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Structure and Functions of an Important Enzyme: Histone Acetylation Transferases (HATs)

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Abstract

Inaccessibility to the features essential to DNA duplication, re-amalgamation, restoration, and gene transcription is due to the organization of the eukaryotic genome into greatly compressed chromatin. In order to prevail over this despotic obstacle levied by the chromatin, intricate mechanisms have advanced in eukaryotes. 146 base pairs of DNA are enveloped around four core histones (H3, H4, H2A, H2B) which make up the nucleosome. Several distinct classes of enzyme can modify histones at multiple sites. Histones undergo a number of post-translational modifications, such as methylation and acetylation, which control transcription and gene expression. The enzymes responsible for adding or removing these epigenetic marks are often referred to as "writers" and "erasers", respectively. In histone methylation, histone methyltransferases add the methyl mark and histone demethylases remove the methylation; while in acetylating histones, histone acetyltransferases catalyze the addition of acetyl groups and histone deacetylases remove the acetylation mark. The workhorses of the epigenome are the histone acetyltransferases (HATS). In epigenetic control of gene manifestation, HATS play a key part. In this review, histone acetylation transferases (HATs) function and structure will be discussed.

Keywords: Histone acetylation transferases (HATs); Post-translational modifications: epigenetic marks

Categorization of HATs

Generally, a three-stranded β-sheet which is ensued by a long α-helix parallel to and spanning one side, is what typifies the structurally preserved central area of HATs (Figure 1) [1]. Opposite sides of N- and C- terminal α/β segments that are structurally exclusive to a given HAT family encompass the central area complying with motifs A, B, and D of the GNAT proteins. Histone substrates can bind preceding catalysis where the center and the contiguous parts together form a cleft over the former. While acetyl-CoA binding and catalysis involves the central core domain (motif A in GNATs), binding of histone substrates is assisted by the N- and C-terminal segments [2]. For dissimilar HAT families, exclusive facets linked to the structure and/or arrangement of the N- and C- terminal regions may assist in elucidating some pragmatic dissimilarities amid HATs in histone substrate category. Broadening of the histone binding groove in the central core has been witnessed through CoA binding. This has been done by moving the C-terminal segment of Gcn5 outward. Furthermore, it is probable that CoA binding paves way for histone binding *in vivo* as interactions between CoA and protein enable the creation of satisfactory histone-protein interactions (Figure 2) [3,4]. Based on the subcellular localization of HATs two categories have been designed. Type A are situated inside the nucleus and are acetylate of histones in chromatin (Figure 1). The other group are located in the cytoplasm and acetylate newly translated histones to enable assemblage into nucleosomes [5]. In terms of structure and function, HATs can be grouped based on their catalytic domains. Five families have been created for some known HATs in humans which amount to around 30. The first group is termed Gcn5-related N-acetyltransferases (GNATs). This is due to of their resemblance to the Gnc5 enzyme. The HAT domain of GNATs have four conserved motifs and unusually also have chromodomain or bromodomain for binding methylated or

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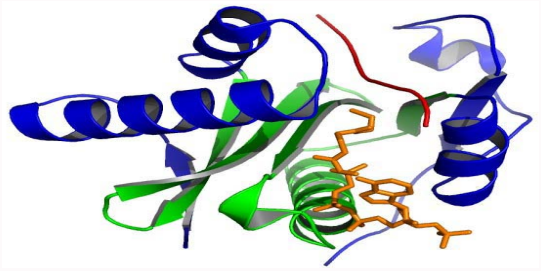

Figure 1: Crystal structure of Tetrahymena Gcn5 with bound coenzyme A and histone H3 peptide. The central core, flanking N- and C-terminal segments, coenzyme A, and histone peptide are shown.

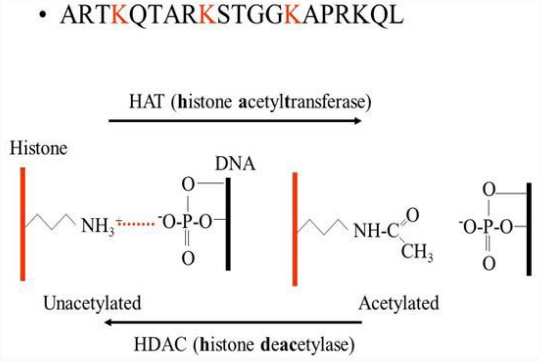

Figure 2: Acetylation of the N-terminal sequence of Histone H3 (Transcription Control in Eukaryotes by David Hood).

acetylated lysine respectively [6]. Gcn5-related N-acetyltransferases are implicated in growth of cells. Ybf2, MOZ, Sas2 and Tip60 are the founding members of MYST HATs after which the name is coined. What defined the MYST HATs is the incidence of MYST domain comprising a zinc finger and an acetyl-CoA binding motif [7]. They have other domains for recognizing other proteins and are part of cell growth and survival and the control of transcription. Much smaller are the other three families which are the steroid receptor co-activators (SRC)/nuclear receptor co-activators (NCoA) family; the general transcription factor HATs, categorized by the existence of the TAF250 domain; and the p300/CBP HATs [8].

Structure, Reactivity and Functions

In histone, lysine residues are usually catalyzed by the HATs at the alpha-amino side chain through transferring an acetyl group from a cofactor, acetyl CoA (Figure 3). This important Post translational modification that occurs at the N-terminal end of histones is considered as a crucial step for the gene transcription initiation (Figure 2) [7]. These acetyltransferases are coupled with complexes comprising of numerous proteins which in turn contains necessary transcriptional coactivators. HATs are categorized into two broad types named as Type A and Type B. Type A HATs encompass GNAT, CBP 300 and MYST families as a further subdivision. The former category i.e. Type 1 has a role in modifying nucleosome associated proteins after translation and is mainly found inside a nucleus. However, the latter category, Type B is present in outside the nuclear region and acetylates the free histones, freshly constructed molecules before incorporating into the chromatin [7].

Different biological effects are expressed when different residues of Lys are acetylated or deacetylated. H4 Lys5, 8 and 12 acetylation for example, are intricate in nucleosome assembly while H4 Lys16 acetylation is intricate in transcription but does not affect nucleosome [9]. Genome stability and DNA repair are promoted through histone H4 Lys56 acetylation as recent demonstrations in yeast cells have shown. Apart from histones, Lys acetylation can also modify other proteins. Signaling proteins, metabolic enzymes, cytoskeleton proteins, and transcription factors are some of the proteins which can be acetylated [10]. There is inadequate information on the enzymes which acetylate non-nuclear proteins. Nevertheless, it is known that transcription factors are substrates of HATs. As scientific research in post translational modifications surges, especially in the field of acetylation, the number of proteins controlled by acetylation is expected to increase and possibly discovery of new proteins controlled by acetylation is expected to increase and possibly discovery of new proteins. Protein-protein interaction can be affected by non-histone protein acetylation. In addition, non-histone protein acetylation can increase protein stability by suppressing ubiquitination and regulate enzymatic activity [11].

Histone tails interaction with the nucleic acids and protein are usually affected when the acetyl groups transferred to the lysine residue neutralizes its positive charge. Usually bromodomain of acetyl groups provides the active and binding site for various proteins [12]. However, sometimes the entire opposite or reverse functional consequences result as the substrate modification may not compete indirectly, for instance at H3-K9. Histones' acetylation status is basically determined by the two classes of protein i.e. HATs and HDACs [13,14]. Recent studies have revealed that HATs acetylation ability is not only confined to the histone proteins but can acetylate a number of other important proteins like p53 and transcriptional factors. In fact, more importantly it is necessary to presume the lysine acetylation as a wide spread phenomena unlike realized inversely in the past as HATs do not exclusively produce their effects via histones modification only [15]. HATs families have been observed to have a very crucial role in the growing number of transcriptional factors. GNAT, MYST and p300/CBP which are the principle groups of HAT are the part of multiprotein complexes that are employed to definite promoters through DNA coupled transcription factors [16].

By loosening up the chromatin structure on histone acetylation and mobilizing other proteins through acetyl Lys, correlation between acetylation of histones and transcription activation can be clarified. Some elements of the core histone octamers comprising two copies each of histone H2A, H2B, H3, and H4 in eukaryotic cells is wrapped by the chromosomal DNA [17]. The association is termed nucleosome. The nucleosome can pack into a very compressed structure which is shown to suppress transcription while relaxed structure favours transcription activation. Lys and Arg residues concentrate at the N-terminal tails of histones where post translational modifications affect the compressed and relaxed forms of the nucleosome [18]. Nevertheless, upon critical analysis, covering the positive charges on the histone as a result of lysine acetylation is likely to reduce the association with the negatively charged DNA thereby relaxing the chromatin structure [19]. More so, proteins with bromodomains can recognize acetylated Lys and in the process aid in the recruitment of other proteins which may help in the activation of gene transcription.

Disturbance in HAT functionality can be witnessed in numerous types of ailments. For instance, a developmental disorder known as (RTS) Rubenstein Taybi Syndrome is characterized with the abolish HAT activity due to the mutation in the CBP. Such

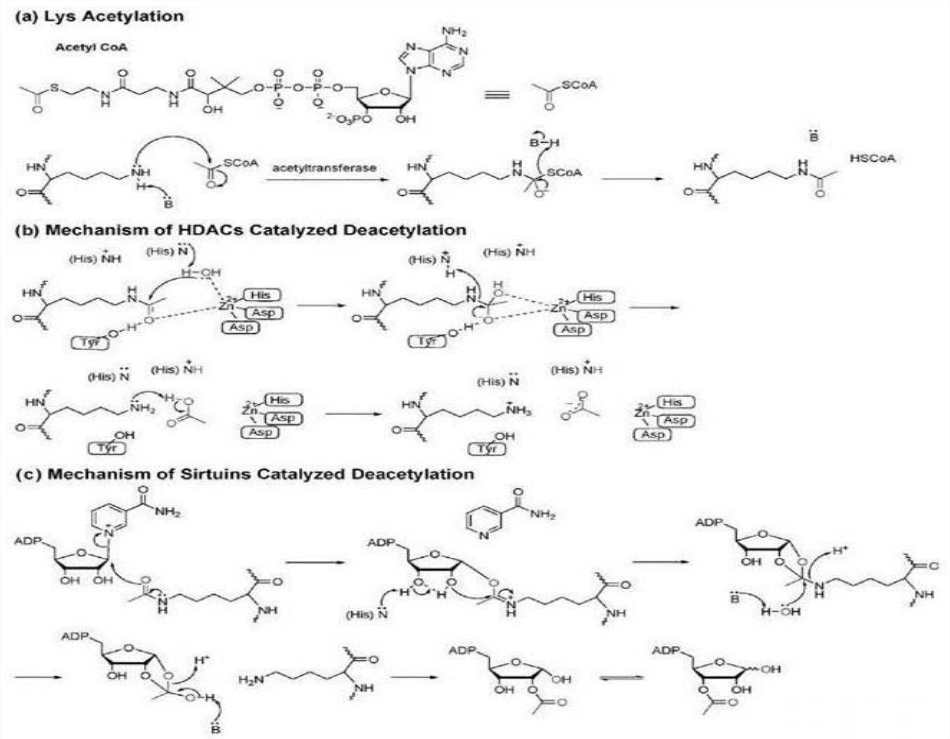

Figure 3: (a): Lys acetylation catalyzed by acetyltransferases; (b): mechanism of Zn-dependent HDACs-catalyzed deacetylation; (c): mechanism of sirtuins-catalyzed deacetylation. (Hening Lin et al, Post-Translational Modifications to Regulate Protein Function).

individuals are very prone to develop a type of childhood cancer with neural crest origin having increased risk of 350 fold [20]. A hematological malignancy has been eventually resulted in a mouse knockout model for heterozygous CBP that has originally RTS like phenotype. However, in these types of malignancies, the second allele is somatically mutated. Studies have witnessed no germline mutations in p300 protein however, in some cancers like gastric and colorectal, missense mutations in p300 frequently result in deletion of second allele. Moreover, the critical role of p300 and CBP as a tumor suppressors have been experimentally proved when the blastocysts injected with embryonic stem cells knockout for p300 resulted in histiocytic sarcomas originated from null cells in chimeric mice [21].

MOZ, MORF, CBP and p300 which are HATs, are seldom part of fusion of proteins that develop from chromosomal translocations related to leukemia or secondary to myelodysplastic syndrome management. Abnormal acetylation and gene activation may be a result of a leukemogenic effect that may be due to misdirection of HATs. Furthermore, fusion proteins give the impression that they represent gain of function mutants [2].

In the MLL–CBP fusion for instance, prospective aims for acetylation are the *Hoxa7* and *Hoxa9* genes. It is essential to note that MLL–CBP fusion lacks the SET domain of MLL necessary for its H3-K4 HMT activity; *Hoxa* genes are requisite for transformation of myeloid through unsuitable myeloid progenitors self-renewal that cannot critically discriminate. Oncoprotein which is the MLL synthesis abnormally preserves the manifestation of these *Hoxa* genes [1]. Adding to the Lys side chains, acetylation can also be done to the N-terminal. N-terminal methionine peptidase and the released N-terminal amino acid slices Met, the first residue in eukaryotic cells, and then Met is acetylated. Although genes that play a part in the change has phenotypes, the exact role of this alteration is still not clear in most cases [22]. Most of the enzymes which reverse acetylation called deacetylases, are enzymes that use Zn^{2+} in the active spot to stimulate water molecules to hydrolyze the amide bond (Figure 3) [23]. Sirtuins or nicotinamide adenine dinucleotide (NAD)-dependent enzymes have been discovered as another group of deacetylases [24]. The ability of this enzyme to pair deacetylation of Lys to degradation of NAD indicates that the enzyme can detect the cell's metabolic state and utilize that signal to control the acetylation and consequently the substrate proteins' function. Researchers at Wistar institute first described Rtt109, a yeast HAT that forms the comprehensive atomic structure, and one of its related proteins. Professor Wistar suggests that to form a ring binary duplicates of Rtt109 bind to binary duplicates of a chaperone protein. The research team discovered that much like a halo the ring fits on a histone, and by influencing the exact position of acetylation the type of chaperone prescribes precisely how the enzyme affects the histone [16]. An acetyl group with a small chemical structure is added to a lysine—one of the amino acids that make up a particular protein through acetylation (Figure 4, shown in red). According to researchers, any three specific lysines on histones are acetylated by Rtt109. The chaperone which escorts Rtt109 into place decides precisely which of the histone lysines are altered. The "behavior" of a histone can be greatly affected by altering a particular lysine in a single part of the structure such as exposing a certain set of genes to be read. This is because histones are such critical DNA-associated proteins [25]. Demonstrations have shown that Asf1, which is a chaperone that associates with Rtt109, enables the Rtt109 to alter lysines in dissimilar location on a particular histone. This produces a dissimilar outcome with reference to histone interaction with DNA. Consequently, this changes the cell's biological characteristics. The Wistar researchers are the first to show that in order to form a ring binary Vps75 chaperones pair up with binary Rtt109 enzymes. The laboratory created crystals of the

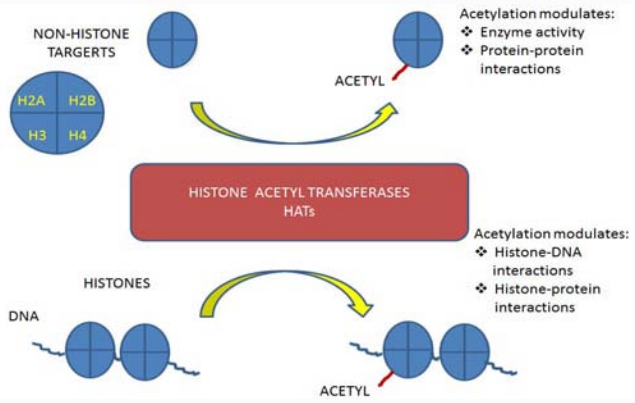

Figure 4: Schematic representation of Histone Acetyl Transferases (HATs) reactions.

protein complex and by analyzing the patterns formed when X-rays bounce off the crystals was able to see the structure of the complex. X-ray crystallography was the technique used in this process.

With the assistance of the Argonne National Laboratory's Advanced Photon Source the team was able to regulate protein complex structure. Using a potent X-ray at a resolution of 2.8 angstroms (2.8 billionths of a meter), this is smaller than the distance between individual rings on the DNA ladder [15].

Possible Research Areas and Limitations

Current structural and enzymatic researches have paved the way for a remarkable understanding of the HATs molecular mechanisms. In vitro studies of this nature made use of truncated proteins because of their accessibility and easy manipulation for biochemical and structural research works [26].

Nevertheless, information gathered from current literature about in vitro studies on the complexity of the recognition of nucleosome plus intricate control mechanism of HAT activity directs to the point that it's only the beginning of a journey towards comprehension of the interesting range of mechanisms regulating HAT activity [27]. Further investigations need to be conducted to advance our current knowledge base on protein substrate selection and alternate acyl-CoA substrates by shuttling HATs between different protein complexes. Histone acetyltransferases (HATs) are vital in epigenetic studies which observe inherited adjustments in gene expression not due to changes in DNA sequence [28]. Although not fully explored, in cancer outset and progression, chromatin epigenetic alterations have been demonstrated to play a major role. Since acetylation and methylation have fundamental functions in the epigenetic regulation of gene expression they are most studied chromatin marks. Modification of histones epigenetically is a reversible process. Histone acetyltransferases (HATs) are the enzymes responsible for the introduction of acetyl groups on histones. Notwithstanding histone methyltransferases (HMTs) and DNA methyltransferases (DNMTs) can facilitate the addition of methyl groups on both histones and DNA [29]. Histone demethylases (HDMs) and histone deacetylases (HDACs) enzymatically catalyze the deletion of methyl and acetyl groups respectively. In turn, on particular protein domains such as bromodomain and malignant brain tumor (MBT) epigenetic marks can be recognized by and bound to them. In the control of gene expression epigenetically these complexes are vital intermediates [30]. Recently, changes or mutations in genes orchestrating histone modifications, DNA methylation or nucleosomal setting in an assortment of malignancies have been reported. This provides further support to the theory that alterations of an epigenetic nature supplement oncogenesis but their detailed mechanism ought to be further explored. Much is not known concerning the degree of disruption of an epigenetic nature due to extensive malnourishment in women with anorexia nervosa. This means that in order to determine the degree of association between anorexia nervosa and particular epigenetic adjustments, massive genome-wide studies of epigenetic modifications are necessary. This includes both DNA methylation and other epigenetic marks capable of being altered through relevant prescriptions that enhance nutrition [31,32]. Regarding drug addiction, investigations in animals have established that constant exposure to drugs changes gene expression in the brain and produces long-term alteration in neural networks that serve as the basis for compulsive drug abuse. There is also mounting evidence for a role of epigenetic changes in interceding in the addictive potential of various drugs commonly abused such as alcohol, amphetamine, and cocaine. For instance, evidence is available for brain-derived neurotrophic factor (*BDNF*) gene expression following chronic cocaine exposure controlled by epigenetic mechanisms [33]. Novel, efficacious treatments for drug craving and relapse may result from identification of epigenetic signatures that define psychostimulant addiction.

In the control of gene function, reversibility activity of histone acetylation and deacetylation at the N-terminus of histone tails have a significant function. In transcriptional activation hyper-acetylation of histones is implicated as they relax chromatin structure. On the other hand, gene repression and chromatin compaction are induced by hypo-acetylation of histones. Histone acetylation is mediated by histone acetyltransferases (HATs) whereas deacetylation is mediated by histone deacetylases (HDACs). Current data exposes the important roles that plant HATs and HDACs play in control of gene expression in plant growth and responses to environmental strains[34]. More so, HATs and HDACs interacted with transcription aspects and various chromatin-remodeling aspects involved in transcriptional control of several progressive courses. However, this area is not fully investigated. Thus much research is needed in animal cell models and its possible benefits in clinical use. Furthermore, less is known about other substrates of HATs. HATs may be screen against other proteins for possible interaction and studies [35]. Further studies in these areas through in vitro studies and gene knockouts need to be done to elucidate the potential roles of these enzymes in development, although these analyses are likely to be complicated because these HATs potentially have many substrates.

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