Histones are basic proteins that are responsible for packaging genomic DNA into a higher-ordered structure termed chromatin. The fundamental repeating unit of chromatin is the nucleosomal core particle that comprises an octamer of two copies each of the histones H2A, H2B, H3, and H4, around which is spooled ~150 base pairs of DNA. Nucleosomes can be arrayed into hierarchical architectures that efficiently condense DNA within the nucleus, thus governing access to the DNA template. One mechanism by which chromatin structure can be altered involves post-translational modifications of histones. The 1960s and 1970s witnessed the discovery of numerous histone modifications, including acetylation, lysine methylation, arginine methylation, phosphorylation, and ubiquitination. The majority of these modifications cluster in the N-terminal tails of the core histones and the C-terminal tails of histones H2A and H2B (Figure 1). Throughout the 1960s to the 1980s, studies by multiple groups yielded circumstantial data implicating histone modifications in gene regulation, DNA replication, and other genomic processes, but the precise functions of these modifications remained largely enigmatic.

The 1990s represented a period of major milestones in elucidating the biological roles of histone modifications. The turning point in this field was the discovery and characterization of the first histone acetyltransferases and deacetylases that had been previously characterized as transcriptional regulators, thus providing the first direct links between histone modifications and gene regulation. These discoveries were followed in rapid succession by the identification of other classes of histone modifying enzymes, including ubiquitinases, arginine and lysine methyltransferases, lysine demethylases, and protein arginine deiminases that hydrolyze arginine to citrulline. Concomitant with these discoveries, numerous families of effector proteins were identified that recognize specific modification states to mediate signal transduction in transcriptional regulation, DNA replication, repair, and recombination, and other nuclear processes. Together, these studies have provided a conceptual foundation for understanding the biological functions of histone modifications.

This issue of Biopolymers features a series of reviews that explore recent advances in our understanding of the structures, mechanisms, and regulation of chromatin modifying enzymes and the functions associated with various histone modification states. Yuan and Marmorstein summarize histone acetyltransferase structure and regulation by autoacetylation and describe the widespread nature of protein acetylation, drawing comparisons to protein kinases and phosphorylation. Fierke and colleagues examine the substrate specificity, catalytic mechanism, and regulation of metal-dependent histone deacetylases, focusing on studies of HDAC8. Two reviews explore topics pertaining to lysine methylation. Black and Whetstone provide a comprehensive overview of the different biological functions associated with histone lysine methylation and the biochemical basis by which methylation status is controlled through the concerted activities of lysine methyltransferases and demethylases. In a related article, Couture and colleagues explore the structure, assembly, and regulation of the MLL1/SET1 complexes that methylate Lys4 in histone H3. Garza and Pillus round out the reviews on lysine modifi-
cations by providing a perspective on SUMO-Targeted Ubiquitin Ligation (STUbL), focusing on enzymes that display STUbL activity and their chromatin-related functions. Finally, Bicker and Thompson review protein arginine deiminases, their roles in chromatin modifications and links to various diseases, and the development of small molecule inhibitors as cellular probes to study their functions.

A common theme that emerges in these articles is that post-translational modifications are not confined to histones but are prevalent in many nonhistone proteins. Indeed, many nuclear proteins have been shown to undergo a multitude of modifications analogous to histones, particularly transcription factors, as exemplified by the tumor suppressor p53. Correlatively, many modifying enzymes initially categorized as histone-specific have since been shown to possess nonhistone substrates and functions beyond chromatin modification. Collectively, these findings illustrate the complexity of post-translational modifications in nuclear signal transduction. Efforts to characterize these signaling pathways are fundamentally important to understanding the physio-
logical functions of post-translational modifications of nuclear proteins and how dysregulation of these pathways contributes to the incidence of various diseases, particularly cancer.

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REFERENCES