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Introduction to the multi-author review on methylation in cellular physiology

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Protein post-translational modifications (PTMs) have long been a topic of intensive investigation. Covalent additions to the 20 genetically encoded amino acids can alter protein interactions and can even change enzymatic function. In eukarya, PTMs can amplify both the complexity and functional paradigms of the cellular environment. Therefore, PTMs have been of substantial research interest, both for understanding fundamental mechanisms and to provide insight into drug design. Indeed, targeting proteins involved in writing, reading, and erasing PTMs important for human pathologies are some of the most fruitful avenues of drug discovery.

PTMs come in many flavors, including covalent additions that alter fundamental aspects of amino acid chemistry such as charge (e.g. phosphorylation and acetylation) and hydrophobicity (e.g. methylation). Some PTMs, like phosphorylation and acetylation, are highly dynamic, while others, like lysine and arginine methylation, are more stable. The varied chemical nature of PTMs are key aspects of their biological function. Overall, PTMs are regulators of most eukaryotic cellular processes.

As previously reviewed by Paik and Kim, protein methylation was first discovered in the 1950s and early 1960s on flagella and muscle proteins, and significantly, on histone proteins [1]. Histones are the protein building blocks of chromatin, the physiological form of the eukaryotic genome. The specific discovery of ε-N-methyl-lysine (Kme1/2/3), N^G-monomethyl-L-arginine (mono/Rme1/MMA); N^G,N^G-dimethyl-L-arginine (asymmetric/Rme2a/ADMA), and N^G,N^G-dimethyl-L-arginine (symmetric/Rme2s/SDMA) on histones, and the tantalizing early experiments by Allfrey, Faulkner, and Mirsky suggesting their functional role in regulating transcription [2] set the stage–more than 30 years later–for proposal of the histone code hypothesis [3, 4]. In this hypothesis, addition of methylation and other PTMs to specific histone residues, alone or in combination, participate in the regulation of gene expression. The idea of a PTM code, while not without controversy over the nature of its instructive or passive signaling role, has since been extended to many other fields. In the subsequent two decades, much progress has been made over the specific functions of histone and non-histone methylation.

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In this multi-author review, we explore exciting new work on lysine and arginine methylation, novel insights into nucleic acid methylation, and how the enzymes responsible for writing these PTMs and readers responsible for recognizing these PTMs could be drugged. While much attention has been directed at histone lysine methylation, Dan Levy (*this issue*) examines recent work on how lysine methylation of non-histone proteins regulates nuclear function. Levy highlights both how new approaches are employed to detect lysine methylation and how these methylations alter the cellular functions of important proteins like p53. Continuing the theme of nuclear function of lysine methylation, Crump and Milne (*this issue*) explore the mystifying role of the large family of Mixed Lineage Leukemia (MLL) lysine methyltransferase family. The question of why there are so many seemingly redundant enzymes, but which all are individually critical for mammalian development, is important for understanding their normal and oncogenic roles. Li, Ahn, and Wang (*this issue*) review literature on a specific histone methylation–H3 lysine 36 (H3K36me1/2/3)–and how its deregulation contributes to human disease. What is most striking from their review is the elaborate web of regulation and cellular consequences of a single histone PTM.

Switching focus to arginine methylation, Tewary, Zheng, and Ho (*this issue*) review up-to-date details of Protein Arginine Methyltransferase (PRMT) enzymatic function and atomic structure. Important insights from this review include understanding of how this family of nine structurally similar enzymes recognizes discrete substrates and uniquely catalyze the three methylarginine isotypes. To understand the cellular consequences of PRMT-catalyzed arginine methylation, Lorton and Shechter (*this issue*) comprehensively review the literature on the known arginine methylated proteins. What is most emergent from this review is the important role that methylarginine plays in regulating interactions involving protein intrinsically disordered regions (IDRs) and modulating liquid-liquid phase separation.

Methylation is not limited to proteins. Alderman and Xiao (*this issue*) review new insights into a modestly studied eukaryotic nucleic acid modification: N(6)-methyladenine. This modification, challenging to study due to poor detection approaches, has recently gained attention due to its regulatory role in important cellular processes like gene expression, stress response, and retrotransposon suppression. This review highlights areas of controversy and as well as paths forward for new technological developments to further the study of this modification.

We conclude with a chapter by Dilworth and Barsyte-Lovejoy (*this issue*) chemical probes and precision medicines targeting protein methylation. Important information presented in this review are both general principles for drugging methyltransferases or methyl-binding proteins and current best-in-class examples heading for the clinic.

In the past decades, a tremendous body of work has expanded our knowledge of the important contributions of protein and nucleic acid methylation to all aspects of cellular physiology. This multi-author review brings together state-of-the-art insights into lysine, arginine, and adenosine methylation. With this expanded knowledge, we can move the methylation field forward into new discoveries critical for understanding basic biology and for improving human health.

References

1. Paik WK, Paik DC, and Kim S, Historical review: the field of protein methylation. Trends Biochem Sci, 2007 32(3): p. 146–52. [PubMed: 17291768]
2. Allfrey VG, Faulkner R, and Mirsky AE, Acetylation and Methylation of Histones and Their Possible Role in the Regulation of Rna Synthesis. Proc Natl Acad Sci U S A, 1964 51: p. 786–94. [PubMed: 14172992]
3. Strahl BD and Allis CD, The language of covalent histone modifications. Nature, 2000 403(6765): p. 41–5. [PubMed: 10638745]
4. Jenuwein T and Allis CD, Translating the histone code. Science, 2001 293(5532): p. 1074–80. [PubMed: 11498575]