Journal of
Proteomics & Bioinformatics

Tackett, J Proteomics Bioinform 2013, S2
DOI: 10.4172/jpb.S2-e001

Editorial Open Access

The Role of Mass Spectrometry in Chromatin Biology

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Mass spectrometry has played a vital role in defining what we understand about mechanisms regulating chromatin structure and function. With the speed, sensitivity and resolution of new generation mass spectrometers, researchers are now well-positioned to not only analyze bulk chromatin features, but to also begin to explore lower abundance chromatin signatures that help define the detailed epigenetic landscape of a chromosome. The components of chromatin that have been the primary focus of analysis by mass spectrometry are proteins and protein posttranslational modifications (PTMs). Below I discuss each of these components and provide insight into how mass spectrometry is helping to reshape how we study epigenetic mechanisms.

The major protein component of chromatin is recognized as histones. The core component of a chromosome is the nucleosome, which contains two copies of each core histone: H2A, H2B, H3 and H4. These core histones are marked with a variety of PTMs that help direct activities such as gene transcription, recombination and repair. The PTM of histones occurs most often on the N-terminal tails of the proteins, which extend from the nucleosome core structure. Some of the more common histone PTMs are lysine acetylations, arginine and lysine methylations, and serine and threonine phosphorylations. These PTMs on histones serve as molecular recognition motifs to direct binding of 'effector' proteins that promote some aspect of chromatin metabolism [1]. For example, H3K4me3 is a histone PTM localized to promoter chromatin and it has been found that specific histone acetyltransferases contain domains such as PHD fingers that localize the histone acetyltransferase to promoter chromatin and thereby induce lysine acetylation such as H3K14ac [2]. When histone H3 at promoter chromatin is marked with H3K4me3 and H3K14ac, gene transcription is induced through the subsequent localization of transcriptional machinery [3]. The scientific literature has numerous examples of how histone PTMs direct many types of chromatin activities, but a key in uncovering these histone PTMs is the use of mass spectrometry. Mass spectrometry has provided for the identification of global or bulk histone PTMs as well as combinations of histone PTMs on individual histone molecules [4]. In relation to the histone acetyltransferase study above, high resolution mass spectrometry uncovered the co-existence of H3K4me3 and H3K14ac on the same histone molecule [5].

In addition to histones, there are a variety of proteins and protein complexes that make up chromatin. As detailed above for a histone acetyltransferase, proteins can be directed to particular regions of chromatin to drive various activities. This can be the localization of transcription machinery, DNA replication machinery, proteins that establish particular chromosome regions like centromeres and telomeres, etc. Mass spectrometry coupled with traditional biochemical approaches has provided for the analysis of these types of chromatin bound proteins. One such approach is to use affinity enrichment of a target protein to determine what other proteins are associated with the particular chromatin bound protein complex. For example, we have performed detailed studies on DNA polymerase epsilon and the NuA3 histone acetyltransferase [2,6]. Mass spectrometry plays the role of protein identification as well as quantitative readout of which purified proteins are true members of the chromatin bound protein complex [7,8].

One of the limiting factors for studying proteins and protein PTMs on chromatin is that most studies analyze bulk populations. For example, one may use mass spectrometry to identify proteins and histone PTMs that are simply isolated in bulk from cells. In this manner, one loses the ability to determine at what position in the chromosomes that these chromatin features were localized. ChIP and ChIPseq approaches provide the genomic localization of a known protein or protein PTM; however, these approaches are limited by traditionally poor quality antibodies and that one must know the molecular target for the antibody. Recently, approaches using affinity purification and high resolution mass spectrometry have overcome the inability to site-specifically define chromatin features along a chromosome. Researchers were able to affinity purify large chromatin structures like telomeres, engineered plasmids or engineered loci for proteomic identification of proteins and PTMs [9-14]. These are true groundbreaking studies as researchers were isolating stretches of chromatin unbiasedly (i.e., targeting the DNA site specifically for enrichment and not the protein or PTMs) and identifying what proteins/PTMs were located in these regions. The most recent breakthrough in these types of approaches was the reported ability to isolate native 1 kb stretches of chromatin without any engineering of the target DNA sequence [15]. In this manner, there is no engineering of the DNA to provide for purification, thus one can in principle target any 1 kb section of a chromosome for high resolution identification of what proteins and PTMs are associated. The immediate future of this field is to explore various types of DNA targeting affinity reagents to purify short stretches of chromosomes for mass spectrometric analysis, while in the long run these approaches could be applied to map epigenetic landscape along long stretches of chromosomes and to study differential epigenetic regulation at particular regions as a function of disease state. Mass spectrometry has helped define the field of chromatin biology and there is a bright future ahead for this analytical approach in helping to better understand epigenetic mechanisms.

Acknowledgements

Dr. Tackett would like to acknowledge support from NIH grants R01GM106024, R33CA173264, UL1RR029884, P30GM103450, and P20GM103429.

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Received November 22, 2013; **Accepted** November 25, 2013; **Published** November 27, 2013

Citation: Tackett AJ (2013) The Role of Mass Spectrometry in Chromatin Biology. J Proteomics Bioinform S2: e001. doi:10.4172/jpb.S2-e001

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This article was originally published in a special issue, **Applications of Mass Spectrometry in Epigenetics** handled by Editor(s). Dr. Alan Tackett, University of Arkansas for Medical Sciences, USA