Chromosome and expression mechanisms: a year dominated by histone modifications, transitory and remembered

Jerry Workman

Sarah C.R. Elgin
Washington University in St. Louis, selgin@wustl.edu

Follow this and additional works at: https://openscholarship.wustl.edu/bio_facpubs

Part of the Biology Commons

Recommended Citation
Workman, Jerry and Elgin, Sarah C.R., "Chromosome and expression mechanisms: a year dominated by histone modifications, transitory and remembered" (2002). Biology Faculty Publications & Presentations. 204.
https://openscholarship.wustl.edu/bio_facpubs/204

This Article is brought to you for free and open access by the Biology at Washington University Open Scholarship. It has been accepted for inclusion in Biology Faculty Publications & Presentations by an authorized administrator of Washington University Open Scholarship. For more information, please contact digital@wumail.wustl.edu.
Chromosomes and expression mechanisms
A year dominated by histone modifications, transitory and remembered

Editorial overview
Sarah CR Elgin and Jerry L Workman

In recent years, the study of gene regulation has changed dramatically, as the complete genome sequences of many model organisms have become available, allowing assessment of genome-wide patterns of transcription. Genome databases and advances in mass spectroscopy have allowed rapid identification of protein complexes that modify chromatin and regulate transcription. (For new strategies to identify protein complexes, see [1–3].) The finding that many transcription co-activators and co-repressors are linked to histone modifications has placed chromatin structure at the center of gene regulation. Histone acetylation, phosphorylation and methylation are all utilized in the control of transcription; histone variants have also been implicated. Studies of the protein complexes that either generate or recognize modified histones are revealing sophisticated pathways of information exchange, modulation, and memory. The surface of the chromosome now appears to be similar to the surface of the cell: studded with ligands and receptors controlling the receipt and response to environmental signals. Comparable to signaling networks used in the cytoplasm, a linked sequence of histone modifications appears to function in signal transduction. Deepening appreciation of how histones — and complexes that act on them — generate, read and maintain epigenetic marks is revealing the molecular basis of epigenetics. The study of gene regulation has been revitalized with new tools, new players, and a newly discovered code of signals decorating the chromatin.

This issue of Current Opinion in Genetics & Development begins with a genome-wide viewpoint, as Wyrick and Young (pp 130–136) discuss genomic tools for deciphering gene expression regulatory networks in Saccharomyces cerevisiae. They describe three approaches towards studying such global processes: genome-wide expression analyses using DNA microarrays, genome-wide factor location using chromatin immunoprecipitation (ChIP) products analyzed using DNA microarrays, and DNA motif-finding algorithms that search for factor-binding sites. The combined information can identify clusters of genes responding to the same direct effectors, as well as indicate secondary interactions. New technologies for examining the kinetics and structure of effector–template interactions have also emerged. Fluorescence microscopy and photobleaching of living specimens has allowed analysis of protein mobility in the cell nucleus. As described by Hager, Elbi and Becker (pp 137–141), recent results indicate that many factors involved in regulating gene activity move rapidly and exchange quickly with their targets, raising interesting questions concerning the stability of the effector complexes detected by ChIP assays.
In an overview of histone modifications, Berger (pp 142–148) describes the breakthrough discoveries — many important coactivators and corepressors possess histone acetyltransferase or deacetylase activity, respectively. Histone phosphorylation, methylation, and ubiquitination have since been analyzed. Berger describes recent results supporting the concept of the ‘histone code’, in which specific patterns of histone modification provide signals indicating the intended transcription state of the locus. Featherstone (pp 149–155) then details the functions of coactivators in both chromatin modification and transcriptional stimulation. Coactivators include general transcription factors, histone modifying complexes, and ATP-dependent chromatin ‘remodeling’ complexes. The ordered recruitment of these complexes may lead to a fluid choreography of events resulting in alteration of chromatin structure and activation of a gene. However, the dance may not be precisely set — the ordered appearance of the dancers appears to vary on different genes. Recent findings have emphasized that coactivator function can be switched by post-translational modification [4]. Elongating RNA polymerase faces an array of nucleosomes ahead of it. As Svejstrup (pp 156–161) describes, the polymerase might either ride over a histone octamer, pass the octamer behind it, or dissociate the octamer when it encounters a nucleosome. Elongation is facilitated by several accessory protein complexes. Complexes such as FACT can bind histones directly, and may hold some of the histones while the polymerase passes.

In addition to histone modification, histone variants are used in important defined sub-populations of nucleosomes. A highly conserved histone H3 variant, CENP-A, plays a critical role in centromere formation [5]. Here, Redon et al. (pp 162–169) report on the conserved H2A variants. H2AX is specifically phosphorylated in response to double-strand breaks in DNA, and may play a role in signaling DNA repair, whereas H2AZ appears to alter nucleosome stability, impacting transcriptional regulation. A third variant, macroH2A, is utilized in X inactivation (see Cohen and Lee [pp 219–224]).

Histone modification patterns also play a role in defining chromatin domains. As reviewed by Bulget et al. (pp 170–177), several — but clearly not all — gene loci, including the β-globin locus, are generally enriched in acetylated histones, in addition to peaks of hyperacetylation at transcribed genes and regulatory elements. It is not known how increased acetylation across the domain is generated. Formation of the β-globin domain appears to involve regulatory sequences beyond the LCR. The mechanism behind β-globin LCR–promoter interactions remains elusive; the transcription factor NF-E2, thought to mediate such interactions, appears to associate with both sequences independently.

A striking step towards definition of heterochromatic domains came with recognition that such domains in higher eukaryotes are marked by methylation of lysine 9 of histone H3 (reviewed by Grewal and Elgin [pp 178–187]). This modification provides a recognition site for Heterochromatin Protein 1 (HP1), a bifunctional protein also able to form complexes with the modifying enzyme SUV39. This provides a molecular mechanism for the inheritance of the histone modification at a specific locus, and a means of spreading the modified state. In Schizosaccharomyces pombe, inverted repeats at the boundaries of the silent mating type locus appear to block spreading. In S. cerevisiae, the spread of heterochromatin appears to rely on histone hypoacetylation. Here, boundaries are characterized by a spike of histone acetylation due to a strong promoter or a specific DNA binding protein (reviewed by Dhillon and Kamakaka [pp 188–192]). Silencing in S. cerevisiae is dependent on the Sir2p deacetylase, which is targeted by DNA binding proteins. Although the means of targeting histone H3-lys9 methylation in higher eukaryotes remains elusive, histone hyperacetylation may mark the ends of such silent domains in some cases. The role of nuclear organization in gene silencing during development is considered by Fisher and Merkenschlager (pp 193–197), with special attention to recent work on the immunoglobulin genes.

Whereas H3 in inactive domains is methylated at lysine 9, in active regions H3 is methylated at lysine 4, accompanied by shifts in histone acetylation. The histone methyltransferases responsible are described by Kouzarides (pp 198–209). Specific forms of methylated histones are important in formation of alternative chromatin domains and in both positive and negative regulation of specific promoters. This seems a complex system, involving highly specific modifying enzymes, positive and negative impacts of prior modifications, and recognition of the modified state by coactivators and corepressors. Interestingly, whereas colocalization of HP1 with H3-mLys9 has been found to play a role in repression of some euchromatic genes, the complex involved in this case appears to remain localized, rather than spreading.

Simon and Tamkun (pp 210–218) describe evidence suggesting that histone modification states play a role in the developmental maintenance of on/off decisions carried out by the trithorax group and Polycomb group proteins. Stability may be conferred by the ability of the Polycomb complex to block chromatin remodeling, whereas the BRM complex of trithorax group proteins promotes remodeling. Changes in the histone complement, and patterns of histone modification, have been implicated in maintaining the stable off state of the inactive X chromosome in mammals (Cohen and Lee [pp 219–224]). Recent work argues that Xist RNA, expressed exclusively from and bound to the silenced X chromosome, is the causative agent for initiating assembly of the silent chromatin. Methylation of H3 at lysine 9 is an early event, whereas histone hypoacetylation and accumulation of macroH2A1 are late events in the process. This H3 methylation does
not appear to involve enzymes that modify heterochromatin nor result in HP1 binding, suggesting a distinct process. Strikingly, Tamaru and Selker [6] have reported that histone H3 lysine 9 methylation is required for DNA methylation in Neurospora. The same relationship could occur in mammals where DNA methylation is a late event in X chromosome inactivation.

Progress in delineating a completely different mechanism for achieving gene inactivation, RNAi, is reviewed for us by Hutvágner and Zamore (pp 225–232). Organisms as diverse as nematodes, flies, plants, and fungi destroy specific RNA transcripts homologous to double-stranded RNA in the cell. Whereas the mechanism is clearly used for biological purposes, it is also valuable for reverse genetics. Progress in identifying the components of the system is leading towards an understanding of the mechanism. It has been reported that RNAs can also trigger DNA methylation in plants; perhaps silencing is initially targeted to the repetitious sequences found in pericentric heterochromatin through an RNA-based mechanism [7].

Our growing understanding of mechanisms of gene regulation has suggested new approaches to manipulating gene activity in humans (Reik, Gregory and Urnov [pp 233–242]). Histone deacetylase and DNA methylase inhibitors show promise in treating disease where activation of a silenced gene is of therapeutic value (e.g. sickle cell anemia). Designer transcription factors are being developed to target activating or repressive chromatin modifying complexes to specific genes. Cloning also presents therapeutic possibilities, but challenges due to loss of epigenetic imprints. Clearly, the genome must be replicated in a manner that duplicates chromatin structures that encompass epigenetic information. Interactions between the replication proteins and the chromatin assembly factors appears critical to subsequent heterochromatin function (Gerbi and Bielinsky [pp 243–248]). Chromatin structure can influence the timing of replication origin use, with potential downstream consequences.

In their Commentary, Kornberg and Lorch (pp 249–251) put this progress into perspective, pointing out remaining gaps in our understanding. What is the structure of the chromatin fiber in vivo? Without an established structure, there is no assay for the affect of acetylation on that structure. What is the state of an active promoter? Is the histone core dislodged, or simply rendered impotent by modification and remodeling? The answer may not be the same for all promoters. Full reconstruction of an in vitro gene activation system, coupled with genetic analysis, will be essential to resolve these issues.

Post-genomic tools are greatly enlarging our range of analysis, from single genes to domains, chromosomes, and genomes as a whole. Long-standing epigenetic phenomena are yielding to detailed biochemical analyses. We now know that the signals include both DNA sequence elements and histone codes. This is a new era in the study of gene regulation, providing opportunities to gain a deeper understanding of chromosome biology. By providing a series of timely reviews, we hope that this issue of Current Opinion in Genetics & Development will illustrate the new connections and novel concepts that will drive this field in the coming years, and we thank the authors for their efforts.

References