Review

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Can changes in histone acetylation contribute to memory formation?

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Neuronal histone acetylation has been postulated to be a mnemonic substrate and a target for memory enhancers and neuropsychiatric drugs. Here we critically evaluate this view and examine the apparent conflict between the proposed instructive role for histone acetylation in memory-related transcription and the insights derived from genomic and genetic studies in other systems. We next discuss the suitability of activity-dependent neuronal histone acetylation as a mnemonic substrate and debate alternative interpretations of current evidence. We believe that further progress in our understanding of the role of histone acetylation and other epigenetic modifications in neuronal plasticity, memory, and neuropsychiatric disorders requires a clear discrimination between cause and effect so that novel epigenetics-related processes can be distinguished from classical transcriptional mechanisms.

Histone acetylation and information storage

The N-terminal tails of histone proteins (see Glossary), around which DNA is wrapped to form nucleosomes, have long been known to be substrates for numerous and diverse post-translational modifications (PTMs). Nearly 15 years ago, Allis and Strahl proposed that the distinct combinations of PTMs could act as instructive cues for transcription in what is now known as the 'histone-code' hypothesis [1]. According to this hotly debated hypothesis (Box 1), histone PTMs represent a natural substrate for cellular memory by locking genes in different transcriptional states.

More recently, this hypothesis has been extended to neuroscience, where it has been suggested that the formation of long-term memory, which requires the activation of tightly regulated transcriptional programs by learning [2], may be driven in part by histone PTMs and other epigenetic mechanisms [3–7]. In particular, recent studies have hypothesized that activity-dependent changes in the acetylation of specific lysine (K) residues (Box 2) in neuronal histones could drive or facilitate changes in the expression of neuroplasticity genes associated with memory formation and so contribute, in a combinatorial manner, to encoding information about the past history of activation of the neuron. This view is based on three independent lines of evidence.

(i) Genetic evidence indicates that mutations in histone-modifying enzymes, including activities that regulate the acetylation of histone tails, impact cognition. Thus, reduction in K acetyltransferase (KAT) activity is associated with memory impairment in mice and intellectual disability in humans, whereas reduced levels of some histone deacetylases (HDACs) have been associated with memory enhancement (see [8,9] for recent and comprehensive reviews of this evidence).

Glossary

Acetylation (of K residues):: a highly dynamic reaction regulated by the opposing enzymatic activities of KAT and KDAC domains. In the case of the histone tails, the addition of an acetyl group to K residues neutralizes their basic charge and is thought to weaken the interaction between histones and DNA and cause a relaxation of the chromatin that is compatible with transcription.

Epigenetics:: here we use the term 'epigenetic' to refer to processes that affect chromatin function independently of DNA sequence regardless of the heritability of the process. Because we focus on neurons and these are non-dividing cells, the question of whether histone PTMs can be transmitted from mother to daughter cells is not considered in the definition. It is the potential of these marks to perpetuate over time and lead to distinct gene states that is relevant in this context. See also Transcriptional.

Histone deacetylase (HDAC):: an enzyme that removes acetyl groups from an ε-N-acetyl K amino acid residue. Despite their name, HDACs show little substrate specificity and have very numerous non-histone substrates. Here we refer to these proteins as HDACs, but use the abbreviation KDAC when referring specifically to their enzymatic activity.

Histone deacetylase inhibitors (HDACis):: compounds that interfere with the function of HDACs. These compounds were first identified as promising antitumor drugs because they interfere with cell division and arrest tumor cells in G1 [21,80]. Comparatively, we know much less about their mechanism of action in neural tissue, although their therapeutic potential in numerous neuropsychiatric disorders has been clearly established [10].

Histones:: a group of five small, basic proteins that form molecular complexes with genomic DNA. Histones H2A, H2B, H3, and H4 constitute the protein core of nucleosomes and are known as nucleosome histones, while histone H1 is involved in the packaging of nucleosomes into higher-order structures and is referred to as linker histone.

Lysine (K) acetyltransferases (KATs):: enzymes that add acetyl groups to K amino acid residues. These proteins were previously known as histone acetyltransferases (HATs) to denote that they have histone proteins as prominent targets. Given that these enzymes have many non-histone substrates, the K terminology was recently adopted by the field [81]. Here we also use KAT to denote the enzymatic activity of KAT proteins.

Lysine (K) deacetylase (KDAC):: the enzymatic activity of HDAC enzymes.

Memory:: retention over time of experience-dependent internal representations [82].

Nucleosome:: the basic structural unit of eukaryotic chromatin. In each nucleosome, approximately 150 bp of DNA is wrapped around a basic-protein core comprising two copies of histones H2A, H2B, H3, and H4.

Transcriptional:: referring to the process of transcription; that is, the production of RNA molecules using DNA as a template with resulting transfer of genetic information. Transcriptional mechanisms are totally dependent on DNA sequence. Although it is not uncommon to find the terms 'transcriptional' and 'epigenetic' indistinctly intermingled to describe regulatory mechanisms of gene expression, they have classically qualified different types of process. See also Epigenetic.

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Box 1. The histone-code debate

The histone-code hypothesis proposed that 'multiple histone modifications, acting in a combinatorial or sequential fashion ... specify unique downstream functions' [1]. More than 100 distinct histone PTMs have been identified to date and the number is still increasing [83,84]. If each possible modification was independent and had a specific meaning, the combinatorial potential would be enormous and could define millions of different gene states. Although the appeal of this view was immediate, the hypothesis has been hotly debated since its inception. One of the most controversial issues is the use of the word 'code'. A code is supposed to be the central component of a semiotic system that links a collection of signs (in our case, the various histone PTMs) to their meanings (transcriptional output). According to this semiotic definition, a code must be arbitrary and the signs must be independent of the meanings or outcomes [29,85]. Based on these criteria, some histone PTMs should be excluded from the concept of 'code' because the biophysical properties of these signs are not neutral to their meaning (e.g., the cancelation of positive charges by acetylation and the link to open chromatin). Another argument used by the detractors of the histone-code concept is the interdependency between histone PTMs. These modifications influence one another in defined and predictable manners, ranking from overlapping to mutually exclusive, but these interactions may rely on chemistry and steric effects more than defining a code. A third argument is the large redundancy in histone marks. Genome-wide mapping of histone PTMs has invariably shown that they occur in groups of multiples of highly correlated modifications, demonstrating that the combinatorial potential originally postulated in the histone-code hypothesis is apparently not used *in vivo* [86]. Because of these and other arguments, some scientists have considered that the term 'code' should be replaced by the less rigorous term 'language' [87,88], whereas others directly call for abandonment of the histone-code framework [70]. Importantly, this is not just a semantic debate; the underlying question refers to the capability of individual histone PTMs and their combinations to convey differential information relevant to function. Regardless of this debate, the coding metaphor has been valuable in promoting discussion and driving new experiments [29,87].

(ii) Pharmacological evidence, mainly arising from studies using HDAC inhibitors (HDACis), demonstrates that increased histone acetylation is associated with beneficial effects in diverse models of cognitive disorders and enhanced memory in wild type animals (see [10,11] for extensive reviews).

(iii) Correlative evidence indicates that neuronal histone acetylation is modulated by experiences such as learning or recall. Furthermore, different conditions in which cognitive abilities are diminished, such as Alzheimer's disease, Huntington's disease, or aging, are associated with neuronal histone hypoacetylation. We again refer the reader to [8,9] for detailed discussions of this line of evidence.

Together, these three lines of evidence make a strong case supporting a key role for histone acetylation in neuroplasticity, mnemonic processes, and the etiology of some brain disorders. However, we feel that there are three matters of debate concerning this attractive hypothesis: (i) the existence of alternative interpretations for the available experimental evidence; (ii) the apparent conflict between the postulated instructive role for histone acetylation marks in memory-related transcription and the insight derived from genomic and genetic studies exploring the role of histone acetylation in transcription in yeast and invertebrates; and (iii) the suitability of histone acetylation marks in neuronal chromatin as a mnemonic substrate. These three aspects, we believe, make it premature to conclude that histone acetylation is an active player in memory formation.

Revisiting the evidence

Genetic evidence: KATs and HDACs target more than just histones

The interpretation of cognitive and behavioral phenotypes associated with reduced KAT or HDAC activity should take into consideration the fact that these enzymes have hundreds of non-histone substrates [12] including many other nuclear proteins, such as transcription and chromatin-remodeling factors and regulatory subunits of the RNA polymerase II complex (Box 2 and Table 1).

The situation is further complicated by the fact that KATs and HDACs are large proteins that often exist in large, multiprotein complexes that can contribute to the regulation of transcription by means that are independent of their catalytic activities. For example, the CREB transactivation complex may contain KAT3a (also known as CBP) and KAT3b (also known as p300), but the complex can still activate transcription in the absence of KAT activity [13]. Similarly, experiments in yeast indicate that KAT-dead mutants remain largely functional [14]. The importance of the enzymatic activity of HDACs is also not universal; a recent study has shown that the inhibitory role of HDAC3, a canonical class I HDAC, in transcription is deacetylase independent and may exclusively rely on its interaction with the nuclear receptor corepressor (NCOR) complex [15]. Moreover, it has even been questioned whether class IIa HDACs (HDAC4, 5, 7, and 9) possess intrinsic K deacetylase (KDAC) enzymatic activity at all [16,17]. Whereas the active site of the other HDAC classes contains a tyrosine residue (Y) that acts as transition-state stabilizer, class IIa HDACs in all vertebrates have a histidine (H) in that position, which compromises enzymatic activity. Intriguingly, genetic experiments have shown that replacing that H with Y confers catalytic activity in class IIa HDACs [17]. The reason for the evolutionary conservation of this apparently defective active-site configuration remains unknown.

Given the multiple functions and substrates of KATs and HDACs, genetic evidence alone may be insufficient to definitively demonstrate their involvement in a specific transcriptional process. For example, experiments in transgenic mice expressing a mutated CBP bearing a catalytically dead KAT domain in forebrain neurons suggested that there are long-term memory deficits caused by loss of CBP's KAT activity [18]. However, the dominant-negative action of the transgene could arise from the overexpression of protein domains involved in the interaction with transcription factors (TFs) or the basal transcription machinery and not from the lack of acetyltransferase activity. The reversal of the memory deficit by HDACis nonetheless supports a direct mnemonic role for KAT activity [18]. These observations highlight the difficulty in interpreting the mechanisms underlying the roles of histone-modifying proteins.