpd3 can both activate and repress specific transcription of different genes, overall it seems to be more of a transcriptional repressor. However, a study in both yeast and *Drosophila* showed that *rpd3* mutation results in enhanced gene silencing at specific regions of the genome (De Rubertis et al., 1996). The discovery that Rpd3 is an orthologue of a mammalian HDAC came in 1996 when the HDAC1 protein was purified from nuclear fractions of bovine thymus (Taunton et al., 1996). The authors also showed that it contains histone deacetylase activity. Human HDAC2 was cloned and identified as a negative regulator of transcription (Yang et al., 1996). Human HDAC3 shares 63% identical amino acids with HDAC1 and HDAC2 and was cloned based on sequence similarities to HDAC1 and HDAC2 (Seto and Yoshida, 2014). HDAC1, HDAC2, and HDAC3 can each repress transcription by being recruited to DNA as co-repressors.

4. Class I HDAC complexes

Members of the Class I lysine deacetylase family are vital regulators of chromatin structure and gene expression. Rpd3 has been shown to function as part of multisubunit protein complexes to exert its regulatory effects since it does not contain a DNA-binding domain (Kasten et al., 1997). The multi-protein complexes consist of proteins required for DNA- and chromatin-binding and substrate specificity. Kasten et al. showed that Rpd3 co-purifies with Sin3, and that transcriptional repression by Sin3 was dependent on Rpd3 (1997). Interestingly, Sin3 is also known as Rpd1, because mutations of this gene in yeast also conferred a reduced dependency for potassium in yeast (Vidal et al., 1991). This overlap in phenotype provides further evidence for a complex containing Rpd3 and Sin3. Now it is known that two different Rpd3/Sin3 complexes form in yeast, known as Rpd3L and Rpd3S for large and a small, respectively (Yang and Seto, 2008). The Rpd3L complex is generally found to deacetylate histones at promoters, yet the Rpd3S complex targets transcribed regions of genes. The Rpd3/Sin3 complex does not bind DNA directly, but instead is targeted to specific genes via interactions with other DNA-binding proteins (Pile and Wassarman, 2000). This study in *Drosophila* salivary glands showed that this complex is associated with hypoacetylated regions of chromosomes, yet it is not associated with actively transcribed regions, where RNA polymerase II is located (Pile and Wassarman,

2000). The authors infer from their data that the Rpd3/Sin3 complex probably regulates 2 to 13% of genes in *Drosophila*, which is consistent with HDAC inhibition in mammalian tissue culture cells. A later study by this group shows that *Sin3*-deficient *Drosophila* cell lines had altered expression of 3% of genes (Pile et al., 2003). Of these genes, loss of Sin3 resulted in upregulation of genes involved in fatty-acid oxidation, the electron transport chain, and glycolysis. In addition, there was an increase in mitochondrial mass in these cells. Additionally, HDAC1/HDAC2 are part of the nucleosome remodeling and deacetylating (NuRD) complex and the corepressor for element-1-silencing transcriptional factor (CoREST) complex (Seto and Yoshida, 2014). Other HDAC1 complexes include the NODE complex, a HDAC1/HDAC2 complex present in embryonic stem cells, and the SHIP complex, which has a role in spermatogenesis (Seto and Yoshida, 2014).

5. Role of HDACs in metabolism and physiology

The Class I HDACs deacetylate a wide range of non-histone proteins including transcriptional factors, DNA repair proteins, signal transduction proteins, tumor suppressors, structural proteins, and steroid receptors. Use of high-resolution mass spectrometry revealed the presence of 3600 lysine acetylation sites on 1750 human proteins (Choudhary et al., 2009). Use of MS-275, a class I HDAC inhibitor, revealed a subset of these proteins as non-histone targets of HDAC1. Interestingly, HDAC1, HDAC2, and components of their complexes can also be deacetylated (Seto and Yoshida, 2014). Non-histone targets include transcription factors such as P53 and Stat3 (Yuan et al., 2005; Ito et al., 2002; Juan et al., 2000).

Gene expression profiles in yeast revealed that *rpd3* deletion result in a two-fold down-regulation of 264 genes and up-regulation of 170 genes (Bernstein et al., 2000). Flies treated with the HDAC inhibitor 4-phenylbutyrate (PBA) have increased or decreased levels of several hundred genes including genes involved in detoxification, translation, metabolism, and other cellular processes (Kang et al., 2002). Recent findings have implicated Class I and II HDACs as key regulators of intracellular signaling, metabolism, cell cycle control, cell differentiation, and tissue development (Mihaylova and Shaw, 2012). Both HDAC1 and HDAC2 are necessary for cardiac development and growth. Application of HDAC1 inhibitors in adults prevented mice from developing cardiac hypertrophy by suppressing autophagy (Cao et al., 2011). Additionally, the role of HDAC1 and HDAC2 in adipogenesis, muscle development, and autophagy has been revealed (Mihaylova and Shaw, 2012). Adult liver-specific HDAC3 knockout (KO) resulted in hepatic steatosis and increased expression of lipogenic enzymes (Feng et al., 2011). Binding of HDAC3 to lipogenic gene loci is diurnal and mediated by Rev-erbα, a nuclear receptor under circadian control. Further support for the role of HDAC3 in metabolic homeostasis was reported by Knutson et al. (2008). Embryonic liver-specific HDAC3 KO mice and whole body adult HDAC3 KO mice developed hepatomegaly. These mice have altered carbohydrate and lipid metabolism illustrated by reduced fasting blood glucose and increased levels of genes involved in lipid and fatty acid metabolism (Knutson et al., 2008). The authors hypothesize that such changes result from increased activity of PPARγ2, and supported their hypothesis by reversing some of the lipid accumulation with the PPARγ agonist GW9662 (Knutson et al., 2008). Liver-specific HDAC3 KO mice also have activated mammalian target of rapamycin complex I

(mTORC1) pathway, and treatment of mice with rapamycin reduced this liver phenotype. Class I HDACs have a key role in regulating activity of FoxO in muscle atrophy during catabolic conditions via acetylation (Beharry et al., 2014). Inhibition of class I HDACs by using MS-275 (class I HDAC inhibitor) *in vivo* prevents skeletal muscle atrophy during nutrient deprivation (Beharry et al., 2014).

HDAC1 and HDAC2 are required for normal central nervous development supported by findings showing that HDAC1 and HDAC2-knockout mice have major defects in central nervous system development and die young (Montgomery et al., 2009). HDAC1 deacetylates yeast AMPK β subunit Sip2 that leads to increased AMPK activation (Lu et al., 2011). A recent report showed that HDAC1 depletion in intestinal epithelial cells affects metabolism and responses to oxidative stress by AMPK activation (Gonneaud et al., 2015). Considering that AMPK has a central role in nutrient sensing and metabolism, this also highlights role of HDAC1 in regulating metabolism.

6. Effects of Rpd3 on longevity

Several groups have investigated the effects of Rpd3 and its relation to aging. Deletion of *rpd3* in *S. cerevisiae* results in an increased replicative life span (Kim et al., 1999). This study suggested that in yeast Rpd3 functions through its modifications of histones and changes in gene expression. Another study in yeast showed that *rpd3* deletion extended the yeast replicative life span, but there was not further increase in life span when these cells were placed on low-glucose medium (Jiang et al., 2002). More recently, a study in yeast has shown results suggesting that Rpd3 acts independently of DR through its ability to post-translationally modify proteins in the AMPK signaling pathway (Lu et al., 2011). In this study, yeast Rpd3 was shown to deacetylate Sip2, a β-regulatory subunit of Snf2, which is the yeast orthologue of mammalian AMPK. The increased acetylation of Sip2 by generation of lysine-to-glutamine mutants, which mimics hyperacetylation, or by deletion of *rpd3* resulted in an increased replicative life span. They also showed that *rpd3* deletion led to increased trehalose levels compared to wild-type yeast, and that hyperacetylated Sip2 mutants were more resistant to hydrogen peroxide, a form of oxidative stress. Both of these studies hypothesize that Rpd3 and DR may have common downstream effectors, but Lu et al. provide evidence that these longevity-extending alterations are in two different pathways (2011). They propose that both the nutrient-sensing Target of Rapamycin (TOR) pathway and AMPK converge on Sch9, the yeast homolog of mammalian Akt/S6K.

The first mutational analysis of *rpd3* in *Drosophila* was published in 1999, in which Mannervik and Levine showed that *rpd3* mutant strains had decreased levels of *rpd3* RNA expression and show strong defects in segmentation of the *Drosophila* embryo (Mannervik and Levine, 1999). They and the Grigliatti group showed that homozygous *rpd3* mutations were embryonic lethal in *Drosophila* (Mannervik and Levine, 1999; Mottus et al., 2000). Previously our lab has shown that 2 different strains of heterozygous *rpd3*-mutant fruit flies had an extended life span compared to their genetic controls (Rogina et al., 2002). Interestingly, the life span of these mutants was not further increased by placing them on food with half of normal caloric content, suggesting that the mechanism of life span extension in *rpd3*-mutant flies may overlap with the mechanism of extension seen in DR.

dSir2 has been implicated in mediating the response to DR in yeast, worms, flies, and mice (Rogina and Helfand, 2004; Chen et al., 2005; Parashar and Rogina, 2009; Haigis and Sinclair, 2010). Our lab expanded on these results with further analysis of the interactions in *rpd3* and *dSir2* in aging *Drosophila* (Rogina and Helfand, 2004). Flies who were generated with mutations in *rpd3* and *dSir2* had a median life span less than control flies, while *rpd3* mutants alone lived longer. These results suggested that *dSir2* may be a downstream mediator of *rpd3*'s effects on longevity.

A recent study confirms that reduction of *rpd3* extends fly longevity. Using a *UAS-rpd3-dsRNAi* transgene and different drivers it was shown that strong whole body *rpd3*-reduction is lethal, consistent with previous findings of lethality associated with *rpd3*−/− mutation (Kopp et al., 2015). However, use of a weaker *actGAL4* driver resulted in 60% reduction of *rpd3* mRNA and extended fly longevity. Additionally, specific *rpd3* downregulation in fly heart tissue extends fly longevity and increases fly resistance to oxidation, starvation, and heat (Kopp et al., 2015). Consistently, increased resistance to stress is associated with longer life in many other long-lived flies, such as *mth* and *Indy* mutants (Lin et al., 1998; Rogers and Rogina, 2014).

This tissue-specific *rpd3* reduction was also associated with enhanced cardiac function illustrated with increased heart rate, decreased heart failure, and accelerated heart recovery. Heart-specific *rpd3* reduction increases expression of *foxo*, *Thor,* and *sod2* genes, as well *dSir2*, in RNA isolated from the whole body of two days old flies. Consistently, heart-specific *rpd3* overexpression reduces heart function and fly resistance to stress. The beneficial effect of *rpd3* reduction was shown previously in another study. Heterozygous *rpd3* reduction in the whole body provides neuroprotection and increases the survival of *Drosophila* in a model of Huntington disease (Pallos et al., 2008).

Recent work from our lab further examined relations between DR and *rpd3*- mediated longevity effects. When longevity studies were done on diets with varying caloric content, *rpd3*-mediated longevity was additive with extension mediated by some diet levels, suggesting that the interplay between Rpd3 and DR is more complex then previously thought (Frankel et al., 2015). We also showed potential interaction between *rpd3*-mediated longevity and the protein synthesis regulator 4E-BP, based on a reduction of longevity effects in flies mutant for both *rpd3* and *4E-BP* compared to the longevity of flies only mutant for *rpd3*. 4E-BP is a downstream effector of the TOR signaling pathway that negatively regulates translation (Katewa and Kapahi, 2011). While heart-specific *rpd3* reduction increases the levels of *4E-BP* mRNA in the whole body of 2 days old flies, we found that flies carrying *rpd3* mutations have decreased levels of *4E-BP* mRNA in the heads and thoraces at 20 and 40 days of age (Frankel et al., 2015). Therefore, it is most likely that there are complex interactions between Rpd3, 4E-BP, and DR (Frankel et al., 2015).

The effect of *rpd3* reduction on longevity has been also confirmed with drugs that reduce Rpd3 activity. Pharmacological inhibitors that reduce the activity of Rpd3, such as 4-phenylbutyrate (PBA), sodium butyrate (NaBu), trichostatin A (TSA), or suberoyanilide hydroxamic acid (SAHA) extend fly longevity (Kang et al., 2002; Zhao et al., 2005; McDonald et al., 2013). Treatment with PBA extends fly longevity when applied early or

late in life span. This longevity extension does not affect fly locomotor activity or fecundity (McDonald et al., 2013).

7. Inhibitors of HDAC I in diseases

Pharmacological inhibition of HDACs is possible through multiple compounds, and the clinical effectiveness of these compounds has been shown for a variety of disorders. Defects in the neuronal epigenome have been associated with developmental disorders such as autism and cognitive disorders. Valproic acid, sold under the brand name Depakote, is a drug that is approved for treatment of epileptic seizures (Kostrouchova et al., 2007). Valproic acid, which is an inhibitor of Class I and Class II HDACs, is also thought to be important for its potential to treat malignancies (Gurvich et al., 2004). Suberoylanilide hydroxamic acid (SAHA), also known as Vorinostat or Zolinza, is another Class I and II HDAC inhibitor that was approved by the FDA for treatment of cutaneous T-cell lymphoma in 2006 (Marks and Breslow, 2007). Use of HDAC inhibitors in cancer treatment is based on HDAC induction of the cell cycle regulator p21 in cancer cells. Epigenetics and genetic regulation are very important in the initiation and metastasis of cancer. Thus HDAC inhibitors may be able to play a role in prevention or treatment of cancers (Drummond et al., 2005).

Histone deacetylation regulates transcription of the genes involved in learning and memory processes. Age-associated changes in enzymes responsible for acetylation status of the chromatin have been recently associated with loss of processes involved in cognitive function, such as neuronal memory, learning neuronal regeneration, and synaptic plasticity (Ganal et al., 2015). The reduction in HAT activity that occurs with age results in reduced acetylation, which prompted investigation in the use of HDAC inhibitors for delaying cognitive decline. As a result, there is an emerging role of HDAC inhibitors for possibly enhancing memory and learning processes. HDAC inhibition may be a future tool for ameliorating symptoms related to neurodegenerative disorders (Ganal et al., 2015). Inhibition of histone deacetylation with NaBu, TSA, or SAHA improved mice performance in several memory tests (Fontan-Lozano et al., 2008; Fischer et al., 2007). Systemic administration of HDAC inhibitors reversed learning and consolidation deficits in mice models of neurodegeneration and aging. The biology of HDACs and their inhibitors will continue to be an important topic of research due to the potential to treat a variety of disorders including Alzheimer’s disease, cancer, and cardiovascular disorders (Kazantsev and Thompson, 2008; Zhao et al., 2012).

8. Summary

HDACs are a highly conserved family of proteins that have been implicated in regulating diverse aspects of physiology including metabolism, stress response, cell survival, and replicative senescence. The findings reviewed here prove the importance of studying HDACs as they are able to modify health and life span of many organisms, and they are targetable by numerous drugs and compounds. Of particular importance is HDAC1, which has been implicated in metabolism, various diseases, and longevity. Understanding the biology of HDACs and their role in aging could hold the key to increasing the number of healthy years we as humans are able to live.

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Abbreviations

HDACs	Histone deacetylases
HATs	histone acetyltransferases
SIR2	*Silent Information Regulator 2*

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Highlights

HDACs are key epigenetic regulators of chromatin structure.

HDAC1 affect metabolism via acetylation.

Rpd3 reduction extends fly and worm life span.

Table 1

Classification of histone deacetylases.

Family	Class	Subclass	*C. cerevisiae*	Human
HDACs	Class I		Rpd3	HDAC 1–3, 8
	Class II	a	Hda 1	HDAC 4, 5, 7, 9
	Class II	b	Hda 1	HDAC 6, 10
	Class IV			HDAC11
Sirt2	Class III		Sir2, Hst1, 2, 3, 5,	SIRT 1–7

HDACs: Histone deacetylases

Sir2: Silent information regulator-2

Hda1: Histone deacetylase-A 1

Rpd3: Reduced potassium dependency 3