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International Journal of Mass Spectrometry 259 (2007) 40–45
International Journal of Mass Spectrometry
www.elsevier.com/locate/ijms

"Hunt"-ing for post-translational modifications that underlie the histone code

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Received 23 May 2006; received in revised form 13 July 2006; accepted 15 July 2006
Available online 22 August 2006

Abstract

Eukaryotic cells package their DNA with histone proteins to form chromatin that can be regulated to enable transcription, DNA repair and replication in response to cellular needs and external stimuli. A wealth of recent studies of post-translational histone modifications and histone variants have led to an explosion of insights into and more questions about how these processes might be regulated. Work from Donald Hunt and colleagues contributed greatly to our understanding of the "histone code" by developing novel methods to study and identify histone modifications in both generic and specialized variant histone proteins. Without his expertise, the field of chromatin biology would not be where it is today. In recognition, we are pleased to contribute to a special issue of the *International Journal of Mass Spectrometry* dedicated to the many advances pioneered by the Hunt laboratory, which have enhanced the science of many fields and the careers of many scientists.
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Keywords: Donald Hunt; Mass spectrometry; Post-translational modifications; Histone code

1. Introduction

In the eukaryotic nucleus, an enormous amount of DNA must be tightly packaged in order to fit inside. Compaction is achieved in part by wrapping DNA around a core of histone proteins (two of each H2A, H2B, H3 and H4), to form a nucleosome, the fundamental repeating unit of chromatin. This "beads on a string" chromatin [1] is further condensed through the binding of the linker histone H1 to DNA that connects two adjacent nucleosomes.

To ensure proper access of nuclear factors to specific genes and, moreover, to demarcate large stretches of the genome for structural purposes and functional readout, eukaryotes have developed many histone-based strategies to introduce variation into the chromatin fiber. Two of the most common strategies employed are the post-translational modification (PTM) of histones and the exchange of major histone species with variants (variants are histone proteins that either differ slightly in their amino acid sequence as has been shown for H3 variants, or histones that have a significant variance in their primary sequence as has been found in histone H2A variants (reviewed in [2])). By developing specialized mass spectrometry techniques and instrumentation, University of Virginia chemist Donald Hunt has spearheaded many seminal and groundbreaking contributions to the field of chromatin biology that have allowed for the identification and functional characterization of histone PTMs and variants (Fig. 1). Deciphering PTM "signatures" and understanding the impact that histones have on chromatin function is especially relevant as an increasing body of literature describes how PTM "mistakes" are involved in human disease, notably cancer.

2. The early years: the "hunt" begins

Although the discovery that histones are acetylated *in vivo* dates to 1964 [3], the current list of post-translational modifications includes acetylation, methylation, ubiquitination and sumoylation of lysine residues, methylation of arginine, phos-

Abbreviations: MS, mass spectrometry; PTM, post-translational modification

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doi:10.1016/j.ijms.2006.07.009

Fig. 1. The "Hunt" for rare and exotic histone modifications continues . . .

phorylation of serine and threonine, and ADP-ribosylation (reviewed in [4–6]). In sum, a wealth of early, mostly correlative, studies have shown that covalent modifications of histone proteins play important roles in diverse processes such as transcription, silencing, histone deposition, DNA repair, and replication.

Histones also can be post-translationally cleaved by specific proteolytic activity. It was examining histone proteolysis that would serve as Hunt's introduction to chromatin biology. In the early 1990s, in back-to-back publications working together with Juan Ausio, Hunt characterized a protamine-like chromosomal protein (PL-II*) from the sperm of the bivalve mollusk *Mytilus californianus* as a member of the histone H1 (linker) family [7], and demonstrated that the protein is post-translationally cleaved at its C-terminus *in vivo* [8] (Table 1). Hunt's mass spectrometric analysis of PL-II* and its proteolytic fragments yielded an unprecedented resolution of the molecular masses when compared to the values obtained by more commonly employed sedimentation equilibrium techniques [9]. These studies not only represent some of the first to analyze the role of H1-like proteins in sperm chromatin organization, but also signify one of the earlier uses of mass spectrometry to analyze the post-translational modification of a histone protein.

In 2001 and 2002, together with Lucy Pemberton (University of Virginia), Hunt identified the members of a network of karyopherins in the budding yeast *S. cerevisiae* that mediate the nuclear import of histones H2A and H2B [10] and the histones H3 and H4 [11] (Table 1). They showed that both H2A and H2B contain a nuclear localization sequence (NLS) in the amino-terminal tail, and that Kap114p, Kap121p, and Kap95p interact directly with both NLSs, directing H2A-H2B into the nucleus as a dimer. Furthermore, they identified Kap123p and Kap121p as members of the H3–H4 import-complex, and showed that they bind to N-terminal NLSs in these histones. The identification of the specific subset of karyopherins that bind to histones and the dissections of their import pathways helped address several longstanding nuclear/histone transport questions, such as how complex specificity and functional overlap is achieved in histone import processes.

3. Code breakers and the mod squad

Many technical and methodological innovations from the Hunt laboratory have helped power the search for histone PTMs and histone binding proteins for a generation of chromatin biologists. Furthermore, their ability to help identify the enzymatic machinery responsible for specific histone PTMs has provided inroads to understanding their biological roles. However, to understand and appreciate fully the impact of the Hunt laboratory on the histone field, it is important to describe the dramatic changes that occurred to the histone biology landscape in the mid-nineties.

Although histone acetylation (reviewed in [12]) had been correlated with transcriptional activity since 1978 [13], it was in 1996 that discoveries in the laboratories of David Allis, who showed that the transcriptional co-activator Gcn5 was a histone acetyltransferase (HAT) [14,15], and Stuart Schreiber, who showed that a mammalian protein with histone deacetylase (HDAC) activity was similar to the yeast transcriptional regulator Rpd3 [16], firmly cemented the link between histone post-translational modifications and chromatin function. These findings also supported a widely held view that large amounts of complex information could be integrated within histones and the nucleosome template (reviewed in [17]). In 2000, Allis and his postdoctoral associate Brian Strahl proposed the "histone code" hypothesis [18]. Briefly, this hypothesis suggested that distinct histone post-translational modifications (PTMs) or combinations of PTMs could serve as targets for different chromatin-templated activities. This model and its implications for major biological questions provided a new impetus for the chromatin field to determine novel histone PTMs and to discover PTM "writers" (enzymes that post-translationally modify histones) and "readers" (modules or motifs that specifically recognize histones based on the modification state) of this code. Although this hypothesis continues to be the subject of ongoing debate [19,20], the "histone code" continues to gain experimental support [21,22]. Some of the most engaging arguments for a "histone code" have blossomed out of Hunt's collaborative studies with dedicated chromatin biologists, particularly David Allis.

By 2000, fellow UVa professor and Hunt collaborator David Allis had used antibodies and *in vivo* radioisotopic labeling techniques to demonstrate an increase of several PTMs upon biological stimuli, notably the phosphorylation on histone H3 at serine 10 (H3S10ph) during mitosis and meiosis in a wide range of organisms [23,24]. However, the "writer" of this histone modification remained unknown. Hunt's analysis of *in vitro* kinase reactions with H3 N-terminal tail peptides helped identify Ipl1/aurora as the H3 S10-specific mitotic kinase activities in budding yeast and nematodes [25] (Table 1). In 2001, Hunt and collaborators were among the first groups to report *in vivo* sites of arginine methylation on histones, and identified PRMT1 (protein arginine methyltransferase) to be the major, if not exclusive, H4 R3 methyltransferase in humans [26,27] (Table 1). This work also showed that histone H4 is methylated at R3 in many different eukaryotes, suggesting that this mark is evolutionarily conserved. More importantly, this data played a critical role in

Table 1
Chronological list of Don Hunt's contributions to the histone field

Date(s)	Result(s)	Fragmentation Method(s)	Sample Treatment(s)#	Instrument(s)*	Organism(s)	Ref.(s)
1993	PL-II* is member of histone H1 family and is post-translationally cleaved	CAD		TSQ70 and home-built QFTMS with LSIMS	*Mytilus trossulus*	[7, 8]
2000	H3 S10 phosphorylation is governed by Ipl1/aurora kinase and Glc7/PP1 phosphatase during mitosis	CAD		LCQ ion trap	*S. cerevisiae, C. elegans*	[25]
2001, 2002	Karyopherins mediate nuclear import of core histones	CAD		LCQ ion trap	*S. cerevisiae*	[10, 11]
2001	PRMT1 mediates histone H4 arginine 3 methylation	CAD		LCQ ion trap	Mammalian cell lines	[26]
2002	Set2 is a H3 K36-specific methyltransferase	CAD		LCQ ion trap	*S. cerevisiae*	[28]
2002	Ubiquitination of H2B K123 by Rad6 regulates H3 K4 and K79 methylation	CAD		LCQ ion trap	*S. cerevisiae*	[29]
2003	Different HMTs facilitate different methylation states on H3 K9	CAD	PA	LCQ ion trap	Mammalian cell lines	[30]
2004	H4 and H2A S1 phosphorylation is evolutionary conserved	CAD	PA	LTQ-FT	Worm, fly and mammalian cell lines	[31]
2004	PTM differences between H3 from mitotic and asynchronously growing cells	CAD	PA, ST	LTQ-FT	Mammalian cell lines	[32]
2004	Identification of phosphorylation sites on histone H1 isoforms	CAD	PA, IMAC	LTQ-FT	Human cell lines	[33]
2004	H3.2 and H3.3 differ in their PTM spectra	CAD	PA, ST	LTQ-FT	*Arabidopsis*	[41]
2005	Identification of existence of dual (phos/methyl) modifications on H3 variants	CAD	PA, IMAC	LTQ-FT	Mammalian cell lines	[39]
2005	HP1-chromatin binding is regulated by H3 methylation and phosphorylation	CAD	PA	LTQ-FT	Mammalian cell lines and *Xenopus laevis*	[21]
2005	H3.3 is phosporylated on S31 during metaphase	CAD	PA, IMAC	LTQ-FT	Mammalian cell lines	[43]
2005	"Lupus" mice differ in their H3 and H4 PTM profile from control mice	CAD	PA, ST	LTQ-FT	MRL-lpr/lpr and MRL/MPJ mice	[45]
2005	Identification of modification status on large peptides from H3.1 and novel H2A.Z isoform	ETD	PA	Modified LTQ with Finnigan 4500 chemical ionization source	Mammalian cell lines	[46]
2006	Mammalian H3.1, H3.2 and H3.3 variants differ in their expression and PTM profile	CAD	PA, ST	LTQ-FT	Mammalian cell lines	[44]

Rows highlighted in gray denote identification of protein, whereas rows with white background depict identification of modifications by mass spectrometry. #Listed are sample treatments besides proteolytic digestion. *If not specified, instruments used are from Thermo Electron. Abbreviations: CAD = collisionally activated dissociation, LSIMS = liquid secondary ion mass spectrometry, ST = stable isotope labeling using d_0 or d_6 ethanol for conversion of peptide carboxylic groups to the corresponding d_0 or d_5 ethyl esters, IMAC = immobilized-metal affinity chromatography, prior to IMAC enrichment the peptide carboxylic groups were converted to methyl esters, PA = derivatization with propionic anhydride to convert monomethylated and endogenously unmodified amino groups on lysine residues and the N-terminus to propionyl amides. All experiments, with the exception of [7,8] are exclusively LC–SI–S (liquid chromatography and electrospray ionization).

demonstrating that transcriptional coactivators, such as PRMT1 and CARM1 target cellular histones as physiologically relevant substrates. In 2002 the Hunt laboratory helped the Allis laboratory identify Set2 as the "writer" of the H3 K36 methyl mark in budding yeast by analyzing candidate bands from column fractions containing peak activity [28] (Table 1). Subsequent work with Set2 suggested that histone PTMs can impact the modification status of other residues on different histones in the same nucleosome. Using budding yeast, the Hunt and Allis groups found that methylation of histone H3 at K4 and K79, but not at K36, is regulated by the ubiquitination of histone H2B at K123 by Rad6 [29] (Table 1). These results not only supported the

prospect of a "histone code," but also suggested for the first time a "*trans*-histone" ("*trans*-tail") regulatory pathway in chromatin.

Lysine methylation is known to occur in mono-, di- and trimethylation states. In 2003, it was unclear if each of these methyl states had a different biological consequence or were "written" by different enzymes. To this end, another Hunt and Allis collaboration showed that H3 K9 mono- and dimethylation localize to silent regions in mammalian euchromatin in contrast to H3 K9 trimethylation, which is enriched at pericentric heterochromatin [30] (Table 1). Moreover, they showed that G9a was the HMT for H3 K9 dimethylation (H3K9me2) and to a smaller extent mono-methylation (H3K9me1), whereas different HMTs, Suv39h1 and Suv39h2, specifically tri-methylate H3 K9 (H3K9me3).

In 2004, the Hunt and Allis laboratories demonstrated that phosphorylation of histone H4 and H2A on serine 1 (S1) during mitosis is evolutionarily conserved in worms, flies, and mammals [31] (Table 1). Furthermore, they established that this phosphorylation mark was also enriched at a low level during S-phase, which suggests that H2A/H4 S1 phosphorylation might have a dual purpose, functioning both during mitosis and histone deposition in S-phase. During this time, the Hunt laboratory pioneered the development of a hybrid linear quadrupole ion trap (QLT) coupled to a Fourier transform ion cyclotron resonance mass analyzer (FTMS) and methodology, such as chemical derivatizations and stable isotope labeling, that permitted characterization of PTM differences between histones (H3 in particular) from asynchronously growing and mitotically arrested cells [32] (Table 1). Utilizing this instrumentation, the Hunt and Allis labs also were able to characterize phosphorylation sites on histone H1 isoforms from human cells [33] (Table 1). In all, 19 phosphorylation sites on the 5 major H1 isoforms and H1.X were identified. Interestingly, in addition to the phosphorylation marks, this method also characterized a peptide in which a lysine residue adjacent to a phosphorylation site on histone H1.4 was methylated.

4. An "on/off" switch

The observation of a dual phospho/methyl peptide was intriguing because it supported and extended the "switch hypothesis," proposed in 2003, by members of the Allis laboratory [34]. In the "switch hypothesis," serine or threonine residues adjacent to methylated lysine or arginine residues can become phosphorylated and prevent effector binding to the methyl mark. This hypothesis proposes a way for the biological effects of the chemically stable lysine or arginine methylation to be abrogated in the absence of a demethylating enzyme (a wealth of which have recently been identified [35–37]) or the exchange of the methylated histone molecule for an unmodified one (a mechanism that has gained more experimental support, in particular the exchange of H3 with H3.3 [38]). Importantly, Hunt's identification of adjacent methyl-lysine and phospho-serine residues in H1.4 showed that these dual marks exist *in vivo* and prompted the search for similar methyl/phos combinations on core histones. These combinations were found a year later in another study characterizing PTMs on histone H3 variants during mitosis [39] (Table 1). Using a combination of immobilized metal affinity chromatography (IMAC) and MS/MS, phosphorylation sites and other marks were identified on human H3.1, H3.2 and H3.3 variants from HeLa cells arrested in mitosis. Again, lysine residues adjacent to phosphorylated serine and threonine residues were found to be methylated, adding support to the "binary switch" hypothesis. A careful examination of the "binary switch" literature gives numerous citations to Hunt's unpublished observations [34].

However, even greater support for this hypothesis came from a recent study by the Allis, Funabiki, and Hunt laboratories, where again crucial MS help was provided by Donald Hunt and his colleagues. Together, these groups supplied experimental evidence that the binding of HP1 to H3K9me3 was interrrupted during mitosis because of the phosphorylation at the adjacent H3 S10 [21] (Table 1). These findings suggest that there exists a regulatory mechanism of protein–protein interactions through a combinatorial readout of two adjacent histone PTMs.

5. Variation on a theme

In many eukaryotes, the four core histones have minor variants that are differentially expressed and incorporated into chromatin. However, in many cases the roles of these variants are difficult to ascertain by antibody-based methodologies due to a high degree of sequence similarities between them. In collaboration with the Jacobsen laboratory (UCLA; Los Angeles, CA), the Hunt lab's analysis of *Arabidopsis* H3 variants (H3.1 and H3.2, now called H3.2 and H3.3, respectively, in accordance with an unified histone H3 variant nomenclature [40]) by nanoflow-HPLC coupled electrospray ionization on a hybrid linear ion trap-Fourier transform mass spectrometer revealed that these two variants differ in the abundance of silencing and activation PTMs [41] (Table 1). The replication-dependent H3.2 variant was enriched in PTMs associated with transcriptional silencing and the replication-independent H3.3 variant was decorated with PTMs associated with gene activation. These data, in accordance with a previous study in *Drosophila* [42], suggest that H3 variants, which differ in only few amino acids, have very distinct biological functions. Accordingly, the Hunt laboratory has remained focused on histone variants, cataloguing their different PTMs as a means of dissecting functional differences.

A classic example of this connection between histone variants and differential function was published by the Hunt and Allis labs in 2005, in a paper describing the identification of a novel histone variant-specific phosphorylation mark. They showed that the human replication-independent histone H3 variant H3.3 is phosphorylated on its unique serine 31 (S31ph) during mitosis [43] (Table 1). Interestingly, H3.3S31ph differs from other, well-established mitosis-specific phosphorylation sites (e.g., H3S10ph and S28ph) in that this mark is only found on a subpopulation of H3.3 that localized to centromere-surrounding regions. Additionally, MS/MS work did not detect any peptides with both S28 and S31 phosphorylated simultaneously. These findings suggest that a subpopulation of H3.3 exists, which might have a function distinct from its proposed role in gene activation. Shortly after this study of H3.3, a comprehensive analysis of the

expression patterns and PTMs in mammalian H3 variants by the Hunt, Allis, and Bazett-Jones groups showed that different mammalian cell lines have unique expression profiles of non-centromeric H3 variants (H3.1, H3.2 and H3.3). With the help of quantitative MS/MS they also observed that these variants are enriched in different PTMs [44] (Table 1). In sum, these data suggest that H3 variants may have different biological functions, in which H3.3 is associated with transcriptional activation and H3.1 and H3.2 with different modes of transcriptional silencing (reviewed in [40]).

6. Implications for the health field

The Hunt group has also made inroads in connecting histone modification states to disease. A recent study by the Mishra and Hunt groups investigated the connections between histone PTMs and disease. Histones H3 and H4 isolated from a mouse model of lupus erythematosus (MRL-lpr/lpr) were quantitatively compared to those from control mice (MRL/MPJ) and were found to differ significantly in their PTM pattern [45] (Table 1). In addition to novel PTM identification, they observed that "lupus" mice have global site-specific hypermethylation (except H3 K4) and hypoacetylation of histone H3 and H4 when compared to histones from control mice histones. Importantly, they also found that treatment of "lupus" mice with trichostatin A (a histone deacetylase inhibitor) resulted in increased acetylation of H3 and H4, and an improvement of the disease phenotype. This was the first study to establish the association between an aberrant "histone code" and the pathogenesis of the autoimmune disease lupus erythematosus.

7. 2006-future: where will the "hunt" for the "histone code" lead?

Innovations from the Hunt research group have become indispensible tools for testing hypotheses such as the "histone code". As the field of histone biology progresses from cataloging a single PTM to determining functional significance of multiple "marks", the Hunt group is on the forefront. They recently developed electron transfer dissociation (ETD) with proton transfer charge reduction, allowing them to concentrate various c- and z-type ion signals into a single charge state. This methodology can be used to rapidly sequence and determine the comprehensive modification status of large histone peptides. Using ETD, they were able to "read" the modification status of the first 50 residues of human H3.1, and also identify a novel H2A.Z isoform from a mixture of intact H2A.Z proteins [46] (Table 1). Aside from histone research, this new technology promises to become a valuable tool for general proteomics as well as applications in the biotechnology and pharmaceutical industries.

Coping with the vast amount of histone and also non-histone post-translational modifications (PTMs) and how they function together remains a significant challenge for researchers. While many descriptions of novel modification sites have been obtained using radioisotope labeling or through immunological (antibody) derived methods, these techniques are often limited by epitope disruption, cross reactivity, or dependence on *in vitro* assays. In this respect, Donald Hunt and his mass spectrometry contributions have played a key role in redefining how histone modifying enzymes and their sites of activity are identified and studied, ushering in a new era of understanding histone PTMs (Fig. 1). His findings have given root to many of the current hypotheses now being tested in chromatin biology and will surely pave the way for countless others in the future.

David Allis recalls hearing Donald Hunt give a lecture at the University of Virginia shortly after his (Allis) arrival there in 1998. "It was clear to me then that Don was a force to be reckoned with, especially in the area of proteomics and post-translational modifications." Now, even after having moved to Rockefeller University, Allis comments that nothing has changed or even slowed down. "We have engaged about a dozen published collaborative studies with the Hunt group and at least that many more projects are somewhere in the pipeline with them. Don will always be at the forefront of my field and, from what I can tell, many others."

Acknowledgements

We especially thank Don Hunt for his excellence in Mass Spectrometry and his contributions to the field of chromatin biology. Without his expertise and knowledge, many break-through discoveries, as well as this review, would not have been possible. His friendship, thirst for knowledge and drive to solve the toughest problems fuel all of our collaborative studies. We also thank Elizabeth Duncan and Beatrix Ueberheide for careful reading of the manuscript and acknowledge members of the Allis' laboratory for their support and discussions. This work was supported by the NIH grant GM53512 to C.D.A., the NIH grant GM63959 to S.D.T. and C.D.A. and the Rockefeller's *Women and Science* Fellowship to S.B.H.

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