The Biochemistry of Chromatin Remodeling

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A fundamental puzzle of biology is how a common genome – the unique complement of DNA-encoded genes associated with all somatic cells of an organism - can produce a multiplicity of biological phenotypes. How is it, for example, that an insect can metamorphose from a larva to a pupa and finally to an adult butterfly without any change in DNA composition? A clear answer to questions like this has emerged from many decades of molecular biology studies. While all cells contain the same full complement of genes, there is a specific set of biochemical control mechanisms that allow some genes to be actively transcribed while other genes are silenced in specific cells at specific points in their life cycles. This collection of transcriptional control mechanisms has been colloquially referred to as epigenetics, but is more correctly termed chromatin remodeling. Much of the history of epigenetic and chromatin remodeling biology has been dominated by descriptive studies. Over the past decade, however, a much clearer understanding of the biochemical basis of chromatin remodeling has begun to emerge as a result of more quantitatively focused studies. These studies highlight the importance of thermodynamic and kinetic elements in the control of chromatin structure and resultant gene transcription.

Chromatin refers to the DNA-histone protein complex that is the fundamental structural component of chromosomes. Transcription is controlled by the conformation of chromatin in proximity to specific gene promoters and this conformational remodeling of chromatin is in turn controlled by a collection of
biochemical reactions; these include enzyme-catalyzed covalent modification of the
DNA and histone components of chromatin, selective binding of transcriptional
machinery to recognition elements on modified chromatin, ATP-hydrolysis driven
changes in DNA-histone topography and modulation of chromatin structure by
interactions with other protein and nucleic acid factors (1). In this special issue of
the journal, devoted to epigenetics, many of these topics are reviewed and brought
into clear, contemporary focus. Current Topics articles are included in this issue
that bring the reader up-to-date on a range of topical issues as they pertain to the
fundamental biochemistry of chromatin remodeling and to the importance of these
processes in human disease. These include reviews of enzyme-catalyzed covalent
modification of chromatin (2), the structural biology of a critical class of chromatin
modifying enzymes: the protein methyltransferases (3), covalent modification of
RNA (4), the biochemistry of the SWI/SNF complex, which uses the energy of ATP
hydrolysis to effect topographical changes to DNA-histone interactions (5),
recognition of lysine methylation by methyl-lysine reader proteins (6), the role of
long, non-coding RNAs in epigenetics (7) and the potential role of prion proteins as
regulators of epigenetics (8).

The contemporary importance of chromatin remodeling relates not only to
basic scientific research but also to the applied science of drug discovery and to
other fields as well. Hence, the American Chemical Society has taken the bold step
of coordinating special issues, focused on epigenetics, across a spectrum of journals:
Biochemistry, ACS Chemical Biology, ACS Medicinal Chemistry Letters and The
Journal of Medicinal Chemistry. The American Chemical Society is to be
congratulated for this ambitious endeavor. Yet, the articles represented in this and
the other journal's special issues, represent merely a starting point for the detailed,
quantitative understanding of chromatin biochemistry and its application to the
development of new medicines. This is a fertile ground for new research, as there
remain many unanswered questions about the biochemical processes of chromatin
remodeling, the biochemical and biological interdependence of these various
reactions in the precise control of gene transcription and the biochemical basis for
diseases that result from alterations of these control mechanisms (9). In the area of
biochemical processes for chromatin remodeling, a large number of enzymes that
catalyze mechanisms of remodeling and proteins that respond to such remodeling
remain to be investigated in biochemical detail. For example, the enzymes that
catalyze methylation of RNA molecules, such as the METTL and NSUN families, have
not been characterized in enzymatic detail as RNA methyltransferases (10).
Likewise, members of these families have been reported to also catalyze protein
methylation, but this has gone largely uncharacterized with respect to biochemical
mechanism and the relative physiological roles of RNA and protein methylation by
these enzymes. Many of the proteins that recognize site-specific chromatin
marking, such as the acetyl-lysine readers and the methyl-lysine readers, function in
cells as members of multiprotein assemblies (1). Yet, the role of conformational
dynamics – via inter- and intra-assembly protein-protein interactions – in
translating binding into transcriptional modulation by these complexes remains to
be described fully. It is increasingly clear that the transcriptional impact of a
specific chromatin mark cannot be understood in isolation, but rather depends on
the background of other chromatin marks that may be occurring simultaneously within the cell nucleus \((2, 5, 9, 11)\). The nature of these chromatin mark interdependencies and their further dependence on non-chromatin based signaling pathways in cells, needs much more investigation if we are to understand these myriad processes and their roles in normal physiology and pathobiology. Many of these questions may best be answered by chemical biology approaches, utilizing potent and highly selective modulators of specific chromatin modifying proteins (CMPs). Indeed, the chemical biology and drug discovery communities have responded to this need and provided appropriate tool compounds for such investigations \((1)\). Nevertheless, there remains a great need to further augment the existing armamentarium of selective compounds so that a broader spectrum of CMPs may be investigated \((9)\). In this regard, it is equally important that the community at large, and particularly the editors and reviewers for journal articles, reject studies performed with non-specific, blunt instruments that serve only to obfuscate our understanding of the role of specific CMPs in biochemistry and physiology. Perhaps the most blatant example of this is the misuse of DZNep (3-deazaneplanocin) and its phenotypic impact in any attempt to divine the role of polycomb repressive complex 2 (PRC2) in physiology or disease \((12)\). A final area that deserves greater study is the phylogeny of CMPs and their biochemical mechanisms. Chromatin remodeling plays an important role in the physiology of almost all multicellular organisms. To date, much of the focus of biochemical studies has been largely restricted to human proteins, as is appropriate for an understanding of the roles of these CMPs in human physiology and disease. There
may, however, be significant understanding to be gleaned from studies of these proteins across phyla. While such studies are of inherent interest to the basic science community, they may also have practical value in diverse commercial interests such as veterinary medicine, agriculture, insect pest control and human parasitic diseases. In short, there is much more work to be done in the biochemistry of chromatin remodeling.

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Guest Editor
References


