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Introduction: Epigenetics

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The mammalian genome is not merely a static combination of the four genetic letters A, T, C, and G. Each adult human body has over 200 distinct cell types that share an almost identical genome sequence. Sequence alone, however, cannot adequately define and reveal cell status, nor can it determine the fate of cell development. In addition to the genomic sequence, reversible chemical modifications occur on DNA and histones which contribute significantly to cell diversity through dynamic regulation of global gene expression. This layer of epigenetic regulation centers on chemical modifications of macromolecules and exists independently of changes to the genomic sequence. In this fast-growing field of research, chemistry and chemists play critical roles in inventing new tools, developing new concepts, and providing mechanistic understanding. This issue presents reviews from experts on recent advances in epigenetics, particularly from the perspective of chemical biology. Researchers interested in this field will find insights into a broad range of subjects all organized around the central theme of chemical modifications that impact gene expression regulation.

DNA methylation at the 5'-position of cytosine has been well-known as a critical epigenetic mechanism in tuning gene expression in eukaryotes. Despite decades of research, the reversible cleavage of the C–C bond for 5-methylcytosine (5mC) in a potential demethylation process was unknown until only recently. In 2009, a new form of DNA cytosine modification, 5-hydroxymethylcytosine (5hmC), was discovered in mammals through enzymatic oxidation of 5mC. He and co-workers review the discovery of 5hmC and its further conversion to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC); 5fC and 5caC can return back to cytosine via base excision repair in an active demethylation mechanism. This review discusses recent advances and regulation of this 5mC oxidation and demethylation pathway.

Balasubramanian and co-workers further introduce chemical methods in order to detect and sequence cytosine modifications in genomic DNA. In order to uncover functional roles of DNA cytosine modifications, their precise genomic locations in different cell lines or tissues must be obtained. Most current sequencing methods depend on PCR amplification of

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Notes

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isolated genomic DNA. Upon PCR amplification, modified cytosines of 5mC, 5hmC, 5fC, and 5caC in genomic DNA all read as regular C with a loss of modification information. In order to overcome this challenge, effective methods are required that can selectively label or modulate the structures of these cytosine modifications for subsequent detection and sequencing. The authors provide a comprehensive review of the developments of chemical approaches that allow for the highly selective and sensitive detection of these modified cytosine bases.

The three billion base pair human genome must be packed into the nucleus of a cell yet still become available for replication and transcription. The genome is organized into a polymeric complex of chromatin. McGinty and Tan review the structure and general function of the basic unit of the chromatin complex, the nucleosome. The dynamic chromatin structure has been realized in recent years to play key roles in gene expression regulation. This review highlights recent advances in the understanding of the nucleosome, with an emphasis on the structural properties of the individual nucleosome, the recognition of the nucleosome by chromatin factors, and recent models for the 30 nm chromatin fiber which may reveal how nucleosomes further pack together into units of higher density.

In their manuscript, Bowman and Poirier discuss the regulation of nucleosome dynamics. They describe how various post-translational modifications (PTMs) on histone tails influence nucleosome assembly, sliding motions, and stability. In general, histone tail modifications appear to affect unwrapping of the DNA around the histone octamer. Sensitive points of interaction between the DNA and octamer involve the DNA entry and exit points. In addition, the authors discuss how various chaperones and remodeling complexes that regulate nucleosome structure and dynamics are influenced by histone PTMs. This article highlights some of the state-of-the-art biophysical approaches brought to bear on studying nucleosome dynamics, including single molecule force microscopy and FRET studies. Key to the studies summarized are techniques that have been developed to generate chemically well-defined nucleosomes, as covered in the paper by Müller and Muir.

Müller and Muir discuss a series of elegant methods that have been applied to produce homogeneously modified histone proteins. This article comprehensively summarizes the use of genetic approaches to generate acetyl-Lys in proteins, the various protein ligation strategies that have been reported to afford semisynthetic histones, and some of the site-specific modification techniques that typically involve the unique reactivity of cysteine residues. At this stage, a whole range of PTMs have been installed site-specifically into histones and then assembled into nucleosomes and chromatin. Some of the more exotic PTMs now accessible in these structures include high quality mimics of phosphohistidine and ubiquitylation. Müller and Muir also discuss emerging chemical biology strategies for screening and analyzing nucleosomes that should be of broad interest to the chromatin biology communities. The power of chemical synthesis in addressing the nuances of nucleosome structure and function is convincingly conveyed in this article.

Jing and Lin provide a thorough review of sirtuin functional roles in biology. The sirtuin enzymatic activities were discovered about 15 years ago as a novel NAD-dependent deacetylase family of enzymes, distinct from the metallohydrolase histone deacetylases

(HDACs) discovered a few years prior. The sirtuins are fascinating in enzymology because of their chemical linkage to O-ADP-ribosyl transfer and cleavage from nicotinamide from the NAD cofactor. Based on this unique chemical mechanism, there have been many reports about the connection of sirtuin deacetylation of proteins to metabolic enzymes and the redox state. This article discusses this connection. It also highlights the relatively recent discovery of sirtuins such as Sirt5 as deacylases that can cleave succinyl and malonyl groups from Lys proteins. Many of the sirtuin pathways and protein substrates are placed in the context of key cellular pathways with important implications for health and disease.

Until relatively recently, a handful of chemical functionalities were established to modify histone side chains, albeit at many different sites. In the paper by Huang et al, an up to date account of the explosion in chemical diversity of histone marks is reviewed, cataloging a mind-boggling series of PTMs that are only just beginning to be understood. Some of the newer modifications, such as 2-hydroxyisobutyrylation and glutarylation, suggest that many novel regulatory linkages between metabolism and chromatin structure/function may be important. A valuable feature of this article is a detailed full discussion of the mass spectrometric methods that have been developed and applied for analyzing protein PTMs, especially in the context of histones. The strengths and limitations of the various mass spectrometry approaches are discussed including sensitivity, reliability, and quantitative accuracy. This article should be a popular resource for those interpreting the increasing number of proteomics studies appearing in the chromatin literature.

Dancy and Cole have contributed an extensive review of the structure, function, and mechanisms of the transcriptional coactivator paralogs p300 and CBP. p300/CBP is a well-established histone acetyltransferase (HAT) enzyme that targets histones as well as many non-histone proteins and has been implicated in a vast array of pathways in gene regulation and pathogenesis. Over 400 proteins have been proposed as binding partners for p300/CBP and nearly 100 protein substrates reported. In contrast to HDACs and several other epigenetic enzyme families, pharmacologically effective HAT inhibitors have been notoriously difficult to develop, and this article describes the current state of progress in this area. Whether p300/CBP acetyltransferase inhibition will prove useful in the clinic remains to be seen, but is under active study.

Cellular proteins can be posttranslationally modified by another biopolymer, poly(ADP-ribose) or PAR, which is catalyzed by poly(ADP-ribose) polymerase (PARP). PARP proteins utilize nicotinamide adenine dinucleotide NAD^+ as a donor of ADP-ribose units and transfer these units to their target proteins. PARP and its catalytic functions play critical roles in a range of diverse biological pathways by regulating DNA damage detection and repair, transcriptional regulation, RNA processing, and metabolism. Kraus and co-workers present a review of the biochemistry and physiology of PAR and PARP with timely coverage of the recent advances of PARP in the regulation of RNA.

Biographies

Chuan He received his B.S. degree in Chemistry from the University of Science and Technology of China (USTC) in 1994. He obtained his Ph.D. degree at Massachusetts Institute of Technology with Professor Stephen J. Lippard in 2000 and received postdoctoral training with Professor Gregory L. Verdine at Harvard University. He is currently the John T. Wilson Distinguished Service Professor at the University of Chicago and an investigator of the Howard Hughes Medical Institute. His research interests cover nucleic acid modifications, epigenetics, chemical biology, RNA metabolism, and bioinorganic chemistry.

Philip A. Cole was born in Paterson, NJ, and graduated from Yale University with a B.S. in Chemistry in 1984 and then spent a year as a Churchill Scholar at the University of Cambridge, England. Cole went on to obtain M.D. and Ph.D. degrees from Johns Hopkins University, where he pursued research in bioorganic chemistry in 1991. Cole then entered postdoctoral fellowship training at Harvard Medical School prior to joining the Rockefeller University in 1996 as a junior lab head. In 1999, Cole moved back to Johns Hopkins as the Marshall-Maren professor and director of pharmacology. His research interests are in the area of protein post-translational modifications and chemical biology.